Army Medicine Peer-Reviewed Publications

January 2013

Executive Summary

January 2013 – Journal coverage for January mirrored the volume of coverage from previous months with a few unique trends.

First, reporting on obesity and nutrition related to obesity dominated medical journal coverage with topics ranging from the physiological reactions to glucose versus fructose to the implementation of accelerometers to incentivize weight loss. In addition to medical advances, Military Medicine also provided the example of the Diabetes and Obesity Research Working Group, the Air Force's task force charged with preventive medicine related to diabetes-related obesity. In other nutrition coverage, the amount of caffeine contained in dietary supplements offered on bases was the central question for the Journal of Internal Medicine study. With media reporting heavily on issues of military obesity in recent weeks, research related to nutrition and obesity offers the Army the opportunity to include the studies' findings in messaging.

Another prominent area of focus was malaria with Primaquine standing out as a drug of interest in preventing malaria, which is important in terms of media coverage given the allegations surrounding Mefloquine, or Lariam, as a previously sanctioned treatment. Additionally, the interaction between HIV antiretroviral medication and anti-malaria medication was the subject of a Journal of the American Medical Association study.

PTSD therapy received a prominent share of research with group, writing, prolonged exposure therapy, and cognitive processing therapy (CPT) serving as the areas of interest. Studies discovered promising results in both writing therapy and the use of prolonged and cognitive therapy as used by the VA. The study on group therapy focused on potential barriers that may help explain Soldiers' reluctance to participate.

Medical Journal Coverage

Behavioral Health

The Lancet: Global pattern of experienced and anticipated discrimination reported by people with major depressive disorder: a cross-sectional survey

This comprehensive study of discrimination against adults with depression includes 1,082 interviews with depressed adults throughout 35 countries. Its findings are particularly worrisome as discrimination prevents depressed individuals from seeking a normal life as well as treatment. The vast majority of respondents (79 percent) note discrimination in one or more aspects of their lives. Regarding the barriers depressed individuals face, 37 percent report they refrain from close personal relationships, and 25 percent avoid work while 20 percent do not pursue education or training. Discrimination increases in individuals who have experienced lifetime depressive episodes, at least one psychiatric hospital admission or who had poor levels of social functioning. The more discrimination respondents experienced, the more likely they were to conceal depression and avoid therapy (with roughly 70 percent keeping their diagnosis secret).

Military Medicine: Prevalence and Characteristics of Military Malingering

In determining the characteristics of malingering, doctors can avoid erroneously accusing patients, damaging trust and worsening actual psychological symptoms. In studying over 1,000 cases of malingering over five years, researchers determined that the typical malingerer is male, young, unmarried and enlisted. As expected, malingering occurs most often in relation to emotional and mental diagnoses rather than physical ones, and it is extremely rare.

Pyschotherapy and Psychosomatics Journal: The Concept of Mental Pain

Turning its focus to mental pain, the Psychotherapy and Psychosomatics journal asserts that the disparity between physical and mental health awareness is due to the lack of distinctive features of mental pain. The journal defines mental pain in the context of depression, suicide, and psychiatric disorders. In addition, various systems of measurement are mentioned to assess mental pain. The author ends the article by urging the adoption of a set of agreed-upon imperatives: consensus on what defines mental pain, threshold of clinical attention, the balance of mental pain and psychological well-being, the under-researched area of neurobiology related to mental pain, and the impact of intervention strategies.

Psychological Medicine: Heterogeneity of amygdala response in major depressive disorder: the impact of lifetime subthreshold mania

The Psychological Medicine study seeks to determine whether individual differences in amygdala activity are related to depressive and/or manic symptoms in adults. The study includes 26 adults matched for age and gender. In the study, adults with MDD show increased amygdala activity on the right side (related to angry and happy conditions), which is associated with higher levels of manic symptoms over the lifespan.

Disease

Military Medicine: Sequential Real-Time PCR Assays Applied to Identification of Genomic Signatures in Formalin-Fixed Paraffin-Embedded Tissues: A Case Report About Brucella-Induced Osteomyelitis

Little is known about brucellosis, a zoonotic infection transmitted from animals to humans. This case study an Iraq War veteran notes that the infection is difficult to diagnose as the patient has non-specific clinical findings with only mild elevations in serum inflammatory markers. In assessing the infection, researchers found tissue gram and silver impregnation stains on bone biopsies, indicating one possible method of diagnosis. This infection is rare and it will continue to be challenging to diagnose, especially in austere environments.

Immunity: Vaccine Induction of Antibodies against a Structurally Heterogeneous Site of Immune Pressure within HIV-1 Envelope Protein Variable Regions 1 and 2

Four years ago, researchers developed an HIV vaccine that showed significant promise for some testers but was ineffective for one-third of those who took it. The research team, including experts from the U.S. Military HIV Research Program, explains how the vaccine works and why it might be ineffective for certain individuals. This research is vital in developing more effective HIV vaccines, and it received some coverage from medical trade publications.

Military Medicine: Myopericarditis and Pericarditis in the Deployed Military Member: A Retrospective Series

This is the first study to test reports that the small pox vaccine may increase the risk that Soldiers develop pericarditis and myopericarditis. Investigating over 700,000 Soldiers' medical records found an incidence rate of 8.35 cases of pericarditis or myopericarditics, which is similar to a comparable subset of the population, indicating no link between the vaccine and he disease.

Cancer Causes & Control: Serum 25-hydroxyvitamin D and breast cancer in the military: a case–control study utilizing pre-diagnostic serum

Researchers set out to determine if there is a link between 25-hydroxyvitamin D and an increased risk for breast cancer in young women. A study of 600 cases of breast cancer found an inverse association between the serum and breast cancer. Researchers indicate that further study is needed on this subject.

The Lancet Infectious Diseases: Primaquine to prevent transmission of falciparum malaria

A worldwide decline in incidents of malaria has led to the belief that the disease can be eliminated. This goal is threatened by falciparum malaria, which is transmitting by mosquitos that have fed on blood containing the germ, *plasmodium falciparum.* Researchers determined that primaquine is not effective enough in treating falciparum malaria to justify the risk associated with taking it.

JAMA: HIV Drugs and Malaria

Ritonavir is useful in treating HIV, but it can inhibit effectiveness of other drugs. This poses a problem for those with HIV who live in areas where there is risk of developing malaria, as Ritonavir counteracts most malaria medication. This brief article summarizes findings that indicate a combination of the protease inhibitors lopinavir and ritonavir or non–nucleoside reverse transcriptase inhibitors decreased the incidence of malaria in children with HIV who are taking ritonavir.

The Lancet: Early-life prevention of non-communicable diseases

The strategy developed by the United Nations to stem the rate of non-communicable diseases responsible for a significant number of deaths globally details four areas of concern: diabetes, cardiovascular disease, cancer, and chronic obstructive pulmonary disease. The analysis points to poor diet, physical inactivity, tobacco use, and alcohol consumption as major contributing factors to these four areas. Given the Army's recent focus on all four issues, there is potential to position Army innovation and strategy as a global leader. By highlighting the global incidence of these issues, messaging can provide global context to Army issues as well.

Reuters Health: Primaquine Protects Against P. vivax Malaria Relapse

In a study involving 113 Indonesian soldiers, Primaquine combined with antimalarials was successful in eradicating parasites associated with malaria, thus preventing a relapse. The study allows for the Army to better understand possible treatments for malaria aside from Lariam.

Military Medicine: Malignant Pericardial Effusion and Pericardial Tumor Involvement Secondary to Cervical Cancer

The case study of a Hispanic female in her 50s discusses the treatment options for progressive, advanced stage cervical cancer. With recent reporting focused on women's health in the Army, research into issues such as cervical cancer can help to highlight warrior care provided to female Soldiers.

The Cancer Journal: Quality of Cancer Survivorship Care in the Military Health System (TRICARE)

The study from the Cancer Journal seeks to determine adequate frequency standards in follow-up care for breast, prostate, and colorectal cancers. The data from TRICARE Prime beneficiaries begins between October 2005 and March 2007 and continues to September 2010. Over 3,148 patients are involved in the study with 65% receiving all minimum care over 3 years. Seventy-four percent of breast cancer patients receive a mammogram each year, while 69% of colorectal cancer patients receive one colonoscopy per year. Pulling data from TRICARE Prime beneficiaries highlights the trove of information available to Army Medicine in aggregating information related to health.

Medical Protocol and Training

Military Medicine: Recommendations for Biomonitoring of Emergency Responders: Focus on Occupational Health Investigations and Occupational Health Research

Emergency responders are constantly presented with ever-changing hazardous environments. Researchers reviewed studies and literature to determine if biomonitoring is appropriate for its intended purposes and if it is feasible for emergency responders. A lengthy discussion ensues with researchers agreeing that biomonitoring is more feasible when the patient has been exposed to a harmful chemical. In this case it is beneficial in assessing the risk of other non-patients who may have also been exposed. Researchers point to the need for discussion of enhancing communications regarding the ethics of biomonitoring.

New England Journal of Medicine: Shared Decision Making to Improve Care and Reduce Costs

The New England Journal of Medicine highlights the Affordable Care Act's implementation of shared decision making but criticizes the implementation by saying it has failed to encourage the patient-centered model. The authors then point to the possibility of reduced costs related to shared decision making, as 20% of patients with access to shared decision-making aids choose a less invasive surgical option than patients without access. Army Medicine has the potential to implement shared decision making but also to highlight the current system of care as it centers on patient needs.

Military Medicine: Traumatic Event Management in Afghanistan: A Field Report on Combat Applications in Regional Command-South

Traumatic Events Management (TEM) strategies are the central component to the analysis from Military Medicine where a particular focus is placed on Event-Driven Battlemind Psychological Debriefings for combat units. The analysis comes from the surge of troops between 2009 and 2010. Three examples of EDBPDS provide context and suggestions for possible variations in conducting the debriefings. The analysis provides on-the-ground examples of the debriefings and the success/failure rates associated with certain approaches. Army Medicine can use the information to alter implementation but can also feature the accounts to highlight efforts to address and treat Soldiers' interpretation of traumatic events.

Military Medicine: Ultrasound in the Austere Environment: A Review of the History, Indications, and Specifications

A Military Medicine article tells the history of the expanded use of ultrasound due to its portability, safety, real-time image display, and rapid data collection. Pointing to austere environments and the military's motivation "to do more with less," the use of ultrasound has become more innovative with further study of the uses of ultrasound in remote locations for various clinical assessments. The study concludes that the use of ultrasound is ideal for remote, austere environments due to its ability to triage injuries in a situation with poor logistics.

Nutrition and Fitness

Journal of Internal Medicine: Caffeine Content of Dietary Supplements Consumed on Military Bases

Researchers analyzed the most popular dietary supplements at military bases to determine the accuracy of their labels in regards to caffeine content. Results indicate that 45 percent of studied supplements listed accurate amounts of caffeine while 25 percent contained 27 to 113 percent of what it listed. Of those supplements studied, less than half provided accurate information regarding caffeine content. Thirty percent of popular products failed to note caffeine content despite containing more than 200 mg. of caffeine per serving, far above the 71 mg. limit for soft drinks. This is detrimental to Soldiers as unreliable information prevents them from keeping their caffeine consumption within safe ranges.

JAMA: Effects of Fructose vs Glucose on Regional Cerebral Blood Flow in Brain Regions Involved With Appetite and Reward Pathways

The JAMA study focuses on the prevalence of fructose and its neurological role in promoting weight gain, obesity, and insulin resistance as compared to glucose. The study included 20 adult volunteers subjected to magnetic resonance imaging sessions. Fructose consumption did result in a distinct pattern of cerebral blood flow (CBF) and a slight increase in systemic glucose and insulin. The repeated focus on obesity levels and the causes of obesity will assist Army Medicine in determining how best to alter the availability of, or restriction of, certain foods and beverages to promote readiness among Soldiers.

JAMA: Fructose Ingestion and Cerebral, Metabolic, and Satiety Responses

Continuing to focus on fructose, JAMA highlights the inclusion of fructose in products such as sodas, energy drinks and sports drinks, items contested to encourage obesity. The article reiterates the above study that found a patterned difference of cerebral blood flow (CBF). The authors urge a second look at the various regions of the brain that also react, such as the thalamus and striatum. Striatum contains “reward” pathways, seen in addictive behaviors that may account for the predilection of the sweetness of fructose over that of glucose. The analysis of the relationship between fructose and glucose can help Army Medicine to educate Soldiers on the health benefits of each variation.

Obesity

JAMA: Does Body Mass Index Adequately Convey a Patient's Mortality Risk?

As an introduction to JAMA’s research on obesity mortality risk, this article briefly reviews the history of the medical community’s effort to determine which weight and BMI are healthiest. The article points to the limitations of assessing risk based on BMI without addressing sex, race, age, fitness differences or fat distribution. Research such as this is vital to Army Medicine in helping evaluate the long-term health consequences of potential recruits as well as evaluating current Soldiers’ weight.

The Lancet: Obesity: many hands to make light(er) work

This article discusses the impact obesity has on the economy in both developed and developing countries and various efforts to incentivize weight-loss and healthier eating options. The article criticizes the UK's effort to stem obesity by noting that political programs and incentives were not coordinated with efforts within the private sector. Given previous reports of rising obesity rates in the Army, Army Medicine can look to global efforts to determine best practices.

Military Medicine: Effect of an Accelerometer on Body Weight and Fitness in Overweight and Obese Active Duty Soldiers

The country's increasing obesity rate poses a risk to national security and has the potential to compound Soldiers' health issues. Researchers determine that mandatory physical training and using an accelerometer to track fitness did not cause significant weight loss among obese or overweight Soldiers, indicating Army Medicine needs to look elsewhere to develop weight-loss initiatives.

JAMA: Association of All-Cause Mortality With Overweight and Obesity Using Standard Body Mass Index Categories

Focusing on obesity, JAMA reviewed 97 relevant articles, representing more than 2.88 million individuals and 270,000 deaths, to determine the risk(s) of death associated with being overweight and/or obese. The study found that higher obesity levels were associated with higher instances of mortality of all causes. For Army Medicine, the correlation between obesity and higher death risk reinforces the need to promote active, healthy lifestyles for Soldiers.

Military Medicine: Increased Adolescent Overweight and Obesity Documentation Through a Simple Electronic Medical Record Intervention

Despite the country's growing obesity rate, doctors are not consistently recording adolescent's weight during checkups. In order to encourage weight monitoring, researchers used military electronic medical records to track weight for overweight and obese adolescents in an effort to address the country's growing rate of obesity. In the military's medical clinics, doctors used the FOCUS-PDCA to track adolescent's weight during doctor visits. The trial was successful in encouraging medical personnel to keep consistent records, and researchers recommend other clinics use the same method. Research such as this underscores how military medical research and protocol can assist the civilian population.

Military Medicine: The U.S. Air Force Diabetes and Obesity Research Working Group: A Model for Building Military-Specific Clinical Research Infrastructure

With continued research on obesity, the Military Medicine article introduces the study by stating that patients diagnosed with diabetes experience doubled healthcare costs. From the Tobacco, Obesity, and Alcohol (TOBESAHOL) study, an estimated $1.1 billion is spent regarding obesity/overweight issues and nearly $300 million among TRICARE Prime beneficiaries. The study identifies six areas of priority for the Air Force: diabetes prevention, technology use to bridge resource gaps, improved efficacy in outpatient and inpatient diabetes care, better definitions of diabetes populations, and operational concerns. The information on how the Air Force has established the Diabetes and Obesity Research Working Group (DORWG) can help Army Medicine determine best practices in confronting the rising issue of obesity in the military.

Physiological Injuries and Surgery

New England Journal of Medicine: The 510(k) Ancestry of a Metal-on-Metal Hip Implant

This article calls attention to a loophole that allows potentially unsafe metal-on-metal implants to be sold as long as the manufacturer developed a similar predicate. In many cases, the hip implant currently being sold is different enough from the previously approved implant that separate clinical tests should have been performed to determine their safety. This 501(k) loophole allows manufacturers to sell hip implants with serious flaws that can cause long-term health consequences. The article ends by pointing to the recently passed Medical Device User Fee and Modernization Act that will make it easier for the FDA to close the 501(k) loophole.

Military Medicine: Pulsed Radio Frequency Energy Therapy Use for Pain Relief Following Surgery for Tendinopathy-Associated Chronic Pain: Two Case Reports

Chronic tendon pain is a common condition in the military with limited pain treatment options. This case study examines two instances where doctors utilized pulsed radio frequency energy (PRFE) therapy to treat patients with chronic tendinopathy. In both cases, pain decreased after two to three weeks of treatment and pain had not returned in a seven-month follow-up, indicating that this may be a viable pain management option. This research is especially timely given recent research pointing to an increasing rate of opioid abuse in the military.

Military Medicine: The Addition of Body Armor Diminishes Dynamic Postural Stability in Military Soldiers

Some Soldiers have reported that the additional weight of their body armor causes poor postural stability, which is a risk factor is lower extremity musculoskeletal injury. Researchers asked 36 Solders to perform single-leg jump landings with and without body armor in order to replicate the dynamic military environment. Results indicate that body armor does in fact diminish dynamic postural stability, increasing Soldiers' risk of lower extremity injuries. One method to alleviate this issue is to have Soldiers wear body armor during training exercises to teach their body to improve dynamic postural stability.

Military Medicine: Silent Aspiration and Recovery From Dysphagia in a Case of Bickerstaff Brainstem Encephalitis

This research focuses on the effects of Bickerstaff Brainstem Encephalitis (BBE) leading to recovery. The article provides a case study of Soldier, E.B., who seems recovered but returns to Italy to discover he has lesions on his brainstem and various other brain regions. The case study follows the course of recovery, including weekly evaluations. The case recognizes that silent aspiration may occur close to one month following initial hospitalization.

Military Medicine: Portable Spirometry in the Deployed Setting

Given that some of the most common nonbattle illnesses are respiratory disorders, the Military Medicine article highlights burn pits as a potential risk in developing these disorders. Aside from burn pits, the article points to other environmental factors as possible causative risks: particulate matter, exhaust fumes, and sandstorms. In order to measure the effects, portable spirometers are used in theater. Given the high profile of coverage related to burn pits, the study details possible factors that contribute or compound respiratory disorders in Soldiers.

Military Medicine: Emergency Physician Evaluation of a Novel Surgical Cricothyroidotomy Tool in Simulated Combat and Clinical Environments

In a study of cricothyroidotomy, a CRIC device is compared to traditional surgery in three different environments: emergency department (ED), day combat situation and night combat situation. Results provide no significant difference between traditional methods and the CRIC in any scenario. Army Medicine can turn to this information to promote the perpetual preparedness of medical professionals in the field or at home.

Military Medicine: Vehicle-Mounted High-Power Microwave Systems and Health Risk Communication in a Deployed Environment

With the addition of high-power microwaves on military vehicles intended to counter the improvised explosive devices in Southwest Asia, the study seeks to stem the anxiety and misconception that the radio frequency (RF) emitted affects Soldier health. Despite an incident where Soldiers reported health effects related to an HPM device, an Army investigation found that the arid climate, carbon monoxide exposure and combat stress are responsible for the changes. The Army can turn to this study to mitigate growing concern surrounding health risks inherent to active duty service.

Military Medicine: Traumatic Carotid Artery Dissection

Military Medicine reports on a study related to traumatic carotid artery dissections (CAD), which is a separation of artery wall layers and is a common cause of stroke in young adults. The article provides examples in the form of a case study that urges physicians to be careful with diagnoses around head and neck pathologies as the dissection can be related. Army Medicine can utilize the information to educate Army physicians on the risks associated with CAD.

PTSD

Psychotherapy and Psychosomatics: Writing Therapy for Posttraumatic Stress: A Meta-Analysis

Given the growing need for treatment for PTSD, it is not always possible for every patient with PTSD to receive face-to-face treatment. In lieu of that, this research points to writing therapy administered over the Internet as a viable option for PTSD treatment. In assessing the treatment, there was no significant difference between writing therapy and trauma-focused cognitive behavioral therapy. Writing therapy is especially effective in reaching victims in remote areas or those who are susceptible to the stigma against seeking formal mental healthcare.

Military Medicine: Service Utilization Following Participation in Cognitive Processing Therapy or Prolonged Exposure Therapy for Post-Traumatic Stress Disorder

This research evaluates the Department of Veterans Affairs prolonged exposure and cognitive processing PTSD therapy programs, focusing on both cost and effectiveness. Promising results indicate that over time veterans recovered and tapered their use of individual and group therapy decreasing direct mental healthcare costs by 39 percent. This research is especially timely given budget cuts and the need to reduce costs without sacrificing care.

Psychological Medicine: Influence of predispositions on post-traumatic stress disorder: does it vary by trauma severity?

This research tests the assumption that predisposition plays a secondary role when an individual is exposed to severe trauma. In assessing over 34,000 respondents' level of trauma (sexual assault being severe while accidents, disaster and death were considered lower magnitude) in relation to six areas of predisposition. Results indicate that predispositions increase the risk for developing PTSD after both severe and moderate trauma.

Military Medicine: Group Therapy Among OEF/OIF Veterans: Treatment Barriers and Preferences

Researchers assessed the specific barriers veterans face in participating in group therapy for PTSD. Results indicate that veterans are most concerned with expressing emotions in a group setting, fear being misunderstood and disliking working in a group setting in general. The majority,

57 percent, of respondents said they preferred individual over group sessions. Understanding barriers to group therapy can help adjust programs to meet the needs of Soldiers and veterans.

Substance Abuse

Military Medicine: Unmet Need for Treatment of Substance Use Disorders and Serious Psychological Distress Among Veterans: A Nationwide Analysis Using the NSDUH

Research evaluates veterans' access to treatment for serious mental health concerns including, substance use disorders, PTSD, TBI, depression or serious psychological distress. Using data from 2004 to 2010, researchers examined veterans aged 21 to 34 and found that substance use disorders were the most common untreated concern. Interestingly, similar rates of untreated substance use and serious psychological distress existed in the civilian and military communities, indicating a need for more access to mental healthcare in the civilian as well as military communities.

Medscape Neurology: Understanding Opioids: Part 1

The unprecedented rise in opioid related death plagues the country and the military, with these deaths accounting for more deaths in the military population than cocaine and heroin combined. In a discussion of opioid abuse, various experts argue that the increase in opioid use is due to the US-healthcare system's insistence on being autonomous and the perceived right to be relieved of pain. Experts note addiction begins when high doses of opioids are prescribed, which they argue also contributes to patients dying of respiratory depression during sleep. Some argue this is possibly the greatest risk of using opioids. Formidable barriers exist to non-opioid pain care, with experts agreeing that more attention needs to be paid to developing alternative pain management options.

Military Medicine: Examining the Association Between Binge Drinking and Propensity to Join the Military

Researchers set out to determine to what extend binge drinking was related to the propensity to join the military. In surveying high school seniors, researchers discovered that those who intend to join the military binge drink more days than those who do not plan on military service. The link was seen even after controlling for sociodemographic and lifetime drinking characteristics. Research such as this highlights the need for recruiters to address the danger of over-consuming alcohol. This research can draw additional attention from traditional media on the military's perceived binge drinking culture.

Military Medicine: Tobacco Product Usage Among Deployed Male and Female Military Personnel in Kuwait

Previous research indicates that smoking is the best predictor of military training failure, is associated with increased hospitalization and lost work days and is a strong marker for alcohol abuse, low physical activity and illicit drug use. Smokers in the military are also more likely to sustain musculoskeletal injuries. This study of service members in Kuwait found that forty-one percent of surveyed report using tobacco products while in the country. Among those users, 87 percent were male with a mean age of 30. Service members report their tobacco use was influenced due to their deployment as 9 percent did not use tobacco prior to the deployment, 21 percent increased their use and 6 percent decreased usage.

American Journal of Preventative Medicine: Substance Use Among Military-Connected Youth

Military families are exposed to a unique set of stressors, including deployment, which can especially have an effect on military-connected youth. This research discovers that military-connected youth are more susceptible to substance abuse, which can lead to a wide variety of lifetime health and social issues. This researched received coverage in traditional media, as it widens the scope of those affected by war.

The Lancet: The 21st century hazards of smoking and benefits of stopping: a prospective study of one million women in the UK

The study, focused on the first adult population where women could spend a significant portion of adult life smoking cigarettes, studied 1 million British women born around 1940 to determine the effects of continued use but also of quitting. Results indicate that two-thirds of deaths (50s-70s) are caused by smoking; whereas the risk of ceasing the habit circa 40 years old is significantly more beneficial. The information on smoking and the risks associated with quitting can help Army Medicine educate Soldiers on risk.

Suicide

Journal of Internal Medicine: Hospitalization for physical illness and risk of subsequent suicide: a population study

Physical illness greatly increases the risk for suicide, as 64 percent of those who committed suicide among a Danish population also had a history of hospitalization for physical illness. Risk increased as hospitalization became more frequent and recent. Comorbidity increased risk as well. Army Medicine should be aware of the potentially critical suicide risk that Soldiers may experience who are hospitalized for frequent and recent physical injuries.

Military Medicine: Gabapentin Overdose in a Military Beneficiary

A case in which one veteran ingested a pain killer, gabapentin, in an attempt to end her life highlights the medicine's wide therapeutic window. Despite ingesting the largest documented dose of gabapentin, the female was able to recover and had no associated health issues three months after ingestion. This sets gabapentin apart from other pain medications with a narrow therapeutic margin, including opioids. Given the country and

military's rate of prescription drug addiction, depression rates and attempted suicide, gabapentin might present an opportunity to use a safer medication.

American Journal for Preventive Medicine: Increase in Suicide by Hanging/Suffocation in the U.S., 2000 –2010

Highlighting the increased incidence of suicide, the study seeks to determine the specific demographics related to suicide increases between 2000 and 2010. The study utilizes the Centers for Disease Control and Prevention (CDC) to plot suicides by firearm, poisoning, and hanging/suffocation. Overall suicide rates rose from 10.4 to 12.1 per 100,000 between the indicated years, a 16% increase. The majority of suicide increases occurs in the category of hanging/suffocation, which accounts for 52% of the increase. Subjects aged 45-59 see a 104% increase in the same category, while those aged 60-69 are more likely to commit suicide by poisoning, up 85%. A 24% decrease in suicide by firearm is seen in ages 15-24.

TBI

JAMA Neurology: More Cognitive Deficits, Depression in Former NFL Players

This research attempts to determine the long-term health consequences of concussive events with results indicating that an NFL player's previous concussion does not predispose him to dementia, though he may be more susceptible to cognitive impairment and depression. After examining 34 retired NFL players, researchers found that 24 percent has mild cognitive impairment, which is higher than the general population. Instances of cognitive deficits, fixed cognitive deficits and dementia were roughly comparable to the general population. Twenty-four percent of retired players had depression, which is higher than expected for the age group.

Military Medicine: Dehydroepiandrosterone and Dehydroepiandrosterone Sulfate: Anabolic, Neuroprotective, and Neuroexcitatory Properties in Military Men

Dehydroepiandrosterone (DHEA) and Dehydroepiandrosterone Sulfate (DHEAS) are secreted with cortisol from the adrenal cortex. Though researchers are not certain of their function they believe they are precursors to the steroids testosterone and estrogen. Previous research has linked DHEA and DHEAS to operational stress, resilience and TBI. Researchers analyzed the saliva of 42 male Soldiers for testosterone, nerve growth factor and salivary alpha amylase. DHEA demonstrated anabolic properties while DHEAS showed neuroprotective and neuroexcitatory properties, which has significant implications on TBI treatment as well as regenerative medicine.

Military Medicine: Occurrence of Secondary Insults of Traumatic Brain Injury in Patients Transported by Critical Care Air Transport Teams From Iraq/Afghanistan: 2003–2006

Following the initial traumatic brain injury (TBI), Military Medicine suggests TBI patients are susceptible to secondary injuries. The retroactive study analyzes secondary injuries to 63 combat casualties from 2003 to 2006. Of those recorded, 53% of TBI patients had one documented episode of a secondary insult to injury. The revelations on secondary insult to TBI injury offers Army Medicine the opportunity to discuss and possibly highlight the expertise of medical personnel in evacuating Soldiers.

Other

Obstetrics & Gynecology: Unintended Pregnancy Among Active-Duty Women in the United States Military, 2008

Researchers compare the rate of unintended pregnancy among a large sample size of active-duty military females in 2008 with a rate in 2005 as well as with the national rate. The rate of self-reported pregnancy increased from 2005, as 11 percent of female Soldiers reported unintended pregnancies, which is 50 percent higher than the general U.S. population. Younger, nonwhite, unmarried and less educated women had higher rates of unplanned pregnancy. Deployment did not affect pregnancy rates. This research received significant coverage in traditional media with outlets pointing to need for better access to birth control and education. Some noted that laws against consensual sex may prevent women from seeking birth control.

Military Medicine: The Association of Self-Reported Measures With Poor Training Outcomes Among Male and Female U.S. Navy Recruits

The study of 2,956 Navy recruits focuses on self-reported health habits of recruits who are separated from training, such as graduating late. The study enrolled subjects from January to April 2007. Of the participants, approximately 17% of men and 21% of women fail to graduate or graduate late with 76% of those men reporting low physical activity prior to training. Women who self-report low physical activity compared to their female counterparts also have a high rate of poor training outcome – 3.1 times more likely. Information related to recruiting standards and general training help Army Medicine to discuss health policies intended to stem the rate of failed or delayed training graduation.

Medical Journal Clips

Behavioral Health

Global pattern of experienced and anticipated discrimination reported by people with major depressive disorder: a cross-sectional survey

The Lancet
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Summary

Background

Depression is the third leading contributor to the worldwide burden of disease. We assessed the nature and severity of experienced and anticipated discrimination reported by adults with major depressive disorder worldwide. Moreover, we investigated whether experienced discrimination is related to clinical history, provision of health care, and disclosure of diagnosis and whether anticipated discrimination is associated with disclosure and previous experiences of discrimination.

Methods

In a cross-sectional survey, people with a diagnosis of major depressive disorder were interviewed in 39 sites (35 countries) worldwide with the discrimination and stigma scale (version 12; DISC-12). Other inclusion criteria were ability to understand and speak the main local language and age 18 years or older. The DISC-12 subscores assessed were reported discrimination and anticipated discrimination. Multivariable regression was used to analyse the data.

Findings

1082 people with depression completed the DISC-12. Of these, 855 (79%) reported experiencing discrimination in at least one life domain. 405 (37%) participants had stopped themselves from initiating a close personal relationship, 271 (25%) from applying for work, and 218 (20%) from applying for education or training. We noted that higher levels of experienced discrimination were associated with several lifetime depressive episodes (negative binomial regression coefficient 0·20 [95% CI 0·09—0·32], p=0·001); at least one lifetime psychiatric hospital admission (0·29 [0·15—0·42], p=0·001); poorer levels of social functioning (widowed, separated, or divorced 0·10 [0·01—0·19], p=0·032; unpaid employed 0·34 [0·09—0·60], p=0·007; looking for a job 0·26 [0·09—0·43], p=0·002; and unemployed 0·22 [0·03—0·41], p=0·022). Experienced discrimination was also associated with lower willingness to disclose a diagnosis of depression (mean discrimination score 4·18 [SD 3·68] for concealing depression *vs* 2·25 [2·65] for disclosing depression; p<0·0001). Anticipated discrimination is not necessarily associated with experienced discrimination because 147 (47%) of 316 participants who anticipated discrimination in finding or keeping a job and 160 (45%) of 353 in their intimate relationships had not experienced discrimination.

Interpretation

Discrimination related to depression acts as a barrier to social participation and successful vocational integration. Non-disclosure of depression is itself a further barrier to seeking help and to receiving effective treatment. This finding suggests that new and sustained approaches are needed to prevent stigmatisation of people with depression and reduce the effects of stigma when it is already established.

Funding

European Commission, Directorate General for Health and Consumers, Public Health Executive Agency.

Background

Depression is the third leading contributor to the global burden of disease and the first in middle-income and high-income countries. It can be reliably diagnosed in both primary care and specialised services. Antidepressant drugs and brief structured psychotherapy sessions are effective in 60—80% of individuals with depression. However, fewer than half the people with depression are treated. Barriers to effective care include inadequate policy, mental health services, community resources, human resources, and funding, and stigma associated with having a mental disorder.

Stigma is a mark or sign of disgrace usually eliciting negative attitudes to its bearer and, from a conceptual point of view, can be seen as an overarching term including difficulties associated with knowledge (ignorance or misinformation), attitudes (prejudice—namely, affective distancing), and behaviour (discrimination—ie, exclusion from normal forms of social participation).

Until a few years ago, the focus of most research was on investigation of stigma in people with mental disorders (mainly schizophrenia) through surveys of the general public's attitudes in specified scenarios, rather than the experiences of people with mental health problems. Without direct assessment of real behaviour, the assumption was that statements (usually about knowledge, attitudes, or behavioural intentions) were linked with behaviour.

Although, the association between stigma and depression has been reported in several studies, how discrimination (ie, the behavioural aspects of stigma) affects the lives of people with depression has only been reported in one study by Alonso and colleagues. However, they used a one-dimensional approach and did not investigate the range of life domains potentially affected by discrimination.

In this study, we aim to fill a gap in the knowledge by investigating patterns of experienced and anticipated discrimination and their relations with sociodemographic and clinical variables in people with depression. We defined discrimination as rejection of and negative behaviour towards people with mental health problems. Discrimination can cause low rates of help seeking, lack of access to care, under treatment, material poverty, and social marginalisation. These effects can be a consequence of experienced (actual) discrimination (eg, unreasonable rejection after an application for work), or a consequence of anticipated discrimination (eg, when an individual does not apply for a job because he or she does not expect to be successful).

On the basis of previous reports, we wanted to address five questions. Is experienced discrimination positively associated with more episodes of depression? Is experienced discrimination positively associated with having been admitted to hospital for psychiatric treatment? Is experienced discrimination positively associated with poorer levels of social functioning (in relation to education, employment, and marital relationships)? Are higher levels of anticipated and experienced discrimination associated with lower willingness to disclose a diagnosis of depression? Is anticipated discrimination more common in people with depression who have not experienced discrimination than in those who have?

Methods

Study design

The study was a multisite face-to-face, cross-sectional survey undertaken in 35 countries. Data were gathered as part of the European Union (EU)-funded ASPEN (Anti Stigma Programme European Network) study and the INDIGO-Depression (International Study of Discrimination and Stigma for Depression) research network. Overall, there were 19 sites in 18 ASPEN EU-funded countries (Belgium, Bulgaria, England, Finland, France, Germany, Greece, Hungary, Italy [Brescia and Verona], Lithuania, the Netherlands, Portugal, Romania, Scotland, Slovakia, Slovenia, Spain, and Turkey) and 20 sites in 17 countries in the wider INDIGO research network (Australia, Brazil, Canada, Croatia, Czech Republic, Egypt, India, Japan, Malaysia, Morocco, Nigeria [four sites], Pakistan, Serbia, Sri Lanka, Taiwan, Tunisia, and Venezuela). Data were gathered at all sites from Jan 1, to Dec 31, 2010.

Participants

The design for this study was intentionally pragmatic so that as many low-income and middle-income countries as possible could participate using only locally available resources because no external grant provision was available. For the sampling frame, local research staff within each site were asked to identify people attending specialist mental health services (either outpatient or day care in the public and private sectors) in the local area with a diagnosis of major depressive disorder in the previous 12 months. Individuals invited to participate were therefore intended to be reasonably representative of this sampling frame. This method, also used in our previous study, was used to allow local staff to take into account the specific local service configuration and invite participants from the whole range of appropriate local services. Each site was asked to assess a minimum of 25 people with major depressive disorder (this number was determined by feasibility issues, particularly for sites without grant support). Staff at each site ensured that the sample comprised young (18—25 years), middle-aged (25—65 years), and elderly adults (≥65 years) and a 2:1 ratio of women to men (because major depressive disorder is twice as prevalent in women as in men).

Study inclusion criteria were clinical diagnosis of major depressive disorder (single episode or recurrent) according to the Diagnostic and Statistical Manual of Mental Disorders (fourth edition, text revision) criteria during the previous 12 months; ability to understand and speak the main local language; and age 18 years or older. Individuals who had been given psychiatric therapy as inpatients during recruitment were excluded. The study was approved by the appropriate ethical review board at each study site. All participants provided written informed consent.

Outcomes

Participants were assessed face-to-face by independent researchers not involved in the care process using the discrimination and stigma scale (version 12; DISC-12)— a structured interview for recording the discrimination experienced by an individual with a mental disorder. Full details of the psychometric properties of this scale are reported elsewhere. DISC-12 contains 32 questions about aspects of everyday life including work, marriage, parenting, housing, and leisure and religious activities. Items 1—21 are to ascertain experienced discrimination (eg, “Have you been treated unfairly in making or keeping friends?”); 22—25, anticipated discrimination (eg, “Have you stopped yourself from applying for work?”); 26 and 27, positive treatment (eg, “Have you been treated more positively by your family?”); and 28—32, coping strategies to overcome discrimination (eg, “Have you been able to use your personal skills or abilities in coping with stigma and discrimination?”). Participants' responses were rated with a 4-point Likert scale (0=no difference, 1=a little different, 2=moderately different, and 3=a lot different). The DISC-12 items were divided into four subscales—experienced discrimination (0—21), anticipated discrimination (0—4), overcome discrimination, and positive treatment. Only the first two subscales will be addressed here. For each subscale a total score is generated by counting the number of items in which participants score 1, 2, or 3. DISC-12 also allows qualitative information to be gathered to add detail to the experiences rated, providing a strong validation for the occurrence, direction, and severity of the discrimination rated quantitatively, which is not discussed in this report. Sociodemographic and clinical information (age, sex, years since first contact with mental health services, work status, education, current mental health care, knowledge of diagnosis, and agreement with diagnosis) are also recorded.

Statistical analysis

Analyses were done with SPSS (version 17.0) and Stata (11.0) for Windows. All p values were two-tailed with an accepted significance level of 0·05. Non-normality of continuous variables was checked by visual inspection of distribution and probability—probability plots and confirmed with Kolmogorov-Smirnov tests; non-parametric tests were chosen to account for skewed distributions. Summary statistics for independent groups were compared with $\chi 2$ for categorical variables and Mann-Whitney *U* test for continuous variables. Bivariable correlations between scores were assessed with Spearman's rank correlation coefficient. A series of univariable negative binomial regression models (nbreg Stata command) were estimated with the subscore for experienced discrimination as the dependent variable and a set of potential explanatory variables (anticipated discrimination, sex, age, knowledge of diagnosis, disadvantage of having major depressive disorder, current outpatient care, ever admitted to hospital for psychiatric treatment, six or more lifetime episodes of major depressive disorder, marital status [married or cohabiting as reference category], low level of education, working status [full-time or part-time as reference category]) specifically selected to address the five research questions. For pairs of highly correlated independent variables, only one was chosen; years from first psychiatric treatment was not included because it is significantly associated with lifetime number of episodes of major depression; compulsory admission and living conditions were similarly excluded because they are significantly associated with voluntary admission to hospital and marital status, respectively. Subsequently, a multivariable negative binomial regression model was estimated, introducing as independent variables only those that were significantly associated ($p<0·05$) with the dependent variable in the univariable models. All models had the cluster option, which specified that the observations were independent between groups (ie, 39 sites), but not necessarily independent within groups. The cluster option affected the estimated SE, but not the estimated coefficients, through replacement of the traditional calculation with the robust or Huber—White sandwich estimator of variance.

Role of the funding source

The sponsor of the study had no role in study design, data gathering, analysis, and interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

855 (79%) of 1082 participants had experienced discrimination in at least one domain of their lives. The domains reported most often were family, making or keeping friends, marriage or divorce, keeping a job, personal safety and security, and intimate or sexual relationships. Importantly, nearly a third of participants reported that they had been avoided or shunned by other people because of their mental health problems.

37% of participants had stopped themselves from initiating a close personal relationship, 25% from applying for work, and 20% from applying for education or training. 766 [71%] of 1082 participants actively wished to conceal their depression from other people.

A multivariable negative binomial regression model was fitted with the experienced discrimination scale as the dependent variable. Participants who experienced most discrimination were those who had at least one lifetime psychiatric hospital admission; had several depressive episodes; had lost a spouse or partner (ie, divorced, separated, or widowed); were in unpaid employment; were looking for a job; were unemployed; and had greater anticipated discrimination. Overall, these variables accounted for 28·27% of the variance.

To address the effect of experienced and anticipated discrimination on disclosure of diagnosis, scores for experienced and anticipated discrimination were compared between participants who were willing to disclose their diagnosis (n=307) and those who concealed their diagnosis (n=766); nine participants did not complete the disclosure item of DISC-12. The group that concealed their diagnosis reported higher experienced (mean score 4·18 [SD 3·68] *vs* 2·25 [2·65]; Mann-Whitney p<0·0001) and anticipated (1·95 [0·97] *vs* 0·51 [0·78]; p<0·0001) discrimination than did those who disclosed their diagnosis. To account for possible effects of covariates, comparisons of groups were repeated with stratification by site, sex, educational level, marital status, current employment, type of mental health care, lifetime number of depressive episodes, admission for psychiatric care, compulsory treatment ever, advantage of having a diagnosis of major depressive disorder, and knowledge of diagnosis. Experienced discrimination and concealment of diagnosis lost association once site was accounted for (data not shown). The association between anticipated discrimination and diagnosis concealment also remained significant after controlling for site, because people who concealed their diagnosis reported significantly higher anticipated discrimination in nearly all sites (data not shown).

The relation between experienced and anticipated discrimination in terms of their four possible combinations was analysed for the two aspects of life for which comparable data (experienced and anticipated discrimination) were available—ie, work and intimate relationships. In the work domain, 316 (47%) of 668 participants reported anticipated discrimination despite 147 (47%) of these individuals not having experienced discrimination.

In the intimate relationships domain, 353 (41%) of 863 participants reported anticipated discrimination, but 160 (45%) of these had not experienced discrimination. Experienced and anticipated discrimination were significantly associated in both domains (finding or keeping a job, $\chi 2$ test p<0·0001; intimate relationship, p<0·0001).

Discussion

Overall, the results of our study show that rates of experienced discrimination in people with depression are high in the different countries, with rates in some life domains (eg, family and social relations) substantially similar to those in people with schizophrenia. The levels of discrimination in this study might be underestimates because people with very high levels of experienced or anticipated discrimination could have avoided service contact. However, overall levels of reported discrimination in people with depression seem to be slightly lower than those in people with schizophrenia, which is consistent with the results of surveys of public attitudes towards people with these disorders.

The main source of reported discrimination is from family members, which is also the source of most reported support. Another key source of reported discrimination is employment. Notably, in these two important domains, nearly half the people surveyed reported anticipated discrimination in the absence of experienced discrimination. In other important life domains, such as housing, parenting, education, welfare benefits, and dealing with police, there were few cases of reported discrimination. Overall, our findings suggest that the social environment could be a source of support or discrimination, depending on the context or the personal resources of the individual.

This study has several limitations. Participants were selected from patients who were treated rather than true prevalent cases in the community, thus reducing the generalisability of results to all people with major depressive disorder living in the participating sites. Selection bias could have occurred because participants were recruited on the basis of the judgment of local research staff and on their willingness to participate, further reducing the generalisability of the findings. Disability and clinical severity measures were not used, therefore we could not realistically elucidate how much discrimination reported by respondents was attributable to disorder-related impairments or to negative appraisal of life circumstances affected by current levels of depressive symptoms. The cross-sectional design of the study does not enable ascertainment of causal relations between putative predictors and levels of discrimination. Social desirability is another common limitation of self-report stigma measures, which might vary according to cultures.

The study has several strengths. This is the first study in which a detailed report is given of experiences of discrimination in a large international sample of people with depression, thus providing the basis for results that are comparable between countries and cultures. Interviews were used to gather direct self-reports from people with depression of discrimination that was actually experienced (rather than hypothetical scenarios or vignettes) and that which was anticipated. Most research into discrimination and depression has largely been descriptive, concerning surveys of public attitudes of hypothetical situations rather than how discrimination is experienced by people suffering from depression. The gathering of self-reports of discrimination might empower service users by giving them a voice and acknowledge the validity of their experience.

Systematic review

We searched PubMed for original research published in any language and year with the search terms “depression”, “depression, bipolar”, “prejudice”, and “social discrimination”. We noted that there was not much literature in relation to depression and related discrimination. Much of it referred to racial discrimination towards African-American people in the USA and how this discrimination was associated with increased rates of depression. The focus of the other research was mainly on stigmatisation related to depression rather than perceived social discrimination related

to depression. However, stigma and discrimination are not interchangeable or overlapping terms because stigma (a characteristic that is deeply discrediting and ascribed to individuals with psychiatric problems) covers problems of knowledge (ignorance), attitudes (prejudice), and behaviour (discrimination). In our report, we specifically addressed discrimination related to depression. Perceived discrimination in people with depression was addressed in only one other study, in which a one-dimensional approach was used, without investigation of the broad range of life domains that might be affected by discrimination in people with depression. Therefore, a comprehensive picture of how perceived discrimination affects the various life domains in people with depression worldwide is missing.

Interpretation

Our study is the first in which experiences of discrimination were investigated in a large sample of people with depression from all over the world. The main strength of this study was the use of interviews to gather direct self-reports of discrimination that was actually experienced and anticipated by people with depression. We noted that 79% of people with depression reported experienced discrimination in at least one domain of their lives and the most commonly affected domains were discrimination by family members (40%), making or keeping friends (33%), marriage or divorce (23%), and keeping a job (21%). 71% of participants actively wished to conceal their depression from other people, 37% anticipated discrimination when initiating a close personal relationship, and 25% had stopped themselves from applying for work. These findings led us to conclude that discrimination related to depression acts as a barrier to a satisfying social life and successful vocational integration in people with depression.

We discuss the study results in relation to each of the five key research questions. Is experienced discrimination positively associated with more episodes of depression? Having had several lifetime depressive episodes is a strong predictor of discrimination. This variable (with illness duration) can be a proxy of illness severity. Therefore, the association between number of lifetime depressive episodes and experienced discrimination levels might be spurious because current high depressive symptom levels might increase both reported discrimination and be associated with more past episodes. This reasoning is consistent with the results of a report that levels of reported discrimination are associated with greater depression severity in different countries and cultures. Because current symptom levels were not assessed in this study, this hypothesis warrants further investigation. The association between reported discrimination and clinical severity represents an important clinical concern because discrimination can act as a barrier for people with more needs for care seeking treatment, which if not timely and appropriately given, might greatly increase the risk of suicide or self-harm behaviours.

Is experienced discrimination positively associated with having been admitted to hospital for psychiatric treatment? Having at least one lifetime psychiatric hospital admission is a strong predictor of reported discrimination. It can also be seen as a proxy for illness severity (most severely depressed people needing to be treated on an inpatient basis); or it might suggest that people with depression might perceive specific mental health-care facilities as more (eg, psychiatric hospitals) or less (eg, outpatient settings) stigmatising. Stigmatisation is lower in outpatients without schizophrenia who were treated in a general hospital than in those treated within large state psychiatric hospitals. There might be a service-specific effect on reported discrimination with self-esteem having a mediating effect on service perception (ie, more coercive and institutionalising settings being associated with low self-esteem, and more empowering and recovery-oriented settings being associated with increased self-esteem). These factors could negatively affect self-appraisal, thus leading to self-devaluation and anticipated discrimination.

Is experienced discrimination positively associated with poorer levels of social functioning? Experienced discrimination was positively associated with poor social functioning (as assessed in relation to employment and marital status). This finding is consistent with the findings in other studies. Direct evidence for a specific link between reported discrimination and decreased social functioning in people with depression was obtained with a standardised videotaped role-play test. Stigma-related functional impairment could result from avoidant coping strategies such as behavioural avoidance by some people to prevent discrimination from people outside their family. Those individuals with depression concerned about stigma adapt their social behaviour to avoid exposure to rejection or discrimination. Thus, the relation might be bidirectional, establishing a vicious circle between the anticipation of stigma and the effect at a behavioural or functioning level.

Are higher levels of anticipated and experienced discrimination associated with lower willingness to disclose a diagnosis of depression? We noted that people with higher levels of anticipated discrimination are less likely to disclose their diagnosis of depression. This finding is consistent with the results of a study in patients with depression in the primary-care setting. Non-disclosure of depression might be a barrier to help seeking and receiving effective treatment. People with depression might avoid treatment because of concern that they will be negatively judged or discriminated against by other people, whereas others might avoid addressing issues related to their disorder because of its potential effect on their self-esteem, which is already compromised by depression. Non-disclosure of mental health problems is also a crucial issue in employment because in some countries individualised reasonable adjustments or accommodations in the workplace for people with mental disorders can only be made if the employer has knowledge of the employee's disability. The issue of employment and disclosure is a complex one: complete or selective disclosure might work for some people whereas non-disclosure might be best for others, and the more correct approach (disclosure *vs* non-disclosure) might change as an individual moves through phases of recovery.

Is anticipated discrimination more common in people with depression who have not experienced discrimination than in those who have? Nearly half of participants who anticipated discrimination in the domains of employment and personal relationships had not actually experienced discrimination. This finding, which is in accord with that noted in people with schizophrenia, confirms that anticipated discrimination is not necessarily associated with actual experienced discrimination. Those who anticipate discrimination might withdraw from social and occupational activities and give up important life goals (the why-try effect).

The introduction of methods to minimise discrimination towards people with depression at individual, institutional, and structural levels and the identification of effective strategies to reduce anticipated discrimination by people with depression towards themselves might be necessary to tackle stigma and discrimination related to depression. To reduce discrimination by people with depression towards themselves, some possible interventions could be to foster empowerment that enhances their pursuit of social participation, whereas other interventions could be to improve related attitudes and behaviour in the general public. In conclusion, our findings show that discrimination acts as a barrier to social participation and successful vocational integration for many people with depression, and suggest that new and sustained approaches are needed to prevent and reduce or eliminate discrimination.

BACK TO TOP

Prevalence and Characteristics of Military Malingering

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ABSTRACT

The authors' principle objective was determining the prevalence and characteristics of medical malingering in the military. The authors accessed an electronic database used by the Department of Defense to monitor and manage military health care activities worldwide. The authors searched the database from 2006 to 2011 in the Northern Regional Medical Command for all instances where a health care provider, consequent to an outpatient medical visit, diagnosed malingering, factitious disorder with psychological symptoms, or factitious disorder with physical symptoms. During the time period studied, the Northern Regional Medical Command reported 28,065,568 health care visits. During the same time period, clinicians diagnosed 1,074 individuals with malingering, factitious disorder with predominantly psychological signs and symptoms, or factitious disorder with predominantly physical signs and symptoms. The typical subject diagnosed with one of these disorders was young, male, nonmarried, and enlisted. Although most diagnoses came from a mental health clinic, other medical specialties also contributed to the total tally. These diagnoses are extremely rare based on the findings from this study of outpatient medical care visits.

INTRODUCTION

Very few medical diagnoses invite controversy like malingering. The fraudulent presentation of an illness or an injury is a rogue element in the clinician–patient relationship. Once suspected, it converts the relationship from one of benevolence to one of antagonism. From this point forward, the clinician and patient engage in a series of contretemps, with each hoping to gain the advantage. The clinician gains ground by exposing the deceit, with advances checked by the artful dodging of the malingerer. To help turn the tide of battle, the clinician needs to look no further than the published medical literature, which abounds with tips and tricks to uncover malingering.

Malingering, as described in the Diagnostic and Statistical Manual of Mental Health Disorders (DSM IV-TR), “is the intentional production of false or grossly exaggerated physical or psychological symptoms motivated by external incentives such as avoiding military duty, avoiding work, obtaining financial compensation, evading criminal prosecution or obtaining drugs.” Several important points from the DSM IV-TR deserve emphasis, including the recognition that malingering by itself is not a mental disorder. To further complicate matters, clinicians may also consider the behavior merely a symptom of a broader mental disorder. In other situations, such as “feigning illness while a captive of the enemy,” the DSM IV-TR requires clinicians carefully weigh the contextual components of malingering. This war-time reference, along with an example highlighting “avoiding military duty,” enshrines a commonly proposed but factually devoid premise.

Factitious disorder is a close relative of malingering. In fact, appearances alone cannot discriminate between the behaviors of malingering and a factitious disorder. The only truly distinguishing criterion is the motivation prompting the behavior. Instead of seeking monetary gain or bypassing an unpleasant situation, the individual with a factitious disorder claims only the label of a sick person. The motivation seems to be simply assuming the patient role, ostensibly gratifying deep seated psychopathology.

The estimated prevalence of factitious disorders varies depending on the population. The DSM IV-TR suggests “around 1% of patients on whom mental health professionals consult” in large hospital systems. Authors of a German study reported that 1.3% of senior physicians surveyed diagnosed a factitious disorder. A Spanish study identified 8% of inpatient psychiatric admissions meeting the diagnostic criteria for a factitious disorder with predominately psychological symptoms.

The estimates for malingering also vary by the population studied. An authoritative text suggested 1% prevalence among the general population of mental health patients, 5% among military personnel, and a range of 10 to 20% among medical legal cases. A more cautious and probably accurate assessment concluded that the true incidence of malingering is not known. In spite of the difficulties, researchers' examining the frequency of malingering concentrate on certain groups where dissimulation would seem most profitable, such as patients involved with some aspect of the legal system. Authors in one study, using a structured interview, reported that 20% of defendants asserting the insanity defense met the criteria for malingering. In a different study, the authors' used psychometric testing to identify a 40% rate of malingering among a group of inmates at a correctional facility.

The frequency of malingering seems to spike among patients presenting with certain presentations such as pain, psychiatric disorders, and mild traumatic brain injuries. Anywhere from 20 to 50% of individuals with a pain disorder, in the context of a medical legal claim, may be malingering. Among military veterans seeking disability compensation for post-traumatic stress disorder (PTSD), a group of researchers speculated that a majority of the claimants exaggerated their symptoms. Researchers reported that 7.5% of subjects receiving an assessment for mild traumatic brain injury were malingering.

The prevalence of malingering in the military, the subject of this study, is purported to be around 5%. It seems natural enough to conclude that military service would contribute to higher rates of malingering. After all, the duty can be hazardous, regimented, and authoritarian, attributes which presumably increase the incentive for malingering. Opposing the conventional wisdom that military service begets malingering is the all-volunteer nature of the armed forces and induction screening standards that weed out certain categories such as active illicit drug users and recruits deemed physically or mentally unfit. Even the suggestion that combat veterans exaggerate PTSD symptoms, ostensibly in pursuit of a disability claim, is vigorously opposed by some researchers.

The U.S. military launched the first serious large-scale effort to identify any type of psychopathology during World War I. At recruiting locations across the country, medical examinations sought to eliminate any person who, “has shown an inability to adapt himself in an adult, socially-acceptable manner to the demands of ordinary life should be regarded as psychopathic personality of the inadequate type and should not be chosen for military training.” The World War I era military psychiatrist used the term psychopath rather broadly to include chronic malcontents and malingerers. A particularly troublesome trend denounced by military psychiatrists was the psychopath's manipulative resort to suicidal ideation. Through clinical interviews and psychological testing, medical examiners rejected “15.08 men per 1000 registrants for psychopathy and allied constitutional mental defects …” According to one medical examiner, most feigners favored faking visual or hearing problems. Even so, military doctors ended up hospitalizing 5,146 soldiers for these disorders between 1917 and 1918. Following World War I, in the years immediately preceding the World War II, one estimate placed the prevalence of psychopaths at 2.7 per 1,000 men.

The United States began the mobilization effort in World War II fully convinced that vigorous screening of recruits would mold an effective fighting force, substantially free of neuropsychiatric impediments. The sheer size of the proposal, coupled with inadequate medical resources, hindered the screening effort from the start. Further complicating the task was the lack of uniform psychiatric diagnostic criteria and standardized assessment instruments. Medical examiners rejected a staggering 1,686,000, or 9.4%, of all recruits for presumed psychiatric disorders. Even with this seemingly severe pruning, military discharges for psychiatric disorders continued at an ever increasing pace before peaking at 5% of all releases. Military officials eventually curtailed the screening program given the dramatically negative impact on fielding battle-ready units.

The shotgun approach to screening recruits eliminated an unnecessarily large swath of potential service members. After the war ended, the shortcomings of psychiatric screening began to emerge. In one example, a military doctor followed the careers of 138 soldiers variously tagged as "so-called constitutional psychopathic states." After 5 months of combat, the doctor hospitalized only four soldiers for "exhaustion" from this group. At the war's end 120 men remained, the losses resulting from nonpsychiatric causes. An Army psychiatrist serving an 18-month tour reported a similar experience. The psychiatrist monitored the performance of 395 soldiers "salvaged from the precombat training period…." During 50 days of combat, only nine soldiers succumbed to various psychiatric problems originally diagnosed at induction, a rate the author found indistinguishable from soldiers not previously labeled.

The specific prevalence of malingering in World War II seemed to defy the common notion that malingering was a virulent threat. The U.S. Army's official position on the matter succinctly stated that "The incidence of malingering in the Army or at induction centers has been extremely low in this war. Repeated and extensive investigations of this matter have been made by the Surgeon General's Office both in induction centers and in the field. There is conclusive evidence that malingering, in any form, is less than 1 percent of all patients." Once again, the lack of a uniform diagnostic nomenclature and standardized assessment methodologies surely hobbled such certitude.

The U.S. military does not rely entirely on the medical profession to sweep malingers from the ranks. During World War II, the 96th Article of War permitted the prosecution of service members suspected of malingering. Article 115 of the Uniform Code of Military Justice contains a similar, modern prohibition.

The chasm between suspicion of malingering and confirmation remains a precarious traverse, despite the concentrated efforts pursued during the two World Wars to detect psychiatric disorders, including "psychopaths" predisposed to malingering. Since World War II, the field of psychiatry has made continued progress in standardizing the diagnostic nomenclature. Although the profession can rightly claim great strides in promoting a common diagnostic language, some critics remain convinced that "most of the problems that have bedeviled psychiatric epidemiology since its inception remain unresolved."

The clinical criteria for malingering still leave substantial room for subjective bias. Nonetheless, clinicians continue to devise strategies to improve the detection of malingering. Many of these approaches rely on various psychological tests. A comprehensive review of the neuropsychological assessment of malingering tepidly noted that "The majority of empirical studies suggest that although malingering of brain dysfunction is not easy to detect, it is possible to detect, if looked for deliberately." The authors proposed the use of specific tests to increase the clinicians' accuracy.

The hunt continues for a reliable method to identify the pretenders. Psychological testing is still commonly employed in hopes of unmasking a fraudulent presentation. Psychological tests, such as the Minnesota Multiphasic Personality Inventory-2, may be able to detect symptom exaggeration. Unfortunately, the tests cannot unerringly determine the subject's motivation. In some cases, for example, the apparent symptom exaggeration may simply reflect the subject's dissatisfaction with an unresponsive health care system and the need to “raise the ante.”

Interestingly, the vast literature proposing means to detect malingers is unaccompanied by studies reporting the prevalence of the problem. The authors conducted a search of the Cochrane Database of Systematic Reviews, Embase, PsycINFO, and PubMed stretching back 10 years using search terms such as malingering, military, and prevalence without discovering any data rich publications. Determining an accurate base rate for any disorder would seem an imperative first step to developing management strategies.

Scattered case reports document present-day military malingering. In some instances, the cases are reported in conjunction with a forensic assessment, purporting to show the value of certain diagnostic techniques. In a similar fashion, occasional reports document military criminal convictions under Article 115. Self-inflicted injury can also subject the service member to prosecution under Article 115. The aggregate of these case reports only dimly illuminates the prevalence of military malingering. This study addresses the prevalence of malingering through a different, more comprehensive, mechanism.

METHODOLOGY

The authors accessed an electronic database used by the Department of Defense (DoD) to monitor and manage military health care activities worldwide. The Military Health System Management Analysis and Reporting Tool (M2), “delivers summary clinical, population and financial data.” The authors co-ordinated the data query with M2 analysts. Data were retrieved from the Comprehensive Ambulatory/Professional Encounter Record file. M2 has accessible data beginning with Fiscal Year (FY) 2006, allowing the authors to retrieve data from FY 2006 through the end of FY 2011.Clinical diagnoses, documented by DoD health care providers in the military's electronic health record, are tabulated in the Comprehensive Ambulatory/Professional Encounter Record file using the International Classification of Diseases, 9th Edition. The authors searched the database for all instances where a health care provider, consequent to an outpatient medical visit, diagnosed malingering, factitious disorder with psychological symptoms, or factitious disorder with physical symptoms. In addition, the authors queried the database for the total annual health care encounters, clinical service, unique provider identifier, sponsor service, rank, age, gender, and marital status. Given the prodigious size of the search, and technical limitations, the authors conducted a query restricted to the Northern Regional Medical Command (NRMC). NRMC includes the health care facilities of 21 northeastern states and Washington, DC, and accounts for approximately 7.5% of all DoD health care visits. This study was approved by the Walter Reed National Military Medical Center's Institutional Review Board.

RESULTS

For the inclusive FY 2006–2011, NRMC reported 28,065,568 health care visits. Year over year, there was a nonsignificant change in the number of health care visits (25, $n = 6$) = 30.00, $p = 0.224$. During the same time period, clinicians recorded 1,300 diagnoses among 1,074 individuals (141 individuals received same diagnosis on subsequent visits) with malingering, factitious disorder with predominantly psychological signs and

symptoms, or factitious disorder with predominantly physical signs and symptoms. There was a small but significant increase year over year in the number of health care visits, which concluded with one of the three diagnoses (10, *n* = 1,074) = 18.55, *p* = 0.046.

Clinicians overwhelming chose malingering (*n* = 985/91.7%) in this sample as opposed to factitious disorder with predominantly psychological signs and symptoms (*n* = 71/6.6%) or factitious disorder with predominantly physical signs and symptoms (*n* = 18/1.7%). Youth was significantly related to the likelihood of clinicians' making one of these diagnoses (275, *n* = 1,033) = 399.19, *p* = 0.000. Clinicians overwhelming diagnosed men (5, *n* = 1,074) = 16.78, *p* = 0.005. In a similar manner, the diagnosed subjects' were mostly not married (30, *n* = 595) = 83.32, *p* = 0.000. Lower rank was significantly related to one of the three diagnoses (85, *n* = 947) = 151.03, *p* = 0.000.

Nearly one-third of the diagnoses resulted from a visit to a (*n* = 312/29.1%) behavioral health clinic. A visit to a psychology clinic was the second most likely location (*n* = 119/11.1%) to receive one of the diagnoses. A psychiatry clinic was the most likely location to receive a diagnosis of either factitious disorder with predominantly psychological signs and symptoms or factitious disorder with predominantly physical signs and symptoms.

In terms of profession, social workers diagnosed most cases (235/1,030; 21.9%). Clinical psychologists came next (159/1,030; 14.8%). Psychiatrists were fifth in rank order.

Psychiatrists contributed most to the tally of diagnoses involving factitious disorder with predominantly physical signs and symptoms (16/65; 24.6%), followed by family practice physicians (10/65; 15.4%). Psychiatrists also contributed most to the tally of diagnoses involving factitious disorder with predominantly psychological signs and symptoms (5/18; 27.8%), followed by clinical psychologists (3/18; 16.7%).

The only exception to men exceeding women in terms of diagnosis occurred with the factitious disorder with predominantly physical signs and symptoms. Among subjects diagnosed with this disorder, there was a nearly even split among the genders (*n* = 53, male = 37/52.1%).

DISCUSSION

This is the first study to examine the prevalence and characteristics of malingering based on clinicians' diagnoses as reported in the electronic medical record. Perhaps, the most important finding is the miniscule rate of occurrence. Out of 28 million health care visits over a 6-year period, clinicians only made the diagnoses in slightly more than a thousand instances.

This study's time span covers heath care delivered during United States' wars in Iraq and Afghanistan. Even though the number of cases diagnosed by clinicians statistically increased from 2006 to 2011, the absolute count is tiny. These numbers would not lend support to claims of an increase in malingering during war.

Not surprisingly, visits to mental health clinics account for most of the diagnoses. Even so, clinicians in nonmental health clinics do not shy away from diagnosing malingering. Although the absolute numbers are small, malingering is not unknown in nutrition, neurology, or audiology clinics. The presentation in these clinics gives some suggestion of the subjects' fabricated complaint.

A bit more intriguing is the relative infrequency of psychiatrists diagnosing these disorders. Physician assistants, behavioral health technicians, and nonmental health clinicians account for nearly half of all diagnoses. These numbers hint, but cannot confirm, the possibility that clinical inexperience might be a decisive factor. Another factor buttressing that notion is the psychiatrists' broader use of all three diagnoses, not just malingering. An extension of this analysis might also suggest that nonmental health clinicians should refer suspected cases to mental health professionals for a more rigorous assessment.

The typical malingerer identified by clinicians is a young, single male, with little military rank. It would seem reasonable to conclude that with increasing maturity and military experience, the likelihood of malingering decreases. The only exception to this finding is with subjects diagnosed with factitious disorder with predominantly physical signs and symptoms where the gender difference disappears. These observations might help clinicians tilt the balance in favor of declaring a clinical presentation more likely than not as genuine.

Several factors might inhibit a clinician's diagnosis of malingering. The term is pejorative; after all, it becomes a written declaration of prevarication. Documenting malingering also potentially exposes the subject to prosecution and the clinician to testifying. The same diagnosis can also severely impede a subject's claim for military-related medical disability, such as PTSD. For all of these reasons, the actual number of “true” malingering cases could be underestimated. On the other hand, the diagnoses reported in this study could just as easily be “false” malingering cases awarded more based on bias than rigorous analysis. In any event, this study found a fairly stable rate, year over year, of these diagnoses which might lessen the dominance of the aforementioned factors.

The diagnosis of malingering remains an elusive target. Part of the difficulty stems from the lack of knowledge in defining the prevalence and characteristics of these disorders. Based on the findings from this study of outpatient medical care visits, these diagnoses are extremely rare. Even so, a bit more light illuminates who makes and receives these diagnoses. This should help define the target a little more clearly and improve the clinician's accuracy.

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The Concept of Mental Pain

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Mental pain is no less real than other types of pain related to parts of the body, but does not seem to get adequate attention. A major problem is the lack of agreement about its distinctive features, conceptualization and operational definition. I will examine some suggested descriptions of mental pain, its association with psychiatric disorders and grief, its assessment and the implications that research in this field may entail.

Definition of Mental Pain

In the literature, terms such as mental pain, psychic pain, psychological pain, emptiness, psychache, internal perturbation, and psychological quality of life have been used to refer to the same construct.

Bakan observed that the individual feels psychological pain at the moment when he/she becomes separated from a significant other. From his perspective, pain is the awareness of a disruption in the person's tendency towards maintaining individual wholeness and social unity. Sandler defined psychological pain as the affective state associated with discrepancy between ideal and actual perception of self. Baumeister referred to mental pain indirectly in his theory on suicide. He viewed mental pain as an aversive state of high self-awareness of inadequacy. When negative outcomes fall far below one's standards of the ideal self and aspirations, and outcomes are attributed to the self, that person experiences mental pain. The basic emotion in mental pain is, thus, self-disappointment.

Shneidman defined psychache as an acute state of intense psychological pain associated with feelings of guilt, anguish, fear, panic, angst, loneliness and helplessness. The primary source of severe psychache 'is frustrated psychological needs.' Psychache is the mental pain of being perturbed. Perturbation refers to one's inner turmoil, or being upset or mentally disturbed.

Bolger defined emotional pain as a state of 'feeling broken' that involved the experience of being wounded, loss of self, disconnection, and critical awareness of one's more negative attributes.

Essential characteristics of emotional pain were de- scribed as a sense of loss or incompleteness of self and an awareness of one's own role in the experience of emotional pain.

Orbach et al. have defined mental pain as 'a wide range of subjective experiences characterized as a perception of negative changes in the self and its function that is accompanied by strong negative feelings'. Intense 'un- bearable' mental (psychological) pain is defined as an emotionally based extremely aversive feeling which can be experienced as torment. It can be associated with a psychiatric disorder or with a severe emotional trauma such as the death of a child. Psychological pain has many metaphors borrowed from physical pain (e.g. heartache, broken heart).

Borderlands with Suffering and Other Types of Pain

The International Association for the Study of Pain defined pain as 'an unpleasant sensory and emotion- al experience associated with actual or potential tissue damage, or described in terms of such damage'. The existence of many types of pain can be understood by the identification of four broad categories: nociception, perception of pain, suffering, and pain behaviors. Loeser underlined that 'suffering can be the result of pain, or it can be engendered by many other states, such as fear, anxiety, depression, hunger, fatigue, or loss of loved objects. Suffering exists only in the mind and the events that lead to suffering will differ from one patient to another. There are no physical examination clues or laboratory tests or imaging studies that reveal its presence. We must ask the patient and listen to his or her narrative to find suffering'.

Frankl viewed suffering as a form of emptiness due to loss of meaning in life, underlining that cause of psychological problems originates from existential frustration. He added that '… existential frustration is in itself neither pathological nor pathogenic. A person's concern, even his despair, over the worthwhileness of life is an existential distress but by no means a mental disease' (p.123). The individual basic concern should not be to avoid pain or gain pleasure, but to see meaning in life. Suffering terminates at the moment a meaning is found for it.

Saunders emphasized the connection between physical pain and mental suffering: 'If physical symptoms are alleviated then mental pain is often lifted also'.

This view has many similarities with Cassell's definition of suffering. According to Cassell, suffering can be defined as a state of severe distress associated with events that threaten the intactness of the person, that occurs when an impending destruction of the person is perceived. 'Suffering is experienced by persons, not merely by bodies, and has its source in challenges that threaten the intactness of the person as a complex social and psychological entity.' Suffering alienates the sufferer from self and society, and may engender a 'crisis of meaning' and a disintegration of hope. The term 'suffering' contains nonphysical dimensions – social, psychological, cultural, spiritual – associated with being a person that are relatively unaddressed in medical training. As Sensky noted, the term 'suffering', however, may mean different things to different people. Expressions such as 'suffering from intense pain', 'suffering from a terminal illness' or even 'suffering a hangover' are indicative of these ambiguities.

The borderland between mental pain and pain referred to the body is also of difficult definition, since pain always involves a psychological component. Engel [26, p. 45] defines pain 'as a psychological experience involving the concepts of injury and suffering, but not contingent on actual physical injury. The idea of injury as well as the need to suffer may lead to pain, just as may a real lesion or injury. Similarly, the need not to suffer or not to accept the fact that injury may render a ''painful'' injury painless.'

Mental Pain and Depression

Klein developed a dimensional model of unipolar, endogenomorphic depression based on three specific neurobiologic factors: inhibited central pleasure, disinhibited central pain, and inhibited psychomotor facilitatory mechanisms. Inhibited central pleasure represents an inability to respond to positive internal and external stimuli and results in anhedonia, lowered self-esteem, and hopelessness.

Disinhibited central pain can be de- scribed as 'psychic pain' and represents an over-response to negative images and stimuli. Subjects feel unhappy, guilty, agitated, and experience painful ruminations. Finally, inhibited psychomotor facilitatory mechanism is synonymous with psychomotor retardation, decreased energy, and slowed thinking.

Carroll extended Klein's model to characterize mood states in bipolar disorder. His model included four neurobiologic components (consummatory reward, incentive reward, central pain, and psychomotor function). Central pain is increased in depression, as reflected by agitation, pathologic guilt and hopelessness. In the de- pressed phase, this system is seen as disinhibited; stimuli that were previously non-aversive are experienced as distressing. On this basis, the depressed patient perceives neutral events as catastrophic. Changes in self-image due to central pain dysregulation go beyond feelings of in- competence and devaluation. The depressed patient perceives himself/herself as bad, unworthy, and guilty. In manic

patients, a dis-inhibition of central pleasure represents an overresponse to positive images and stimuli, resulting in inflated self-esteem, grandiosity, increased enjoyment of the environment, excessive activity, intrusive- ness, and unrealistic optimism about the future. Inhibited central pain, proposed to occur in mania, results in an inability to perceive the negative qualities of oneself and one's environment. Clinical symptoms include inflated self-esteem, elation, a disregard for the painful con- sequences of one's behavior, and over-optimism about the future.

Indeed, several psychopathologists have emphasized that the patients with endogenous depression may manifest a 'distinct quality' of dysphoric mood. This feature was recognized by early clinicians and was described as a uniquely aversive, anguished, or uncomfortable experience that is characterized by painful tension and torment.

The study of van Heeringen et al. reported changes in brain functioning in association with mental pain in depressed patients. The results showed that levels of mental pain do not correlate with severity of depression but are associated with an increased risk of suicide. The severity of mental pain in these depressed patients was associated with changes in cerebral blood f low in areas of the brain that are involved in the processing of emotions. The observation that depressed individuals become suicidal when they perceive their emotional state as painful and incapable of change suggests a strong and persisting emotional input at the prefrontal level. Even though the findings of van Heeringen et al. indicate that dorsolateral hyperactivity is associated with in- creased levels of mental pain, the interpretation of this association needs further study.

Mental Pain and Suicide

Psychological pain is a common construct for understanding suicide. Suicide risk is much higher when the general psychological and emotional pain reaches intolerable intensity, particularly in the context of major mood disorders. Shneidman considered psychache to be the main ingredient of suicide and reported that psychological pain may be correlated to the fact that, if suffering individuals could somehow stop consciousness and still live, they would opt for that solution. Shneidman further postulated that psych- ache is intolerable because it results from basic needs that have been thwarted. Suicide occurs when the psychache is deemed by that individual to be unbearable. It is an escape from intolerable suffering. Pain threshold and pain tolerance are highly and negatively correlated with personal distress in suicidal persons. In non-suicidal persons, intense mental pain is associated with high sensitivity to bodily pain. Conversely, among suicidal persons, intense mental anguish is associated with low sensitivity to bodily pain.

Mental Pain and Other Psychiatric Disorders

Patients with borderline personality disorder have a range of intense dysphoric affects, sometimes experienced as aversive tension, including rage, sorrow, shame, panic, terror, and chronic feelings of emptiness and loneliness. These individuals can be distinguished from other groups by the overall degree of their multifaceted emotional pain. This emotional pain has been interpreted as a response attempting to adapt to repetitive traumatic experiences in childhood such as the loss of a parent, parental mental illness, witnessed violence, emotional, physical and sexual abuse. Emotional pain is described as intense by women who suffer from border line personality disorder, and has been associated with a high prevalence of reported childhood abuse.

Leibenluft et al. conceptualized self-mutilation as a need to feel a real physical pain as opposed to just an emotional pain. However this conceptualization is not congruent with the consistent reports of no pain upon self-mutilation. It has also been suggested that deliberate self-harm provides physical stimulation (i.e., pain) sufficiently compelling to divert the individual's attention from painful emotional arousal; deliberate self-harm may serve to shift attentional focus away from emotional pain and toward physical pain.

Mental pain has also been examined in the setting of posttraumatic stress disorder. Avoidance has been postulated to involve strategic, effortful processes aimed at avoiding trauma stimuli, whereas numbing has been theorized to be a form of conditioned 'emotional analgesia' that results from exposure to uncontrollable and unpredictable aversive stimuli. If an emotional pain site is 'anesthetized', it is difficult to recognize emotions, much less discriminate, describe, or regulate these emotions. In a study involving 85 veterans, Monson et al. assessed the relationships among emotion content and process variables and posttraumatic stress disorder symptomatology with military-related trauma; they suggested that depression may be a secondary effect of numbing recognition rather than vice versa.

Grief

Engel underlined that grief is the characteristic response to the loss of a valued object, be it a loved per- son, a cherished possession, a job, status, home, country, an ideal, a part of the body, etc. Further, Engel pointed out that grief is a cause of mental pain, produces a variety of bodily and psychological symptoms and it interferes with our ability to function effectively. Indeed, the most prominent characteristic of grief is its painfulness. The pain of depression is similar to grief as are other depressive symptoms such as low energy, inward turning, preoccupation, guilt, and self-criticism. How- ever, grief is less often characterized by low self-esteem, pessimism, and hopelessness. Losses of resources, including health, material resources, territory, status, relationships or kin, cause comparable emotional pain. Kato and Mann have suggested, for example, that the loss of a spouse is often conceptualized as a loss of the emotional, instrumental, and financial aspects of social support.

Assessment of Mental Pain

Several instruments have been developed to measure mental pain or related constructs.

The Psychological Pain Assessment Scale was influenced in content and structure by the Thematic Ap- perception Test. It incorporates a written essay compo- nent and requires a trained operator to administer the test and interpret the results. It is reported to have modest validity.

The Multiple Visual Analog Scale consists of 23 Visual Analog Scale items based on the Carroll-Klein model of manic depressive illness. Each item is presented as a 100-mm line visual analog scale, with appropriate anchor statements describing the manic and depressive extremes of each symptom. Of the 23 items, 7 represent each of the major dimensions of the Carroll-Klein model (consummatory reward, central pain, and psychomotor regulation) and 2 items represent incentive reward. Results from clinical studies demonstrated high test-retest reliability of the Multiple Visual Analog Scale in depressed subjects and good concurrent validity.

The Psychache Scale was based on Shneidman's definition of psychache that was associated with sui- cidality (i.e., chronic, free-floating, non-situation-specific psychological pain caused by frustration of vital needs) but does not include items relevant to the intensity of psychological pain.

The Psychache Scale is a 13- item self-report scale used to assess psychache; items are coded on a 5-point Likert-type scale. Good construct validity and internal consistency have also been reported. The Psychache Scale can successfully differentiate between suicide attempters and nonattempters.

The Orbach and Mikulincer Mental Pain Scale consists of 44 self-rated items, and draws on a conceptualization of mental pain as a perception of negative feelings. The items of the Orbach and Mikulincer Mental Pain Scale are divided into 9 factors: (1) irreversibility, (2) loss of control, (3) narcissist wounds, (4) emotional f looding, (5) freezing, (6) self-estrangement, (7) confusion, (8) social distancing, and (9) emptiness. Subjects rate each item on a 5-point Likert scale, with higher values reflecting greater mental pain. The Orbach and Mikulincer Mental Pain Scale demonstrated high internal consistency and test-retest reliability and strong association with suicidality.

The Mee-Bunney Psychological Pain Assessment Scale is a 10-item self-rating inventory, where items uniformly used the term 'psychological pain' to measure intensity of the pain (ranging from none to unbearable) and frequency (ranging from never to always). The intent of this scale is to provide the clinician with a quick and reliable assessment of psychological pain in psychiatric and nonpsychiatric populations. The Mee-Bunney Psy- chological Pain Assessment Scale demonstrated convergent validity, known-groups validity and internal reliability. Moreover, major depressive episode subjects with elevated scores on the Mee-Bunney Psychological Pain Assessment Scale had higher suicidality ratings and had an increased likelihood of having a past history of suicide attempts.

Büchi et al. have devised a measure called the Pictorial Representation of Self-Measure which, in validation studies, behaves as expected of a measure of suffering and fits well with Cassell's conceptualization of suffering. This measure does not rely on language skills and can be used to rapidly elicit patients' appraisals of their suffering.

All these scales contribute to quantifying mental pain. However, clinicians tend not to ask their patients about their mental pain or suffering and the most widely used interview-based instruments seem to ignore this aspect. Clinimetrics offers important opportunities for assessing clinical phenomena such as mental pain. Table 1 illustrates how information on mental pain can be obtained during an interview and can be rated. The format of the questions and ratings are modeled upon Paykel's Clinical Interview for Depression, the most comprehensive and sensitive assessment tool for affective disorders.

Clinical and Research Implications

There is pressing need of research on mental pain, after decades of neglect. Some areas that appear to be particularly important are:

– even though mental pain always has an individual meaning, consensus should be developed on its operational definition;

– mental pain may provide the clinical threshold that is essential for determining the amount of distress that is worthy of clinical attention, in conjunction with di- agnostic criteria. It may offer a better specification of the criterion on 'clinically significant distress' that frequently recurs in DSM-IV;

– the balance between mental pain and psychological well-being deserves attention. Engel, in his formulation of the pain-prone personality, outlined how, in some instances, somatic pain is clearly protecting the patient from more intense depression and even suicide, and the psychological profile of the need to suffer;

– the neurobiology of mental pain is a fascinating topic that has been addressed only by a very limited amount of research. It may unravel the brain system that interprets the negative emotional significance of cognitions, with particular reference to the role of amygdala and basal ganglia.

– assessment of mental pain may have important implications in intervention research, particularly in psychopharmacology. For instance, depressed patients frequently report that treatment with antidepressant drugs yields substantial relief of their mental pain. Un- fortunately, in psychopharmacology research the effects of drugs are measured on a limited range of symptoms.

Clinical and research attention to the issue of mental pain may produce important developments in psychiatry and is in line with recent emphasis on patient-reported outcomes, defined as any report coming directly from patients, without interpretation of physicians or others, about how they function or feel in relation to a health condition or its therapy.

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Heterogeneity of amygdala response in major depressive disorder: the impact of lifetime subthreshold mania

Psychological Medicine
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Abstract

Background

Patients with major depressive disorder (MDD) present with highly heterogeneous symptom profiles. We aimed to examine whether individual differences in amygdala activity to emotionally salient stimuli were related to heterogeneity in lifetime levels of depressive and subthreshold manic symptoms among adults with MDD.

Method

We compared age- and gender-matched adults with MDD (n = 26) with healthy controls (HC, n = 28). While undergoing functional magnetic resonance imaging, participants performed an implicit emotional faces task: they labeled a color flash superimposed upon initially neutral faces

that dynamically morphed into one of four emotions (angry, fearful, sad, happy). Region of interest analyses examined group differences in amygdala activity. For conditions in which adults with MDD displayed abnormal amygdala activity versus HC, within-group analyses examined amygdala activity as a function of scores on a continuous measure of lifetime depression-related and mania-related pathology.

Results

Adults with MDD showed significantly greater right-sided amygdala activity to angry and happy conditions than HC ($p < 0.05$, corrected). Multiple regression analyses revealed that greater right-amygdala activity to the happy condition in adults with MDD was associated with higher levels of subthreshold manic symptoms experienced across the lifespan ($p = 0.002$).

Conclusions

Among depressed adults with MDD, lifetime features of subthreshold mania were associated with abnormally elevated amygdala activity to emerging happy faces. These findings are a first step toward identifying biomarkers that reflect individual differences in neural mechanisms in MDD, and challenge conventional mood disorder diagnostic boundaries by suggesting that some adults with MDD are characterized by pathophysiological processes that overlap with bipolar disorder.

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Disease

Sequential Real-Time PCR Assays Applied to Identification of Genomic Signatures in Formalin-Fixed Paraffin-Embedded Tissues: A Case Report About Brucella-Induced Osteomyelitis

Military Medicine
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ABSTRACT

Brucellosis is a zoonotic infection transmitted from animals to human by ingestion of infected food products, direct contact with an infected animal, or inhalation of aerosols. *Brucella* infection-induced osteomyelitis may present only with nonspecific clinical and radiographic findings, mild elevations in serum inflammatory markers, as well as nonspecific histological changes. We studied a case of an Iraqi war veteran with multifocal vertebral body and left iliac bone lesions on radio nucleotide scans and magnetic resonance imaging, clinically suspected osteomyelitis possibly because of *Brucella*. Although histomorphological findings were nonspecific, consisting of chronic inflammatory cell infiltrate and reactive fibrosis, tissue gram and silver impregnation stains of bone biopsies were informative, revealing gram-negative coccobacilli consistent in size with *Brucella*

species. Total nucleic acids were extracted from formalin-fixed paraffin-embedded tissues and amplified by sequential real-time polymerase chain reaction, targeting genes coding (1) outer membrane protein (*omp*-31) of *Brucella* species and (2) insertion sequence (*IS711*) of *Brucella abortus* (*b-abt*). Polymerase chain reaction results confirmed *B. abortus* as the causative pathogens for presumed diagnosis of *Brucella* osteomyelitis.

INTRODUCTION

Brucella bacteria are intracellular bacterial pathogens capable of infecting both animals and humans. They are transmitted by ingesting infected food, direct contact with an infected animal, or inhalation of aerosols. In human infections, the organisms function as facultative intracellular parasites, leading to brucellosis with potential involvement of multiple organs and tissues. Human osteomyelitis caused by *Brucella* has been previously reported. Even though brucellosis is uncommon in the United States, timely and accurate diagnosis remains challenging, as laboratory tests often reveal subtle abnormalities such as mild elevation in serum inflammatory markers and nonspecific plain radiographic changes in affected organ or tissue. The presence of elevated *Brucella*-specific serum antibodies supports a presumptive diagnosis, whereas definitive diagnosis is made only when the pathogen is isolated from tissue, blood, or bone marrow. Because of its slow growth in culture media, a prolonged incubation of 4 to 6 weeks is required for culturing the pathogenic agents. *Brucella* bacteria are similar in morphology to other gram-negative coccobacilli, such as *Burkholderia mallei*, *Burkholderia pseudomallei,* and *Bartonella henselae*, the pathogens responsible for glanders, melioidosis, and cat scratch disease (CSD), respectively. Our recent study on formalin-fixed paraffin-embedded (FFPE) blocks for differential identification of *Brucella* genomic signatures is presented.

MATERIALS AND METHODS

Case History and Clinical Information

In 2009, a 27-year-old male Iraqi war veteran presented with a 6-month history of back pain that progressed gradually. Initial radiologic findings were negative. After experiencing neurological deficits, a magnetic resonance imaging of his cervical spine revealed a C7 lesion with compression of the superior end plate, lesions in the thoracic spine in T2, T5-8, T10, and T12. Similar lesion was also found in the left iliac bone. The patient did not report fever or chills, but experienced sternal chest pain, left hip pain on ambulation, and weight loss. Serologic testing for *Brucella abortus*/*melitensis*/*suis*/*canis* agglutinins IgG/IgM, *Bartonella henselae*/*quintana* IgG/IgM, and Coxiella Indirect Fluorescent Antibody Phase I/II were negative. Further history investigation revealed that, while in Iraq, the patient drank unpasteurized camel milk provided by the villagers and his patrol entered effluent filled with animal wastes downstream from an abattoir. All these factors made the patient at high risk of contaminating with *Brucella*. Core needle biopsies were performed on two lesion areas (thoracic vertebral body at T12 and the left iliac bone). Bacterial cultures were negative. The biopsy tissues were fixed in freshly prepared neutral formalin solution and processed for FFPE procedures. The FFPE blocks were sent to the Armed Forces Institute of Pathology (AFIP) for consultation. In light microscopic examination, prominent mild nonspecific chronic inflammatory change (lymphocytes and plasma cells) with reactive fibrosis was noticed, but no bacteria were seen in H&E staining. The slides were further stained with Brown–Hopps tissue gram stain and the Warthin–Starry silver impregnation stain, which revealed tiny gram-negative coccobacilli, consistent in size with *Brucella* species. Consequently, a multifocal osteomyelitis secondary to brucellosis was presumed.

Nucleic Acids Extraction From FFPE Tissues

Two FFPE blocks containing small pieces of biopsy tissue (1.5 × 3 mm) from the patient's thoracic vertebral body (T12) and left iliac bone were processed for nucleic acids extraction. Additional ten FFPE blocks were undergone same procedures as controls. The ten FFPE blocks include one biopsy case with osteoarthritis (*Brucella* infection was ruled out by polymerase chain reaction [PCR] test), another autopsy case with melioidosis, and eight biopsy cases with CSD. Each block was cut with a microtome (5 μm in thickness, 3 sections per block). All sections were separately collected into DNase-free tubes for nucleic acids extraction. A protocol of FFPE DNA extraction (QIAGEN, Valencia, California) was followed: (i) de-paraffin treatment with xylenes and ethanol washes, (ii) tissue digestion with Proteinase K (20 mg/mL) incubation at 50°C for a minimum of 1 hour (depending on the size of the section), (iii) RNA removal by incubation with RNase A (100 mg/mL) at 37°C for 30 minutes, (iv) DNA recovery following washes and elution through columns (30-μL elution volume for each block), and (v) quantification of DNA samples (NanoDrop, ND-1000 Spectrophotometer, Thermo Fisher Scientific, Wilmington, Delaware). Total DNAs were stored at −20°C for later usage.

Development of Real-Time PCR Assays

TaqMan real-time PCR assays were designed by using Primer Express Software (v 3.0, Applied Biosciences, Carlsbad, California) and referring the genome sequences of an annotated *Brucella* strain (*B. abortus* biovar 1 str. 9-941 chromosome I). One of the assays was designed targeting a gene coding the outer membrane protein (***omp-31***) of the reference *Brucella* strain at the region of 1188003…1188992 (GenBank Accession: AE017223.1). The primers were selected to amplify a short sequence of "**ggctcggttgccaatatcaatgcgatcaagtcgggcgctctggagtccggctttacgcagtc**," which was part of the *omp-31* gene of *Brucella* species. A hydrolysis probe was designed for hybridization with the PCR amplicons. Three other PCR assays were also developed, as *Brucella* species specific, to detect *B. melitensis* (***b-mel***, 1209562…1209713, GenBank Accession# AE008917.1), *B. abortus* (***b-abt***, 701220…701393, GenBank Accession# AE017224.1), or *B. suis* (***b-sui***, 1618822…1618948, GenBank Accession# AE014291.4). Each assay was designed targeting at a specific region of the insertion sequence (*IS711*). The sensitivity and specificity of the PCR assays were tested with a DNA panel including *Brucella* standard DNA (*B. melitensis*, *B. abortus,* and *B. suis*). In addition to the assays developed for *Brucella* species, two additional PCR assays were developed for differentiation of *Brucella* from *Burkholderia pseudomallei* and *Bartonella henselae*, the gram-negative coccobacilli with similar morphology to *Brucella* bacteria in the FFPE tissues. The primers were selected targeting *B. pseudomallei* (***bp-tts1***) at the region of 1919731…1920690 (GenBank Accession# BX571966.1) and *B. henselae* (***ftsK***) at the region of 1791046…1799481 (GenBank Accession# BX897699.1).

Syber Green I (S7567, 10k concentrate in dimethyl sulfoxide, Invitrogen Life Technologies, Grand Island, New York) was used as reporter for ***ftsK*** primer set. All primer and probe oligos were ordered from Integrated DNA Technology (IDT, Coralville, Iowa) and Applied Biosystems (ABI, Carlsbad, California). Real-time PCR assays were performed in a LightCycler (Software 4.1, Roche Scientific, Florence, South Carolina) instrument. Briefly, each capillary (20 μL) contained 10X buffer (with 50 mM $MgCl_2$ and 2 mM of dNTPs, Idaho Technology, Salt Lake City, Utah), primers (300 nM each), probe (50 nM), Taq polymerase (1 unit), and 5 μL of DNA samples. PCR cycle conditions were as follow: incubating capillaries at 95°C for 2 minutes, continued by 40 cycles of 2-step amplification (95°C for 0 second and 60°C for 20 seconds).

T-A Cloning

PCR products (from ***omp-31*** PCR assay) were tested by running an agarose gel electrophoresis. The expected band (62 base pairs) was separated from agarose gel and purified for cloning (TOPO T-A Cloning Kit, Life Technologies, Grand Island, New York). The transformed plasmids were randomly picked out (10 clones), purified, and sent to a commercial sequencing company (MACROGEN-USA, Rockville, Maryland) for processing. The sequencing results were analyzed in our laboratory.

RESULTS

The concentration of DNA samples varied dramatically, ranging from 2.45 ng/μL (left iliac bone biopsy), 3.5 ng/μL (thoracic bone biopsy T12), 13.1 ng/μL (pelvic bone biopsy control), 163 ng/μL (average concentration of 8 CSD biopsy controls) to 295 ng/μL (lymph node autopsy control). The ratio of OD260/280 also shifted from 0.96 to 2.22. Total DNA recovered from lymph node autopsy control (8,850 ng) was 1.81-fold of the average from CSD biopsy controls (4,883 ng); bone biopsy control (393 ng) was 3.74-fold of thoracic bone biopsy (105 ng), and 5.35-fold of left iliac bone biopsy (73.5 ng).

In Silico Analysis of PCR Amplicons

In silico analysis of ***omp-31*** PCR amplicons exhibited 100% alignment with database sequence of *Brucella* species, including genes coding *BCSP-31* protein (*B. abortus* and uncultured *Brucella* spp.), *TAXI family protein* (*B. melitensis*, *B. suis*, *B. pinnipedialis* and *B. canis*), *TetB protein* (*B. melitensis*, strain M28 and *B. abortus*, strain S19), and 31 kDa immunogenic protein (*B. ovis* ATCC 25840), there was no alignment with non-*Brucella*.

Sensitivity and Specificity of Brucella PCR Assays

The sensitivity of *Brucella* real-time PCR assays was checked by amplification of *Brucella* standard DNAs, which were prepared from the cultures of *B. melitensis, B. abortus*, and *B. suis* strains in Biological Safety Level-3 laboratory. Results suggested the limit of detection at 50 fg for ***omp*-31** primer set, and 100 fg for *b-met, b-abt,* and *b-sui* set, which was equivalent to 5 to 10 *Brucella* genomes. The calculation was made according to the genome size of *Brucella* sp. (2.12 Mb) and the real-time PCR standard amplification curve (data not shown). Bacterial DNA panel test results confirmed ***omp*-31** primer/probe set amplified DNAs from all *Brucella* species (10 of 10), whereas the *b-mel*, *b-abt,* and *b-sui* primer/probe set amplified DNA only from *B. melitensis* (2 of 2), *B. abortus* (1 of 1), and *B. suis* (1 of 1), respectively. There was no amplification of DNAs from *Brucella* near neighbors or other bacteria in the

DNA Signatures of Brucella Identified in FFPE Samples

Total DNA samples retrieved from FFPE biopsy of thoracic vertebra body T12 and left iliac bone were amplified by ***omp*-31** and ***b-abt*** (*B. abortus* specific), but not by *b-mel* or *b-sui* (*B. melitensis* and *B. suis* specific). None of FFPE control sample was amplified by ***omp-31*** or other *Brucella* PCR assays.

TaqMan real-time PCR amplification plot and agarose gel exhibition. (**A**) DNAs from two FFPE biopsy tissues (left iliac bone and thoracic bone T12) were amplified (Threshold Cycle [C_T] = 29.79 and 29.81) with *Brucella**omp***-31 primers. The positive control DNA (*Brucella melitensis* 16M str.) was amplified with at least 3-log differences in PCR C_T values (C_T = 19.03). There was no amplification in any of the DNA samples from control FFPE tissues. (**B**) E-Gel (4%) indicated three PCR amplicons with identical size (62 bp) from the two FFPE biopsy tissues (lanes 3 and 5) and the positive control (lane 7). The 25 bp DNA ladder was used (lane 1).

In the study on FFPE control group, the ***bp-tts1*** primers amplified DNA from an autopsy case with melioidosis, whereas the ***ftsK*** primers identified DNAs from all CSD control blocks. There were no cross amplification among the primer sets.

Database Search Results

The sequencing analysis results of ***omp*-31** PCR products showed identical alignment as seen *in silico* analysis. The 62-bp query sequences aligned with database sequences of *Brucella* species with 100% identity. The aligned sequences included the genes coding *BCSP-31* protein (bacterial cell surface protein in some *B. abortus* and uncultured *Brucella* sp.), *TAXI family protein* (transporter solute receptor in *B. abortus*, *B. melitensis, B. suis, B. pinnipedialis, B. microti*, *B. canis,* and *B. ovis*), and *TetB* protein (tetracyclin-resistant protein in some of *B. melitensis* and few *B. abortus* species). There was no alignment with non-*Brucella* genome.

Case Follow-Up

The patient received 4-week antibiotics treatment (doxycycline), and his symptoms were improved following the treatment. A follow-up PCR examination on patient's peripheral blood samples showed negative results and the patient resumed his normal life.

DISCUSSION

In an attempt to confirm the involvement of *Brucella* in a case of osteomyelitis, we used sequential real-time PCR techniques to amplify genomic signatures of *Brucella* DNA from biopsied-FFPE bone specimens. *B. abortus* was confirmed as the causative pathogens following the completion of sequential real-time PCR assays and confirmation of sequencing analysis.

In histopathology, the tiny organisms were similar to *B. pseudomallei* and *B. henselae*, the pathogens for melioidosis and CSD. Since histopathology changes (intracellular bacterium-induced granulomatous reactions) provided insufficient evidence to rule out infection by those bacteria (with similar morphology to *Brucella*), a combination of histopathology and real-time PCR assays (***bp-tts1*** and ***ftsK***) was applied to the bacterial differentiation process. As real-time PCR results indicated, the control FFPE tissues containing *B. pseudomallei* or *B. henselae* were separately amplified by ***bp-tts1*** or ***ftsK*** primer set, but not the *Brucella* PCR primers, suggesting molecular assays help differentiation of bacteria with similar morphological characteristics. In the development of the sequential real-time PCR assays, a bacterial DNA panel was used for the evaluation of PCR specificity. The panel was composed of 38 isolates, including 10 *Brucella* spp. and 28 other genera different from *Brucella* pathogens. Some intracellular pathogens, such as *Burkerholderia mallei*, *B. pseudomallei*, and *Bartonella henselae*, were included in the panel. The genus *Ochrobactrum* was reported to give false-positive results in *Brucella* PCR tests. A recent report verified that bacterial isolates from

frogs were phenotypically identified as *Ochrobactrum anthropi*, but 16S rRNA sequencing showed up to 100% identity with *Brucella inopinata*, indicating a close relationship with *Brucella*. Since none of the *Brucella* PCR primers were designed based on the 16S rRNA sequences, the *in silico* analysis of PCR amplicons (***omp*-31** and ***b-abt***) did not show alignment with sequences of the genus *Ochrobactrum*. Nevertheless, the closest relative of *Brucella* should have been included in the panel if the isolate were available. The results of DNA panel screening confirmed ***omp*-31** as the first line of sequential PCR tests in *Brucella* detection (genus level) and the ***b-abt*** the second line of *Brucella* PCR detection (species level). The sequential assays were approved in the case study, which provided molecular evidence for differential diagnosis of *Brucella* from microbes with similar morphological characters (gram-negative coccobacilli).

Spinal osteomyelitis caused by brucellosis has been reported previously. The diagnosis of brucellosis is typically delayed because of insufficient awareness of the disease, nonspecific radiological findings, or improperly handling blood cultures. Timely collection of blood samples and properly handling of clinical samples are important for an accurate diagnosis of brucellosis. In this study, the patient while in Iraq drank unpasteurized camel milk provided by the villagers and his patrol entered effluent filled with animal wastes downstream from an abattoir, which made him at high risk to have *Brucella* infection. The patient had a 6-month history of back pain that gradually progressed. In clinical examination, his spinal morphology showed compression of superior end plate in multiple vertebral bodies and density changes in left iliac bone. Since the laboratory results, such as serologic tests, were not informative for *Brucella* infection, the core needle biopsies were performed. The routine microscopy showed nonspecific chronic inflammatory changes in H&E stains and the tiny gram-negative coccobacilli in special stains, whereas those were not contributory to a differential diagnosis of brucellosis. The combined methodology of histopathology and the sequential PCR technique proved effective in the identification of genomic signatures of *B. abortus* in affected bone tissue.

Sequencing results of ***omp-31*** PCR amplicons showed alignment with target genes of multiple *Brucella* species, including *B. melitensis*, *B. abortus,* and *B. suis,* the common pathogenic species for brucellosis in animals and human, and several other less common *Brucella* species as well as an emerging *Brucella* species. The result was consistent to *in silico* analysis. In the study, *Brucella* genus- and species-specific PCR assays were used in the determination of genomic signatures originally from the infection of *B. abortus* species in the FFPE tissues.

In the study, only one case was presented. Based on case history and results of clinical examination, clinicians presumed *Brucella* infection as the cause of osteomyelitis, but that information was insufficient to make conclusion of *Brucella* infection. The formalin-fixed biopsy samples and control FFPE tissues were obtained through different methods (biopsy or autopsy) and tissue origins (bones and lymph nodes). The autopsy case of melioidosis was obtained from AFIP's archival repository, which had a prolonged time of fixation. The eight FFPE control cases of CSD contained different amounts of biopsy tissue. All these explained the dramatic difference of DNA recovery. Amplification of DNA from FFPE tissues was challenging because of limited copy numbers of microorganisms, variable amount of nucleic acid recovery from FFPE tissue, and poor quality of DNA samples after prolonged fixation in formalin. This in turn would influence the downstream PCR amplification.

CONCLUSION

Diagnosis of *Brucella* osteomyelitis may be challenging for several reasons including unfamiliarity with the disease and nonspecificity of clinical, radiological, serological, and microbiological as well as histopathological findings. A case with multifocal osteomyelitis was presented in an Iraqi

war veteran whose diagnosis was facilitated by using the sequential real-time PCR. Experiential selection of primers is important to have successful PCR amplification from microdissected samples. We used Primer Express Software (v 3.0) in designing all TaqMan primers and probes. The software is featured in presenting PCR amplicons of smaller size, generally between 50 and 150 bases, that fits the need of optimum PCR efficiency in the amplification of genomic signatures from FFPE samples.

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Vaccine Induction of Antibodies against a Structurally Heterogeneous Site of Immune Pressure within HIV-1 Envelope Protein Variable Regions 1 and 2

Immunity
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10 Jan 2013

Summary

The RV144 HIV-1 trial of the canary pox vector (ALVAC-HIV) plus the gp120 AIDSVAX B/E vaccine demonstrated an estimated efficacy of 31%, which correlated directly with antibodies to HIV-1 envelope variable regions 1 and 2 (V1-V2). Genetic analysis of trial viruses revealed increased vaccine efficacy against viruses matching the vaccine strain at V2 residue 169. Here, we isolated four V2 monoclonal antibodies from RV144 vaccinees that recognize residue 169, neutralize laboratory-adapted HIV-1, and mediate killing of field-isolate HIV-1-infected $CD4^+$ T cells. Crystal structures of two of the V2 antibodies demonstrated that residue 169 can exist within divergent helical and loop conformations, which contrasted dramatically with the β strand conformation previously observed with a broadly neutralizing antibody PG9. Thus, RV144 vaccine-induced immune pressure appears to target a region that may be both sequence variable and structurally polymorphic. Variation may signal sites of HIV-1 envelope vulnerability, providing vaccine designers with new options.

Highlights

Binding of RV44 mAbs CH58 and CH59 to HIV-1-Infected Cells and to HIV-1 V2 Peptides(A) Effect of alanine point substituted mutations on the binding of CH58 (in blue) and CH59 (in red) to the HIV-1 V2 peptide. For each mutation (y axis), results were normalized as EC_{50} relative to wild-type V2 peptide.(B) Shown is the flow cytometric analysis of binding of mAbs CH58 (top left), CH59 (middle left), and A32 (bottom left) to the activated PB $CD4^+$ T cells infected IMC_{CM235}. Synagis (antirespiratory syncytial virus mAb) and mAb HIV-1 A32 were used as negative and positive controls, respectively. Mean fluorescence intensity (MFI) and percent of positive cells are indicated next to the histograms. Data shown are representative of three independent experiments.

Binding of RV144 V2 and PG9 bnAbs to AE.A244 V1-V2 Tags Protein and AE.A244 Δ11gp120Each of the mAbs was captured on a Fc antibody immobilized sensor surface to about 100–125 RU. For binding to A244 Δ11gp120, 2–10 μg/ml (CH58 in A), 2–10 μg/ml (CH59 in B), 10–50 μg/ml (PG9 in C) of monomeric gp120 were injected over each of the mAbs. AE.A244 V1-V2 tags protein was injected at concentrations ranging from 0.5–5 μg/ml (CH58 in D), 0.1–5 μg/ml (CH59 in E), 10–100 μg/ml (PG9 in F). A negative control mAb (Synagis) was used to subtract nonspecific binding. Each plot shows binding curves with increasing concentrations of gp120 or V1-V2 proteins (shown in different colors) injected over two independent flow cells immobilized with the same mAbs. For binding to CH58 and CH59 mAbs, A244 Δ11gp120 protein was injected at 2, 4, 6, 8, and 10 μg/ml and AE.A244 V1-V2 protein at 0.2, 0.5, 1, 2, 3, 4, and 5 μg/ml. For PG9 mAb, A244 Δ11gp120 and AE.A244 V1-V2 proteins were injected at 10, 20, 30, 40, and 50 μg/ml and 10, 25, 50, 75, and 100 μg/ml, respectively. Global curve fitting (shown in black) to a 1:1 Langmuir model was used to derive rate constants and K_d values after simultaneous fitting to binding data from two independent flow cells with the same mAb captured. A third flow cell with each of the mAbs gave similar rate constant values.

Structures of Antibodies CH58 and CH59 Bound to an HIV-1 gp120 V2 PeptideVaccine-elicited antibodies CH58 and CH59 recognize alternative conformations of V2 compared to bnAb PG9.(A) Top: Ribbon representation of the CH58 antigen-binding fragment in complex with an A244 V2 peptide. Heavy chain is colored orange, light chain is blue, and peptide is green. The sequence of the peptide is shown, with modeled residues in green. Bottom: Close-up of the top panel rotated 90° about a horizontal axis. The side chains of residues involved in hydrogen bonds or salt bridges are shown as sticks, with the interactions depicted as dashed lines.(B) Structure of CH59 in complex with peptide, depicted as in (A). The heavy chain is tan, and the light chain is light blue.(C) Structure of bnAb PG9 in complex with the V1-V2 domain from HIV-1 strain CAP45. The PG9 structure is shown as ribbons with heavy and light chains (colored yellow and blue, respectively) in the same orientation as in (A) and (B). The V1-V2 domain is shown as a gray ribbon with residues 168–176 colored green and N-linked glycans attached to residues Asn156 and Asn160 shown as sticks.

Figure 4. Effect of V2 mAbs CH58, CH59, HG107, HG120 Footprint Mutations in HIV-1 Vaccine AE.A244 Env and RV144 Breakthrough AE.427299 and AE.703357 Envs on Ability of V2 mAbs to Mediate ADCCPanels show the ability of mAb A32 and RV144 V2 mAbs CH58, CH59, HG107, HG120 to mediate ADCC against gp120-coated CD4 cell (CEM_{CCR5}) target T cells. Data shown are maximum percent granzyme B activity from ADCC. Top panel shows that CH58, CH59, HG107, and HG120 mAbs all mediate high levels of ADCC against WT AE.244 Env-coated CD4 T cell targets (white bars), and this killing is mitigated by a single K169V mutation (gray bars) and is abrogated by the full V2 mAb footprint set of mutations (black bars). Middle and lower panels show, in contrast, that none of the CH58, CH59, HG107, and HG120 mAbs mediated ADCC against RV144 breakthrough Env AE.427299 and AE.703357 WT CD4 T cell targets (with V2s that did not match the RV144 vaccine) (white bars), and that ADCC was restored minimally with AE.703357 targets with the Q169K mutation (gray bars), and restored in a pronounced manner in both breakthrough Env targets with the full set of mutations that include Q169K that restored the V2 mAb footprint mutations (black bars). Purified NK cells isolated from a normal donor with Fc-gamma receptor IIIα FF phenotype were used as effector cells. The effector to target ratio was 10:1. Error bars show mean ± SEM. Each antibody was tested in a wide dose curve starting at 40 μg/ml with 4-fold dilutions.

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Myopericarditis and Pericarditis in the Deployed Military Member: A Retrospective Series

Military Medicine
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ABSTRACT

In this study, we investigated the incidence and etiology of pericarditis and myopericarditis of military members deployed to Iraq and Kuwait from 2004 through 2008. The importance of acute pericarditis and myopericarditis in the deployed military service member has resurfaced with the reintroduction of the smallpox vaccination by the U.S. Department of Defense in 2002. There are limited epidemiologic data on acute pericarditis and myopericarditis in the general population. As a primary evacuation node for cardiology patients between 2004 and 2008, the United States Military Hospital Kuwait cardiology clinic was uniquely situated to reliably extrapolate epidemiologic data for U.S. Armed Service Members serving in the Middle East. Between these years, approximately 721,600 service members served in Kuwait and Iraq. A total of 70 cases of pericarditis and 9 cases of myopericarditis were diagnosed. This yields an estimated incidence of 7.4 and 0.95 cases per 100,000 per year for pericarditis and myopericarditis, respectively. A total of eleven patients had received the smallpox vaccine 4 to 30 days before being diagnosed with pericarditis or myopericarditis. Four of the eleven patients (36.3%) had pericarditis, with a mean duration of 28.3 days since vaccination. Seven of these eleven (63.6%) patients had myopericarditis, with a mean duration of 13.7 days since smallpox vaccination. The incidence of pericarditis and myopericarditis was lower than previously reported incidence rates in the population. In all cases of myopericarditis and pericarditis, smallpox vaccination was preferentially related to myopericarditis versus pericarditis.

INTRODUCTION

Pericarditis is an inflammation of the fibrous pericardial sac surrounding the heart. Myopericarditis occurs when there is additional involvement of the myocardium. The most common causes include viral, idiopathic, autoimmune, and postinjury pericarditis. The relevance of acute pericarditis and myopericarditis in the deployed military service member has resurfaced with the reintroduction of smallpox vaccination by the U.S. Department of Defense in 2002. Since then, several reports have described vaccine-related myopericarditis in U.S. military members. However, no studies have examined the prevalence of pericarditis and myopericarditis in the military. Data are similarly limited concerning the incidence of acute pericarditis and myopericarditis in the general population. In this study, we investigated the incidence and etiology of pericarditis and myopericarditis of military members deployed to Iraq and Kuwait from 2004 through 2008.

MATERIALS AND METHODS

A retrospective review of all pericarditis cases presenting for medical care was conducted at the United States Military Hospital, Kuwait (USMHK). An ethical review of this protocol was obtained from the Institutional Review Board at USMHK. The cardiology clinic at the USMHK provides care to a patient population of active duty military, reservists, and civilian employees of the U.S. government. USMHK also serves as the referral center for U.S. military personnel with cardiac disease in the Middle East and southwestern Asia. The USMHK cardiology clinic is the main node for

cardiology medical evacuations from Iraq en route to the United States. Between the years 2004 and 2008, using the Defense Manpower Data Center statistics, an average of 189,118 service members served in Kuwait and Iraq at any moment. All cases that were referred to USMHK for cardiology referral were reviewed. The records review was conducted using both computerized and paper medical records. Fourteen data points were extracted from each record to include age, gender, status (active duty, reservist, or civilian), past medical history, family history, medications on presentation, symptoms on presentation, durations of symptoms, physical exam findings, electrocardiography (EKG) findings, treatment, reoccurrence, vaccination history, and elevation in cardiac markers.

Pericarditis was diagnosed by two of the following criteria: typical chest pain, new or worsening pericardial effusion, pericardial friction rub, or EKG changes consistent with pericarditis. When acute pericarditis was present, myopericarditis was diagnosed by the presence of an elevation in serum cardiac biomarkers or of new focal or global left ventricular systolic dysfunction. Postvaccine myopericarditis was defined as acute myopericarditis within 4 to 30 days after vaccine exposure.

Statistical Analysis

Comparison between the patient groups was performed using an unpaired *t*-test for continuous variables and a χ^2 analysis was used for categorical variables. A *p*-value of less than 0.05 was considered significant.

RESULTS

During the five years between January 2004 and December 2008, 70 active duty cases of acute pericarditis and nine cases of myopericarditis presented for care at USMHK. We identified an additional two civilian patients with acute pericarditis. These two patients were excluded from our calculations on measuring incidence as there are currently no published numbers of civilians deployed in Kuwait and Iraq. The remaining 79 cases were used to calculate the incidence of pericarditis and myopericarditis. The incidence of pericarditis among active duty members deployed to Iraq and Kuwait was 7.4 cases per 100,000 per year and the incidence of myopericarditis was 0.95 cases per 100,000 per year.

The mean age of the patients presenting with pericarditis was 31.3 years (standard deviation [SD] 9.2). All patients complained of chest pain; 10.0% presented with friction rubs on examination, 51.4% had changes on electrocardiography, and no pericardial effusions were noted in any of the 26 patients who underwent echocardiography. Typical electrocardiography changes include diffuse ST elevation and PR segment depression.

Patients with myopericarditis had a mean age of 25.7 years (SD 5.1). All patients presented with myopericarditis complained of chest pain; 11.1% had audible friction rubs, 44.4% had electrocardiographic changes, no patients presented with effusions, two had documented decreased low normal ejection fractions, and all were confirmed with positive cardiac markers.

A total of 11 patients had received the smallpox vaccine 4 to 30 days before being diagnosed with pericarditis or myopericarditis. Four of the 11 patients (36.3%) had pericarditis, with a mean duration of 28.3 days (SD 27.5) since vaccination. Seven of these 11 patients had myopericarditis, with a mean duration of 13.7 days (SD 3.9) since smallpox vaccination. The U.S. Armed Forces typically vaccinates service members immediately

before deployment, but only if they have not previously received the smallpox vaccine. Myopericarditis cases were more likely to be associated with smallpox vaccination than pericarditis cases in our case series.

Nonsteroidal anti-inflammatory drugs (NSAIDs) were prescribed in 61 patients (77.2%) and glucocorticoids were used in three patients (3.8%). No glucocorticoids were prescribed to any of the patients with myopericarditis. There was no significant difference in NSAID or steroid use between patient with pericarditis and myopericarditis.

DISCUSSION

Although acute pericarditis is the most common disorder involving the pericardium, we are aware of only one other study that has evaluated the incidence of acute pericarditis and myopericarditis in the general population. Performed in northern Italy, the investigators found an incidence of 27.7 and 4.0 cases per 100,000 per year for acute pericarditis and myopericarditis, respectively. This compares with our incidence of 7.4 and 0.95 cases per 100,000 per year for acute pericarditis and myopericarditis. The average mean age in the Italian study was 54.8 and 36.0 years for pericarditis and myopericarditis. This compares with our mean age of 31.3 and 25.7 years for pericarditis and myopericarditis, respectively.

The most likely factor resulting in our lower incidence is that many cases were probably missed because they were managed locally rather than via referral to a subspecialty clinic or they were aeromedically evacuated out of theater; thereby, circumventing the theater medical evacuation system. Another factor that may influence the decrease in incidence compared with this previous study may include the younger population in this study. Military personnel are, on the average, younger and often more physically fit than the general population, likely decreasing their risks for most medical disorders. Patients in our series with acute pericarditis and myopericarditis were younger than those in the Italian series. Moreover, infectious causes of pericarditis may differ by geography, with the seroprevalence of causative viral agents (such as enteroviruses) varying by region. Deployed military personnel are, in the great majority of cases, not native to the region of deployment and may be immunologically naïve to endemic infections. Lastly, U.S. military populations may be more ethnically diverse than the populations of some European cities, with differing ethnic groups having differing risk factors for autoimmune disorders such as systemic lupus erythematosus, for example. Our reported incidence of myopericarditis was 0.95 cases per 100,000 per year, compared to 4.0 cases per 100,000 per year in the Italian study. All military personnel are vaccinated for smallpox before deployment, with the majority of members being vaccinated months to years before deployment. We originally hypothesized that the incidence of pericarditis and myopericarditis would have increased with the universal exposure to the smallpox vaccine. Rather the opposite was noted and possibly the healthier population and the lack of a smallpox bioterrorism threat could have contributed.

The smallpox vaccine originated in 1798 and consisted of live cowpox virus from infected calves, slightly different from the modern vaccinia-based smallpox vaccine. The modern smallpox vaccine has a well-documented record of effectiveness in preventing disease but is associated with rare but serious adverse events. In 1947, five million vaccinations were given in New York with 10 associated deaths. Autopsies and microscopic examinations demonstrated severe myocarditis with mononuclear inflammatory foci. After 1949, there were no endemic cases of smallpox in the United States, but the disease continued to be a serious problem in other countries. This led the World Health Assembly to call for global smallpox eradication. Because of the successful vaccination process, in 1971, routine smallpox vaccination ceased in the United States, and in 1976, the

World Health Organization requested that all laboratories with smallpox virus either destroy the virus or submit their stocks to the Center for Disease Control and Prevention.

Different strains of vaccines historically have had different incidences of myopericarditis. In 1983, a myopericarditis rate of 10 per 100,000 in Finnish military conscripts was reported following vaccination with the vaccine strain used in Finland. In 1962, Australia reported a myopericarditis incidence of 1.6 per 100,000 vaccines. The vaccine used during the this study in the United States is a live-virus preparation derived from the New York City Department of Health strain prepared in the early 1980s. U.S. military use of smallpox vaccine was restricted to new trainees in 1984 and then discontinued entirely in 1990. However, despite efforts to eradicate smallpox, concern that smallpox could be developed as a biological weapon led to the restoration of the U.S. National Smallpox Vaccination Program in 2002.

Limitations of this study include being a single center study site, the milder cases may have been treated by medics or corpsmen, and other vaccine-associated illnesses may have occurred before deployment and thus not presented in the theater of operations. A lower incidence could also result from a degree of selection bias as military members sent for deployment are prescreened with history, physical exams, and laboratory studies before deployment. Between 2004 and 2008, some patients in Operation Iraqi Freedom were medically evacuated directly to Landstuhl, Germany; however, USMHK cardiology department was established as the referral center to handle cardiology medical evacuations during this period of time. In addition, we do not have any outcome data because of the transient status of military services and deployments making follow-up contact difficult.

In conclusion, there has been little published on the incidence of acute pericarditis and myopericarditis. Despite the younger population, this study was able to document an incidence of acute pericarditis slightly lower to what was previously published. The incidence of myopericarditis is also similar to prior published numbers; however, in our case series, most of the myopericarditis cases were associated with the smallpox vaccine. Among the patients in our case series who developed myopericarditis compared with the patients with pericarditis, there was a statistically significant association with the smallpox vaccine. Pericarditis and myopericarditis is unusual among deployed military members, with an incidence somewhat lower than that described in other settings and with low long-term morbidity.

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Serum 25-hydroxyvitamin D and breast cancer in the military: a case–control study utilizing pre-diagnostic serum

Cancer Causes & Control
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Abstract

Purpose

The objective of this study was to ascertain whether a relationship exists between pre-diagnostic serum levels of 25-hydroxyvitamin D (25(OH)D) and risk of breast cancer in young women.

Methods

About 600 incident cases of breast cancer were matched to 600 controls as part of a nested case–control study that utilized pre-diagnostic sera. Logistic regression was used to assess the relationship between serum 25(OH)D concentration and breast cancer risk, controlling for race and age.

Results

According to the conditional logistic regression for all subjects, odds ratios for breast cancer by quintile of serum 25(OH)D from lowest to highest were 1.2, 1.0, 0.9, 1.1, and 1.0 (reference) (*p* trend = 0.72). After multivariate regression for subjects whose blood had been collected within 90 days preceding diagnosis, odds ratios for breast cancer by quintile of serum 25(OH)D from lowest to highest were 3.3, 1.9, 1.7, 2.6, and 1.0 (reference) (*p* trend = 0.09).

Conclusions

An inverse association between serum 25(OH)D concentration and risk of breast cancer was not present in the principal analysis, although an inverse association was present in a small subgroup analysis of subjects whose blood had been collected within 90 days preceding diagnosis. Further prospective studies of 25(OH)D and breast cancer risk are needed.

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Primaquine to prevent transmission of falciparum malaria

The Lancet Infectious Diseases
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February 2013

Summary

Falciparum malaria is transmitted by anopheline mosquitoes that have fed on blood containing gametocytes of *Plasmodium falciparum*. In areas of low malaria transmission, where symptomatic infections contribute substantially to malaria transmission, the use of gametocytocidal drugs reduces

the incidence of malaria. Artemisinin-based combination therapies provide high cure rates and substantially reduce gametocyte carriage. Artemisinin resistance in *P falciparum* lessens overall gametocytocidal activity, which provides a selective pressure to the spread of these resistant parasites. The 8-aminoquinoline compounds possess unique gametocytocidal properties and rapidly sterilise the mature transmissible stages of *P falciparum*. The addition of one dose of primaquine to artemisinin-based combination regimens could help to counter the spread of artemisinin resistance. Although primaquine is commonly recommended for falciparum and vivax malaria, concerns about drug-related haemolysis frequently prevent its administration. The limited available evidence on transmission-blocking effects of primaquine and its forerunner plasmoquine suggests that doses lower than currently recommended (0·50—0·75 mg base per kg), which would be safer, might still be very effective.

Introduction

The burden of malaria has declined worldwide with increased deployment of insecticide-treated bednets and artemisinin-based combination therapies (ACTs), and the world has begun again to entertain the idea that human malaria can be eliminated. This ambitious but laudable goal is threatened by artemisinin resistance in *Plasmodium falciparum*. Artemisinin resistance increases treatment-failure rates. Slow parasite clearance is associated with increased gametocyte carriage, which provides a selective transmission advantage to resistant parasites, even without subsequent recrudescence, and thereby drives the spread of artemisinin resistance.

All the effective antimalarial drugs kill developing *P falciparum* gametocytes in stages 1—3 and all blood stages of the other human malaria species. Artemisinin derivatives substantially reduce transmissibility in falciparum malaria largely by killing young gametocytes, but are less effective in patients who present with transmissible densities of infectious mature gametocytes. Several of the available antimalarials (eg, antifols and hydroxynaphthoquinones) also interfere with parasite development in the mosquito (sporontocidal activity), but of these only the 8-aminoquinolines and methylene blue kill mature *P falciparum* gametocytes. Primaquine is the only 8-aminoquinoline in general use. Its predecessor, plasmoquine, was discovered in 1924, and was used extensively until the 1940s, when safer and more effective 8-aminoquinolines were developed. Tafenoquine, a slowly eliminated 8-aminoquinoline, is still under development. Elubaquine (bulaquine), which is metabolised to primaquine in vivo, was developed in India but is not widely used.

Primaquine was used in most countries, although quinocide (a rearrangement product that was in the past a substantial contaminant in manufactured primaquine) was also used in the former Soviet Union. Primaquine is now used for prophylaxis, radical cure of vivax and ovale malaria, and as a single-dose gametocytocide (0·50—0·75 mg base per kg) to treat falciparum malaria. When added to an ACT, single-dose primaquine rapidly kills mature gametocytes and, therefore, substantially lowers the risk of transmission. In Kenya and Tanzania, the addition of primaquine to an ACT shortened estimated gametocyte circulation times from 4·6 and 5·0 days, respectively, to 0·5 days. This strategy should, therefore, be effective in the reduction of transmission in low-transmission settings. Primaquine has been recommended as a *P falciparum* gametocytocide by several national malaria control programmes for many years, but is frequently not deployed because of concerns about potential haemolytic toxic effects.

In a comparison of different artemisinin-based combination therapies in Myanmar (Burma), 808 patients were randomly assigned one of five different regimens, and half the patients were randomised to receive additional single-dose primaquine 0·75 mg base per kg. Overall 264 patients presented with gametocytaemia assessed by microscopy. Gametocyte clearance accelerated substantially after primaquine.

Early studies done with 8-aminoquinolines showed that substantial gametocytocidal activity could be achieved with low doses. In the 1920s, Barber and colleagues investigated the effects of plasmoquine on the infectivity of *P falciparum* gametocyte carriers to anopheline mosquitoes in Panama. Oocyst numbers fell rapidly after plasmoquine administration—more rapidly than gametocyte densities. Subsequent studies confirmed that plasmoquine sterilised infections rapidly. Whereas adult doses of 20—60 mg were usually prescribed, lower doses still proved rapidly gametocytocidal. Detailed investigations in one adult patient suggested that 10 mg plasmoquine rapidly rendered gametocytes non-infectious well before gametocyte clearance.

Results of plasmoquine treatment of falciparum malaria

MacKerras and Ercole studied an adult volunteer with falciparum malaria and gametocytaemia who was bitten at frequent intervals by laboratory reared *Anopheles punctalus punctalus* before and after a single 10 mg dose of plasmoquine. The patient's initial count was 920 gametocytes per µL. Development of oocysts and sporozoites after treatment was rapidly inhibited, whereas gametocytaemia remained unchanged over 24 h.

In the early 1950s, primaquine replaced plasmoquine because it was safer and more effective in the radical cure of vivax malaria. No formal dose-finding studies for gametocytocidal activity in acute falciparum malaria were ever done, although Rieckmann and colleagues compared transmissibility after administration of 15, 30, and 45 mg doses to adults. All studies of the gametocytocidal properties of 8-aminoquinolines have shown consistently that transmission is blocked before the number of gametocytes is reduced. The pooled findings of studies that have quantified oocysts 24 h after use of single-dose 8-aminoquinolines show that no oocysts were seen in 56 (70%) of 80 batches of mosquitoes. The median reduction in the number of oocyst-positive mosquitoes in the remainder of the batches was 52% (range −9 to 92). Gametocyte densities were suppressed for many days, despite no activity against the asexual stages, but, eventually, if no effective treatment followed, gametocyte numbers and viability recovered. This latter finding emphasises the central importance of effective treatment to limit malaria transmission from symptomatic individuals.

Oocysts were typically assessed in ten to 20 mosquitoes 6—7 days after they had fed. Each pair of circles or diamonds represents one patient. Gametocytaemia changed little in 24 h, although it generally declined rapidly thereafter, but oocyst numbers fell rapidly to zero in most mosquito batches. When assessed later in parallel batches, sporozoites were correspondingly absent.

In all published studies of mosquito infectivity only ten people have received primaquine at doses of 0·25 mg base per kg or less; eight (80%) remained infectious 24 h after administration (as assessed by oocysts), compared with 12 (32%) of 37 people who had received higher doses. Although this finding suggests slower gametocytocidal activity at low doses, three (38%) of the eight infectious low-dose recipients were no longer infectious the following day and, therefore, the maximum transmission-blocking effects might not differ substantially. Studies have assessed small cohorts in very different circumstances with a wide variety of doses (plasmoquine 0·14—1·00 mg base per kg and primaquine 0·04—1·20 mg

base per kg) and usually without accompanying sexual-stage treatment. More data are needed to characterise the dose-response relation for transmission blockade to identify the optimum dose.

The small number of published infectivity studies testifies to their difficulty. More studies have been reported of gametocyte clearance rates, although they underestimate effects on transmissibility. Most in-vivo studies have shown that 8-aminoquinolines markedly accelerate gametocyte clearance. Infectivity can also be assessed ex vivo by the feeding of gametocytes to anopheline mosquitoes in the presence of varying drug concentrations, but this method of assessment is compromised for 8-aminoquinolines because active metabolites mediate most of their gametocytocidal (and hypnozoitocidal) effects in vivo.

Primaquine-associated haemolysis

The prevalence of the X-linked glucose-6-phosphate dehydrogenase (G6PD) deficiency in malaria-endemic areas typically varies between 3% and 30%. More than 180 different genotypes have been described, and each year more are added. Most functional polymorphisms lower enzyme stability. As erythrocytes age they become increasingly G6PD deficient and, therefore, more depleted in reduced glutathione, which is their principal antioxidant defence. Oxidant foods (eg, fava beans) and drugs (including sulphones and 8-aminoquinolines) lead to dose-dependent haemolysis in proportion to the degree of G6PD deficiency. In people with mild or moderate deficiency, residual red-cell stores of reduced glutathione become exhausted and maximum rates of red-cell destruction are reached within 1—2 days. In severe cases, individuals may experience nausea, vomiting, abdominal or loin pain, and passage of dark to very dark (so-called blackwater) urine. Anaemia develops rapidly and patients become mildly jaundiced. Peripheral blood films show marked poikilocytosis and, if suitably stained, Heinz bodies. Rarely, haemoglobinuric renal failure occurs. In the less-severe cases, haemolysis stops in about 7 days and, despite continuation of primaquine, patients feel better and haematocrit values start to rise because of the replacement of old G6PD-deficient erythrocytes with younger, more primaquine-resistant red cells. Measurement of G6PD activity at this stage, therefore, underestimates the degree of deficiency at steady state. Reticulocytosis may be delayed in individuals with acute malaria. In patients with more severe deficiency, continuation of the drug results in further haemolysis and life-threatening anaemia.

Millions of people have received primaquine. Case reports of severe haemolysis in those with G6PD deficiency have mainly been associated with administration of multiple doses given to eradicate the hypnozoites of *Plasmodium vivax*. 13 deaths from unsupervised primaquine use have been reported: four in Sri Lanka, five in Turkey, two in Brazil, and one each in the UK and the USA. No deaths are known to have followed single-dose administration. Alving and colleagues noted in 1960 that among around 250 000 US troops (of whom 10% were African American) who received 15 mg primaquine base daily for 14 days during return from the Korean War, haemolytic reactions were seen in very few (“about half a dozen”) and none was severe. On the basis of challenge studies done in volunteers in the USA, 0·75 mg base per kg primaquine once weekly for 8 weeks was deemed safe in the African A— variant of G6PD deficiency, and proved an efficacious alternative to the standard 14-day radical cure regimen for vivax malaria. The US army later used chloroquine and 45 mg primaquine base weekly as chemoprophylaxis in the Vietnam War. Although recommended widely for use specficially in patients with vivax malaria and G6PD deficiency, the once-weekly regimen has been little used.

In the heyday of malaria eradication, half a century ago, entire regions and millions of people were exposed to repeated mass treatments with regimens containing primaquine or quinocide without individual G6PD deficiency screening. Little detailed information is available on the safety of this practice. Nevertheless, the absence of reports of major toxic effects after use of primaquine as a radical treatment for vivax malaria, when given weekly in G6PD-deficient individuals as a mass treatment, or when given in single doses (usually 0·75 mg base per kg) as a gametocytocide, must provide some reassurance, even if much of the information comes from areas that have no routine pharmacovigilance. Furthermore, no severe haemolysis requiring blood transfusion was reported in nearly 1500 patients studied prospectively in trials of single-dose primaquine given as a gametocytocide.

On the basis of these diverse observations, the risk of haemolysis with single-dose primaquine was thought to be acceptable except in areas where severe G6PD deficiency is prevalent. Confidence was shaken, however, by a study in Tanzania where an ACT plus 0·75 mg base per kg single-dose primaquine was associated with a significant reduction in haemoglobin concentrations (mean fall 25 g/L in G6PD-deficient children with the *G6PD* A— variant, 16 g/L in heterozygotes [*G6PD* A], and 5 g/L in children with the wild-type genotype *G6PD* B). The withdrawal of combined chlorproguanil and dapsone as a 3-day regimen because of haemolytic anaemia in G6PD-deficient African children was also a salutary lesson. Anaemia is common in children living in areas of high malaria transmission and, therefore, substantial drops in haemoglobin concentrations (to less than 50 g/L) are potentially life threatening. The dangers should be proportionately less in populations living in areas with lower malaria transmission and who have higher baseline haemoglobin concentrations, but the importance of the degree of anaemia, the amount of red-cell loss, and premorbid haemoglobin concentrations have not been quantified. The fundamental issue is that not enough information is available on the safety of single-dose primaquine (0·50—0·75 mg base per kg) in many malaria-endemic areas.

Widespread deployment

The transmission-blocking activity of 8-aminoquinolines in *P falciparum* infections has been assessed in patients with high gametocyte densities, which represent the upper end of the distribution of gametocyte carriage. Gametocyte densities, like asexual parasite densities, generally have logarithmic distributions. Most patients and asymptomatic carriers with transmissible levels of gametocytaemia have low densities close to or just below the limit of detection by microscopy. The corresponding oocyst numbers in wild anopheline vectors are low (median two) compared with those in vectors used in laboratory feeding studies. Gametocytocidal effects are probably fractional, but the resulting transmission blockade is binary: viable sporozoites are formed in the mosquito salivary glands or not. The overall effect, therefore, is a function of gametocyte density and maturity and of drug concentration. Thus, if a drug induces 99% reduction in gametocyte viability when starting densities are less than 100/μL, the result will generally be no transmission, but the same reduction might not prevent transmission if gametocytaemia is initially higher. Studies of gametocytocidal effects of single-dose primaquine in patients with high gametocyte densities, therefore, underestimate the likely transmission-blocking benefits at the population level.

Effect of early antimalarial treatment on transmissibility of falciparum malaria

Early treatment aims to lower the number of viable gametocytes that enter the circulation and thereby reduce transmissibility. (A) Approximate sigmoid relation between *P falciparum* gametocyte density and infectivity to anopheline mosquito vectors. (B) A rapidly effective treatment (eg, an

artemisinin derivative) prevents the maturation of gametocytes, which reduces gametocytaemia more than with other antimalarials and thereby lessens transmissibility. Densities lower than ten gametocytes per μL become progressively less likely to be infectious, although substantial variability in infectivity is seen between individuals.

In areas where primaquine is recommended, it is frequently not given. The main reason seems to be concerns about toxic effects. Cost is unlikely to be a factor, since primaquine is very inexpensive. Use of single-dose primaquine is also virtually confined to health care in the public sector, despite the private sector being the main source of antimalarial drugs in many countries. Some countries that initially recommended primaquine along with ACTs no longer do so. These changes were presumably made because the transmission-blocking effects of ACTs were considered sufficient and, therefore, benefits were perceived to be no longer greater than the risks of potentially serious toxic effects. This view should be altered, particularly in areas with artemisinin resistance. Recommendations for use of primaquine as a gametocytocide are inconsistent, as they are for radical treatment of vivax malaria. Some countries recommend the addition of single-dose primaquine to all falciparum malaria treatments and others with similar malaria epidemiology do not. In some countries the standard adult dose of primaquine is 30 mg, and in others it is 45 mg. Sometimes it is given with the first dose of an ACT and sometimes with the last. In the past month, WHO has recommended that in areas threatened by artemisinin resistance where use of primaquine is not implemented as a gametocytocide for *P falciparum*, and for elimination areas that have not yet adopted it, 0·25 mg base per kg single-dose primaquine with an ACT should be given to all patients with falciparum malaria except pregnant women and infants.

Discussion

Use of primaquine as a gametocytocide in falciparum malaria provides little benefit to treated patients, who are put at risk of toxic effects to benefit their communities. If primaquine could slow the emergence of artemisinin resistance, however, those benefits would extend across the malaria-affected world. Since vivax malaria relapses are the main complication of falciparum malaria in east Asia (typically occurring in 30—50% of cases), malaria treatment in this region could even be simplified to an ACT plus a radical curative regimen of primaquine for all malaria infections. This approach would augment transmission blockade of falciparum malaria and provide substantial individual benefit by prevention of subsequent vivax malaria, but would also increase the risks of toxic effects.

The diversity of policies and practices related to the use of primaquine as a gametocytocide reflects uncertainty over the risks and the benefits. The risks will become evident almost immediately if patients have severe haemolysis, whereas, although the benefits to the population could be great, they are much less obvious. The clear advantage of ACTs over other antimalarials and their effectiveness in reducing gametocyte carriage alleviated the pressure to resolve these uncertainties for a long time. Now that artemisinin resistance in falciparum malaria has emerged in western Cambodia and eastern Myanmar, the pressure has returned. Spread of artemisinin resistance to India and Africa would be disastrous. Use of primaquine could lessen the transmission advantage of artemisinin-resistant *P falciparum* and help to control the spread of resistant disease. WHO recommended the addition of primaquine to ACTs in the global plan for artemisinin resistance containment “when the risk of G6PD deficiency is deemed low or testing for deficiency is available”. Nevertheless, use remained inconsistent. In the private sector, which is the main source of antimalarials in many countries, primaquine is rarely used, and testing for G6PD deficiency is seldom done in the public or private sectors. If the risks and benefits of different primaquine doses were better defined, recommendations could be made stronger and more effective.

The need to obtain further information is a race against time as resistance spreads. Policy decisions might, therefore, have to be made on the basis of inadequate information. In fact, to encourage use, particularly in areas threatened by artemisinin resistance, WHO has just recommended that a low dose of primaquine (0·25 mg base per kg) be deployed as a single-dose gametocytocide without G6PD testing. Fortunately, the critical knowledge gaps could be easily filled and recommendations thereby strengthened. Indeed, in view of the substantial investments now being made in malaria research, it is puzzling why so little attention has been paid to a drug that has been available for 60 years, is inexpensive, and has unique antimalarial properties.

Several practical issues need to be taken into account. The optimum timing of primaquine administration to treat falciparum malaria is unclear. In volunteer studies, where primaquine was given alone, it provided a rapid and protracted sterilising effect and suppression of gametocytaemia in acute falciparum malaria, without changes in asexual parasite densities. This finding suggests broad sexual-stage activity. Delay of primaquine administration to day 3 or later of the ACT regimen, as is often practised, leads to at least 2 days of additional potential infectivity, and might result in a disproportionate increase in transmissibility as the first wave of circulating gametocytes matures. Although acute malaria illness has only small effects on primaquine disposition, haemolysis in G6PD-deficient patients could be exacerbated by fever. Thus, whereas in acute falciparum malaria it might be best to give primaquine immediately at presentation together with an ACT to optimise the gametocytocidal effect, in terms of safety it might be better to delay until patients are afebrile. This simple question is easily answerable.

Safety assessments that focus on haematocrit reduction and G6PD status could be done in the context of routine surveillance studies in areas where primaquine is already recommended as a gametocytocide—indeed a considerable amount of information might already be available—and research studies should be done where it is not recommended. The relation of primaquine dose to haemolysis and G6PD activity must be characterised in acute malaria. Doses lower than 0·50—0·75 mg base per kg are likely to provide sufficient transmission blockade when added to ACTs, and would be safer than currently recommended doses. The early studies of plasmoquine suggested that single doses substantially lower than 0·50 mg base per kg were highly effective, but what these findings mean for primaquine is unclear. Early studies with primaquine suggested that single doses of 0·25 mg base per kg or lower have slightly less gametocytocidal activity than higher doses. These studies in chronically gametocytaemic individuals, who frequently received no other antimalarial, however, might have underestimated the transmission-blocking effects in the treatment of acute malaria in low-transmission settings. Mass treatment of adults with 9 mg primaquine base (around 0·16 mg base per kg) together with artemisinin and piperaquine apparently proved very effective in reducing the incidence of malaria in western Cambodia. Studies of primaquine in artemisinin-resistant falciparum malaria should be undertaken urgently to assess gametocytocidal effects and determine usefulness in this context. The possibility that separation of the primaquine enantiomers or use of methylene blue will provide safer, more effective transmission blockade should also be explored. To find a completely safe and effective dose of primaquine might not be possible, but the threat of artemisinin resistance may necessitate the taking of some risks.

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HIV Drugs and Malaria

Journal of the American Medical Association

M. J. Friedrich
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Treatment with a combination of protease inhibitors reduces the incidence of malaria in children infected with HIV, report researchers in Uganda and the United States (Achan J et al. *N Engl J Med*. 2012;367[22]:2110-2118).

In the open-label randomized trial, the participants—170 children aged 5 months to 5 years in Uganda who were infected with HIV—received antimalarial drugs and either of 2 anti-HIV therapies: the protease inhibitors lopinavir and ritonavir or non–nucleoside reverse transcriptase inhibitors (NNRTIs). Although neither regimen lowered the children's risk of developing malaria during the first 6 months of the study, risk of recurrence of malaria after successful treatment with the antimalarial drug artemether-lumefantrine was reduced by 41% in the group receiving protease inhibitors compared with those receiving NNRTIs. There was an increase in serious adverse events in the group receiving protease inhibitors.

Ritonavir can inhibit the metabolism of other drugs, and the researchers found higher levels of the antimalarial drugs in children who received this drug in combination with lopinavir, suggesting that the protease inhibitors may help prevent the antimalarial drugs from breaking down.

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Early-life prevention of non-communicable diseases

The Lancet
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5 January 2013

Non-communicable diseases (NCDs) are major causes of death worldwide and underlie almost two-thirds of all global deaths. Although all countries face epidemics of these diseases, low-income and middle-income countries, and the poorest and most vulnerable populations within them, are affected the most. There is a global imperative to create and implement effective prevention strategies, because the future costs of diagnosis and treatment are likely to be unaffordable.

At the UN High-Level Meeting on the Prevention and Control of Non-Communicable Diseases, held in New York, USA, in September, 2011, the so-called four by four strategy for NCD prevention was proposed. Prevention efforts for the priority NCDs discussed at the meeting (diabetes, cardiovascular disease, cancer, and chronic obstructive pulmonary disease) focus on four, mainly adult, risk factors: poor diet, physical inactivity, tobacco use, and alcohol consumption. Although paragraphs 26 and 28 of the UN Political Declaration refer to the roles of prenatal nutrition, maternal diseases, and household air pollution on NCD risk in later life, these paragraphs only partially describe the full scope of the problem and

opportunities for intervention. As scientific knowledge emerges on the role of both nutritional factors and exposures to environmental chemicals in the developmental origins of health and disease, evidence suggests that much more attention is needed on early-life interventions, optimisation of nutrition, and reduction of toxic exposures to curtail the increasing prevalence of NCDs.

The present state of the science on the developmental origins of health and disease and NCDs was discussed at the Prenatal Programming and Toxicity III conference, Environmental Stressors in the Developmental Origins of Disease: Evidence and Mechanisms, held in Paris, France in May, 2012, and at a symposium just before the conference. Studies in human beings have shown that nutritional deprivation and maternal metabolic status (eg, diabetes) in early intrauterine life increase the risk of metabolic disorders and cardiovascular disease in adulthood. These effects occur not only in settings of extreme deprivation, but also throughout the normal range of population weights at birth and in early childhood. Investigators have also reported associations between in-utero exposures and childhood diseases, including type 2 diabetes. In-utero and early-life exposures to environmental toxicants, ranging from heavy metals to endocrine-disrupting chemicals, affect adult metabolism, immune system function, neurodevelopment, and reproductive function.

Although causal relations have not yet been established, the new science of epigenetics offers insight into mechanisms of early life predisposition to adult disease risk. During development, epigenetic marks, such as DNA methylation, histone modifications, and non-coding RNA expression, undergo substantial changes. These changes affect genes that are essential for both early life development and later life physiological functions. Epigenetic modifications are stable during cell division and can be transmitted transgenerationally. An increasing amount of evidence suggests that developmental exposure to nutritional imbalance or environmental contaminants—including metals, pesticides, persistent organic pollutants, and chemicals in drinking water, such as triethyltin, chloroform, and trihalomethanes—can affect epigenetic changes, thus suggesting a mechanism for their effects on adult health. Similarly, prenatal exposure to air pollutants has been associated with epigenetic changes and subsequent effects on children's respiratory health.

Knowledge that in-utero and early childhood experiences affect the risk of NCD development provides an opportunity to target interventions at the time when they have the greatest effect. Because these exposures are not controlled directly by the individual, especially when the exposures might have occurred to the individual's parents or grandparents, early-life interventions can reduce the perception of blame that the individual's own lifestyle has caused his or her disease. This notion has policy implications, because the prevailing viewpoint often assumes that NCDs are mainly a matter of individual responsibility, thus obviating societal and governmental responsibility. Substantial reductions of NCD risks could be achieved through the use of existing maternal—child health platforms to educate mothers about both nutritional and environmental exposures and to integrate the health promotion and disease prevention agendas within social and economic development efforts. For example, the Millennium Development Goals (MDGs) address not only maternal and child health problems, but also poverty and malnutrition, sex inequality, and lack of education, all of which are notable drivers of social disadvantage in low-income and middle-income countries and are underlying causes of NCDs. Poverty alleviation, sustainable food production, and reductions in exposures to toxic chemicals are all key themes emerging from the Rio+20 UN Conference on Sustainable Development12 held in Rio de Janeiro, Brazil, in June, 2012, and the development of Sustainable Development Goals (SDGs) and appropriate environmental, nutritional, and health indicators provides another opportunity to incorporate NCD prevention into broader, multisector programmes. The integration of NCD prevention with the attainment of the MDGs and SDGs could leverage major worldwide investments in health and development.

CH, GKJ, AK, and JR are employed by non-profit organisations with activities that focus on global efforts to address non-communicable diseases. MAH and PDG receive research grants and support for travel to meetings from food and pharmaceutical companies for work related to the developmental origins of health and disease. KH is employed by Social and Scientific Systems, a government contractor that supported the logistics and technical writing for the workshop that initiated the development of this Comment. The National Institute of Environmental Health Sciences also supported this workshop. The authors alone are responsible for the views expressed in this Comment, and they do not necessarily reflect those of the National Institute of Environmental Health Sciences, the National Heart Lung and Blood Institute, the National Institutes of Health, US Government, or WHO.

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Screening for Hepatitis C Virus Infection in Adults: A Systematic Review for the U.S. Preventive Services Task Force

Annals of Internal Medicine
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Abstract

Background

Identification of hepatitis C virus (HCV)–infected persons through screening could lead to interventions that improve clinical outcomes.

Purpose

To review evidence about potential benefits and harms of HCV screening in asymptomatic adults without known liver enzyme abnormalities.

Data Sources

English-language publications identified from MEDLINE (1947 to May 2012), the Cochrane Library Database, clinical trial registries, and reference lists.

Study Selection

Randomized trials and cohort, case–control, and cross-sectional studies that assessed yield or clinical outcomes of screening; studies reporting harms from HCV screening; and large series reporting harms of diagnostic liver biopsies.

Data Extraction

Multiple investigators abstracted and checked study details and quality by using predefined criteria.

Data Synthesis

No study evaluated clinical outcomes associated with screening compared with no screening or of different risk- or prevalence-based strategies. Three cross-sectional studies in higher prevalence populations found that screening strategies that targeted multiple risk factors were associated with sensitivities greater than 90% and numbers needed to screen to identify 1 case of HCV infection of less than 20. Data on direct harms of screening were sparse. A large study of percutaneous liver biopsies (n = 2740) in HCV-infected patients with compensated cirrhosis reported no deaths and a 1.1% rate of serious adverse events (primarily bleeding and severe pain).

Limitations

Modeling studies were not examined. High or unreported proportions of potentially eligible patients in the observational studies were not included in calculations of screening yield because of unknown HCV status.

Conclusion

Although screening tests can accurately identify adults with chronic HCV infection, targeted screening strategies based on the presence of risk factors misses some patients with HCV infection. Well-designed prospective studies are needed to better understand the effects of different HCV screening strategies on diagnostic yield and clinical outcomes.

Primary Funding Source: Agency for Healthcare Research and Quality.

The prevalence of anti–hepatitis C virus (HCV) antibody in the United States is about 1.6% (1). Approximately 78% of affected patients have viremia, indicating chronic infection. About two thirds of patients with HCV infection were born between 1945 and 1964, with the highest prevalence (4.3%) in people 40 to 49 years of age in 1999–2002 (1). There were 16 000 new cases of HCV infection in 2009 (2).

In 2007, HCV infection was associated with an estimated 15 000 deaths in the United States (3). Liver disease related to HCV is the most common indication for liver transplantation among U.S. adults (4 - 5) and is a leading cause of hepatocellular carcinoma (6).

The virus is primarily acquired via percutaneous exposures to infected blood, such as injection drug use (7 - 13). Transfusions before 1992 and high-risk sexual behaviors are also associated with increased risk, although the efficiency of sexual transmission seems to be relatively low (7 - 8,14 - 15).

The natural course of HCV infection varies. Studies of community cohorts estimate cirrhosis in 7% of people after 20 years of infection, with rates about twice as high in clinical and referral cohorts (16 - 17). Studies with longer follow-up suggest that disease progression accelerates after 20 years (18).

Screening for HCV infection could identify persons at earlier stages of disease, before they develop serious or irreversible liver damage, and lead to treatments to improve clinical outcomes or reduce transmission risk. Up to three quarters of HCV-infected persons are unaware of their status (19).

In 2004, the U.S. Preventive Services Task Force (USPSTF) recommended against HCV screening in adults not at increased risk (D recommendation) and found insufficient evidence to recommend for or against screening in high-risk adults (I recommendation) (20). Although the USPSTF found that screening tests are accurate and that antiviral treatments improve viremia (21), the recommendations were based on the lower prevalence of HCV infection in persons without risk factors; the relatively low rate of long-term progression, potentially resulting in overtreatment; and lack of evidence that screening improves important health outcomes or reduces transmission risk. Other groups recommend screening in higher-risk patients (22 - 24). The Centers for Disease Control and Prevention (CDC) also recently recommended screening all persons born between 1945 and 1965 (25).

The purpose of this report is to review the evidence on HCV screening in asymptomatic adults without known liver enzyme abnormalities (26). This review focuses on research gaps identified in the 2004 USPSTF review (21) and will be used together with a separate review on antiviral treatments (27) by the USPTF to update its HCV screening recommendations.

Methods

Scope

We developed a review protocol and analytic framework that included the following key questions:

1. Does screening for HCV infection in nonpregnant adults without known abnormal liver enzymes reduce mortality and morbidity due to HCV infection, affect quality of life, or reduce incidence of HCV infection?

2. What is the effectiveness of different risk- or prevalence-based methods for screening for HCV infection on clinical outcomes?

3. What is the sensitivity and number needed to screen to identify 1 case of HCV infection of different risk- or prevalence-based methods for screening for HCV infection?

4. What are the harms associated with screening for HCV infection, including diagnostic liver biopsies?

Detailed methods and data for the review, including search strategies, detailed inclusion criteria, data abstraction tables, and tables with quality ratings of individual studies, are available in the full report, which includes the analytic framework and additional key questions (26). The protocol was developed using a standardized process with input from experts and the public. The analytic framework focuses on direct evidence that HCV screening improves important health outcomes compared with not screening, as well as the chain of indirect evidence (diagnostic accuracy of screening, clinical utility and harms of subsequent testing in HCV-infected persons, and benefits and harms of treatments) linking screening with improved health outcomes. Key questions related to risk modification of mother-to-infant transmission are presented in the full report (26) and in a separate article (28). We did not re-review the diagnostic accuracy of HCV antibody testing, which the 2004 USPSTF review found to be high (21).

Data Sources and Searches

A research librarian searched Ovid MEDLINE (1947 to May 2012), Embase, the Cochrane Library Database, Scopus, and PsycINFO; clinical trial registries (including ClinicalTrials.gov); and grants databases. We supplemented electronic searches by reviewing reference lists of retrieved articles.

Study Selection

At least 2 reviewers independently evaluated each study to determine inclusion eligibility. Papers were selected for full review if they were relevant to a key question and met the predefined inclusion criteria. For screening, we included randomized trials, cohort studies, case–control studies, and cross-sectional studies that compared different screening strategies in asymptomatic adults without known liver enzyme abnormalities and reported clinical outcomes or sufficient information to compute the sensitivity and number needed to screen to identify 1 HCV-infected person. We also included large studies (sample size >1000 participants) reporting harms associated with diagnostic liver biopsy published since 2004 and uncontrolled or controlled studies reporting direct harms associated with screening.

Clinical outcomes were mortality, end-stage liver disease, cirrhosis, hepatocellular carcinoma, need for transplantation, quality of life, HCV transmission, harms associated with screening (such as anxiety, labeling, and effects on quality of life), and harms associated with liver biopsy (including death, bleeding, and severe pain).

We restricted inclusion to English-language articles and excluded studies published only as abstracts. We excluded studies of posttransplant patients, HIV-infected patients, patients undergoing hemodialysis, and persons with occupational exposures, in whom screening and treatment considerations may differ from those in the general population (29 - 33).

Data Abstraction and Quality Rating

One investigator abstracted details about the study design, patient population, setting, interventions, analysis, follow-up, and results. A second investigator reviewed data for accuracy. Two investigators independently applied predefined criteria (34 - 36) to assess the quality of each study as good, fair, or poor. Discrepancies were resolved through a consensus process.

Data Synthesis

For studies reporting the diagnostic yield of different screening strategies, we computed the number needed to screen to identify 1 case of HCV infection by dividing the number of screening tests performed by the number of HCV cases identified. The proportion screened was the number of patients screened upon application of a particular screening strategy, divided by the total number of patients assessed.

We assessed the overall strength of each body of evidence as “high,” “moderate,” “low,” or “insufficient” in accordance with the AHRQ “Methods Guide for Effectiveness and Comparative Effectiveness Reviews” (37), based on the quality of studies, consistency between studies, precision of estimates, and directness of evidence.

Role of the Funding Source

This research was funded by AHRQ's Effective Health Care Program. Investigators worked with AHRQ staff to develop and refine the scope, analytic framework, and key questions. AHRQ staff had no role in study selection, quality assessment, synthesis, or development of conclusions. AHRQ staff provided project oversight, distributed the draft report for peer review, and reviewed the draft report and manuscript. The investigators are solely responsible for the content of the manuscript and the decision to submit for publication.

Results

The Appendix Figure shows the results of the search and study selection process. No study compared clinical outcomes between individuals screened and not screened for HCV infection or between individuals screened by using different risk- or prevalence-based strategies.

Yield of Risk-Based Screening Methods

Four cross-sectional studies (samples sizes ranging from 985 to 3367) provided data to calculate the diagnostic accuracy and yield of alternative HCV screening criteria (Table 1) (38 - 41). Two studies evaluated patients attending sexually transmitted disease clinics (38,41) and 2 evaluated patients attending urban primary care clinics (39 - 40). Three studies evaluated higher-prevalence populations (HCV prevalence, 4.6% to 8.3%) (38 - 40) and 1 a lower-prevalence population (HCV prevalence, 1.0%) (41). One study of patients in primary care and gastroenterology clinics (n

= 429) also evaluated alternative screening criteria but used a case–control design (42). All of the studies applied and evaluated alternative screening criteria retrospectively. Other limitations of the studies were that high proportions of potentially eligible patients were not included in analyses because of unknown HCV status or that the study did not report the proportion with unknown HCV status. Although the studies used different criteria for targeted screening, several factors (a personal history of injection drug use, sexual intercourse with an injection drug user, and pre-1992 blood transfusion) were consistently used across studies to identify higher-risk individuals.

One cross-sectional study of a lower-prevalence population in a Dutch sexually transmitted disease clinic (n = 985; HCV seroprevalence, 1%) found that screening based on presence of 1 or more positive items on a 20-item questionnaire was associated with a sensitivity of 90% for identifying persons with HCV infection and a number needed to screen to identify 1 case of HCV infection of 2.4 (Table 2) (41).

Three cross-sectional studies in higher-prevalence populations found that screening strategies targeting multiple risk factors were associated with sensitivities of more than 90% and numbers needed to screen of 9.3 to 18 (Table 2) (38 - 40). One cross-sectional study in a sexually transmitted disease clinic (n = 3367; HCV seroprevalence, 4.9%) found that screening patients with 1 of 5 risk factors (injection drug user, sex partners of injection drug user, received a pre-1992 blood transfusion, bacterial sexually transmitted disease in last 5 years, or age ≥30 years) would have resulted in testing 63% of clinic attendees, with a sensitivity of 97% for identifying HCV infection and a number needed to screen of 13 (38). One study of patients in an inner-city primary care clinic (n = 1000; HCV seroprevalence, 8.3%) found that screening patients with positive findings in at least 1 of 3 domains (medical history, exposure history, or social history) would have resulted in screening 71% of the population, with a sensitivity of 92% and a number needed to screen of 9.3 (39). A study of U.S. veterans (n = 2263; HCV seroprevalence, 4.6%) found that screening patients according to presence of 1 or more of 5 risk factors (Vietnam-era veteran, tattoo/body piercing, blood transfusion before 1992, abnormal liver enzyme levels, past or present injection drug use) would have resulted in screening of 78% of the population compared with screening based on the presence of these or 6 additional risk factors (multiple sexual contacts, intemperate alcohol use, intranasal cocaine use, blood exposure [mucous membranes], unexplained liver disease, hemodialysis), with a sensitivity of 97% and number needed to screen of 18 (40).

More narrowly targeted screening strategies evaluated in these studies were associated with specificities of more than 95% and numbers needed to screen of less than 2, but missed up to two thirds of infected patients (38 - 40). Two studies found screening only injection drug users would have resulted in testing of 3.0% or 5.8% of the population, with sensitivities of 41% and 60%, and numbers needed to screen of 1.6 and 1.9, respectively (38,40). One study found screening patients with positive findings in 3 domains (medical, exposure, or social history) would have resulted in testing of 5.6% of the population, with a sensitivity of 34% and number needed to screen of 2.0 (39).

A case–control study (222 cases) found screening based on presence of 4 or more of 7 risk factors (self-reported history of sex with a prostitute, history of exposure to potentially infected blood transfusion, rejections as a blood donor, refused life insurance, witnessed use of injecting drugs, sexual intercourse with an injection drug user, or self-reported hepatitis B virus infection) would have identified 24% of HCV-infected persons, with a specificity of nearly 100% (203 of 204) (42). Screening patients with 1 or more risk factors would have identified 94% of infected persons, with a specificity of 35%.

The 2004 USPSTF review (21) included a post hoc analysis of National Hepatitis Screening Survey data that found that screening using 1 of 3 risk factor models would have identified 53% to 69% of HCV-infected persons (43).

Potential Harms Associated With Screening

Three studies (n = 15 to 161) found diagnosis of HCV infection associated with some negative effects on psychological status, strain on spousal relationships, or binge drinking, but these studies had important shortcomings, including no control group of HCV-infected persons unaware of their status, reliance on retrospective recall, and poorly defined outcomes (44 - 46). A small, fair-quality cross-sectional study (n = 34) included in the 2004 USPSTF review found that HCV-infected intravenous drug users aware of their status reported worse quality of life than those who were unaware (47) of their status.

One study of percutaneous liver biopsies (n = 2740) in HCV-infected patients with compensated cirrhosis and at least moderate fibrosis reported a 1.1% rate of serious adverse events, most commonly bleeding or severe pain, with no deaths (48). Two other small studies (n = 126 and n = 166) included in the 2004 USPSTF review reported no episodes of bleeding, perforation, or death after percutaneous liver biopsy in HCV-infected persons (49 - 50).

In patients undergoing liver biopsy for various indications, large series (n = 1398 to 61 184) published since 2004 reported periprocedural mortality rates of 0% to 0.2% and major complications (primarily bleeding) in 0.3% to 1.0% (51 - 55), consistent with studies included in the 2004 USPSTF review (56 - 62).

Discussion

The evidence reviewed in this report is summarized in Table 3. As in the 2004 USPSTF review (21), we found no direct evidence on effects of HCV screening versus no screening on clinical outcomes, or on the comparison of clinical effects of alternative screening strategies. Retrospective studies found that screening strategies targeting multiple risk factors were associated with sensitivities exceeding 90% and numbers needed to screen to identify 1 case of HCV infection of less than 20 (38 - 41). More narrowly targeted alternative screening strategies (such as screening only persons with a history of injection drug use) were associated with numbers needed to screen of less than 2, but they missed up to two thirds of infected patients.

Although direct harms of screening seem minimal, such harms as labeling, anxiety, and stigmatization remain poorly studied and difficult to quantify (63 - 65). Harms of biopsy include a risk for death of less than 0.2% and serious complications (primarily bleeding and severe pain) in about 1% (48,51 - 55). As detailed in our full report, noninvasive tests have fair to good accuracy for diagnosing fibrosis and good to excellent accuracy for diagnosing cirrhosis compared with liver biopsy (26). Although clinical practice has evolved toward less routine use of liver biopsy before antiviral therapy and the proportion of HCV-infected patients undergoing liver biopsy has decreased overall, no study reported the proportion of screen-detected patients who undergo biopsy. Thus, it is difficult to determine the magnitude of harms associated with liver biopsy subsequent to screening.

In the absence of direct evidence on clinical outcomes associated with screening, an indirect chain of evidence showing the availability of accurate diagnostic tests and effective treatments could link screening with improvements in clinical outcomes. The 2004 USPSTF review found HCV antibody testing to be highly accurate (21). Much of the benefits from screening are likely to be based on the effectiveness of antiviral treatments, including newly approved direct-acting antiviral agents, which are addressed in a separate review (27). Therefore, screening recommendations should be based on the evidence for screening and treatment in totality (27). Studies showing that screening or subsequent interventions are associated with decreased transmission risk could also significantly affect estimates of potential benefits, but these are not yet available (26).

Our study has limitations. We excluded non–English-language articles, which could result in language bias, although we identified no non–English-language studies that would have met inclusion criteria. We could not formally assess for publication bias because of small numbers of studies. We also excluded modeling studies, which might be informative for understanding benefits and harms of screening, given the challenges in conducting the large, long-term studies needed to assess clinical outcomes associated with screening. Available evidence regarding screening yield is derived from a few retrospective studies. High or unreported proportions of potentially eligible patients in these observational studies were not included in calculations of screening yield because of unknown HCV status.

The CDC recently recommended that all persons born between 1945 and 1965 be screened for HCV infection, in addition to persons with risk factors for HCV infection (25). The CDC based its recommendation on the prevalence of patients with HCV infection in this birth cohort (accounting for about three quarters of patients with HCV infection in the United States), the high proportion of patients with undiagnosed HCV infection, projected disease burden after several decades of infection, and estimated benefits from antiviral treatments. Although cost-effectiveness analyses suggest that the birth cohort screening approach is highly cost-effective, no clinical data are yet available (13). The CDC's birth cohort approach was not evaluated in the studies included in our review on the yield of alternative screening strategies. Clinical studies that prospectively evaluate the accuracy, yield, and outcomes of alternative HCV screening strategies, including the birth cohort approach, are needed.

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Primaquine Protects Against P. vivax Malaria Relapse

Reuters Health Information
Lorraine L. Janeczko
2 January 2013

Primaquine combined with newer non-chloroquine antimalarials killed dormant Plasmodium vivax parasites and prevented malaria relapse in a recent study of Indonesian soldiers.

"The results of our study came as a rather pleasant surprise," said study designer and technical adviser Dr. J. Kevin Baird of the Center for Tropical Medicine of the University of Oxford in the U.K.

"Primaquine has been in continuous use for sixty years as the only treatment option for vivax malaria relapse, and this study provides the first relatively unambiguous estimate that it offers good efficacy when combined with dihydroartemisinin and piperaquine for radical cure of vivax malaria," Dr. Baird told Reuters Health by email.

The only licensed therapy against relapse is primaquine plus chloroquine for the primary attack. But worsening chloroquine resistance threatens this 60-year-old treatment, he and his colleagues said in a paper online December 17 in Antimicrobial Agents and Chemotherapy.

"Preventing multiple relapses of vivax malaria, an often pernicious and life-threatening infection, is a crucial clinical and public health issue. The 80% relapse rate in this study among the controls not treated with primaquine clearly emphasizes the health benefits of administering primaquine safely and effectively and the consequences of not doing so," Dr. Baird said.

The research team enrolled 116 soldiers with acute P. vivax malaria contracted in Papua, Indonesia. The soldiers -- men ages 22 to 42, weighing 52 to 90 kg, with similar parasitemias, vital signs and blood laboratory values -- were randomly assigned to one of three treatments in the open-label trial.

They received either artesunate (a 200-mg dose followed by 100 mg/day for six days); or quinine (1.8 g/day for seven days) plus primaquine (30 mg/day for 14 days); or dihydroartemisinin (120mg) plus piperaquine (960mg) daily for three days followed 25 days later by primaquine (30 mg/day for 14 days).

After 12 months, 113 patients were analyzed.

The relapse rate was 78% with artesunate alone (32 of 41 subjects had 2.71 attacks/person-year); 19% with quinine plus primaquine (seven of 36 patients had 0.23 attacks/person-year); and 6% with dihydroartemisinin-piperaquine plus primaquine (two of 36 patients had 0.06 attacks/person-year).

The efficacy against relapse was 92% for quinine plus primaquine and 98% for dihydroartemisinin-piperaquine plus primaquine, the researchers say.

Adverse events included appendicitis, colitis, and trauma.

Dr. Nirbhay Kumar, professor and chair of tropical medicine of the Tulane University School of Public Health and Tropical Medicine in New Orleans, Louisiana, noted in an email to Reuters Health that World Health Organization guidelines specifically recommend primaquine for vivax malaria and malaria relapse. (The WHO guidelines can be downloaded from http://bit.ly/UJrebW.)

"However, it is important to screen patients for glucose-6-phosphate dehydrogenase (G6PD) deficiency to avoid the risk of hemolytic anemia," said Dr. Kumar, who was not involved in the study.

Dr. Baird agreed. "Unfortunately, the hemolytic toxicity of primaquine in patients with G6PD deficiency remains a serious problem for the vast majority of people exposed to this infection," he said. The drug can't be used in pregnant women and young children, he added.

Dr. Kumar added that now the research needs to be repeated in different geographic areas, perhaps studying primaquine doses and regimens, and that, "if found effective elsewhere, this treatment could play a significant role in dealing with P. vivax relapses."

Dr. David Sullivan, of the Malaria Research Institute of Johns Hopkins Bloomberg School of Public Health, said, "drugs that are active but do not cause extravascular hemolysis are a promising research area."

The authors note that P. vivax malaria threatens several billion people living and visiting in endemic zones.

This study received financial support from the Medicines for Malaria Venture Geneva to the ALERTAsia Foundation in Jakarta and Sigma Tau in Italy. Dr. Baird was also supported by a grant from the Wellcome Trust in the United Kingdom.

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Malignant Pericardial Effusion and Pericardial Tumor Involvement Secondary to Cervical Cancer

Military Medicine
Maj Robert M. Ore, USAF MC; Maj Beverly G. Reed, USAF MC; Lt Col Charles A. Leath, III, USAF MC
January 2013

Abstract

Background

Antemortem discovery of a malignant pericardial effusion secondary to cervical cancer is uncommon and management should focus on symptom control.

Case

A patient was diagnosed with widely metastatic cervical cancer following a simple hysterectomy for presumed benign etiology. Sixteen months later, she was diagnosed with pericardial tumor involvement and a malignant pericardial effusion resulting in severe dyspnea. The patient underwent a pericardial window procedure that temporarily alleviated her symptoms. She again developed symptoms 2 weeks following the procedure and ultimately elected supportive care.

Conclusion

Malignant pericardial effusion is a challenging clinical scenario. Although multiple treatment options exist, prognosis is poor and usually limited.

Introduction

Cervical cancer remains a fairly uncommon malignancy in industrialized countries secondary to the presence of robust screening programs. Moreover, most patients in industrialized countries present with early stage disease, which is amenable to curative therapy with either surgery or radiation with or without chemotherapy. For patients with widely metastatic disease, curative therapy does not exist, nor is it an option in patients with distant recurrent disease. We present an unusual case of a patient presenting with a malignant pericardial effusion in the setting of distant metastatic cervical cancer.

Case

A multiparous Hispanic female in her fifth decade with progressive, advanced stage cervical cancer was transferred to our hospital for management of recurrent dyspnea. Two weeks before transfer, she had undergone pericardiocentesis, subxiphoid pericardiostomy (pericardial window procedure), and pericardial biopsy (Fig. 1) for a malignant pericardial effusion with evacuation of 400 cc of malignant fluid for cardiac tamponade. Confirmatory immunohistochemical staining was performed with a variety of markers and was positive for CK-7, P-16, and MOC-31, whereas negative for CK-20, Calretinin, WT-1, TTF-1, S-100, and CEA. Figure 2depicts representative positive immunohistochemical staining.

She complained of dyspnea without chest pain and initial evaluation noted tachycardia, pulse between 110 and 120 beats per minute, intermittent low systolic (range: 50–90 mm Hg) and diastolic blood pressures (range: 44–62 mm Hg), and tachypnea in the upper 20s. Review of systems was pertinent for three-pillow orthopnea, a nonproductive cough and anxiety. Physical examination revealed distant heart sounds, jugular venous distension, and pulsus paradoxus measured at 21 mm Hg. Baseline laboratory values were remarkable for anemia with hemoglobin of 8.5 g/dL. Echocardiography demonstrated mitral and tricuspid inflow, and increased transthoracic velocity secondary to increased transvalvular flow with respiratory variation consistent with tamponade physiology.

Her oncologic history began at an outside facility 16 months before the current evaluation with a complaint of menorrhagia without anemia. Her most recent Pap test, at least 2 years before presentation, was reported normal; she denied a history of abnormal Pap test results and reported being sexually abstinent for the previous 6 years. Pelvic examination revealed a dilated cervix with an apparent prolapsing anterior uterine myoma. As the lesion was not thought amenable to a myomectomy, she underwent a transvaginal hysterectomy and was discharged to home the day following surgery. Pathology demonstrated a poorly differentiated squamous cell carcinoma at least 4.5 cm in greatest dimension with extensive lymphovascular space invasion in addition to parametrial involvement. Postoperative computed tomography (CT) revealed suspicious pelvic, para-aortic, and supraclavicular lymphadenopathy. Combined positron emission tomography/CT imaging was obtained and demonstrated hypermetabolic activity in the noted nodal groups. Biopsy of the supraclavicular nodal disease revealed metastatic squamous cell carcinoma.

Secondary to the presence of incurable widely metastatic disease, she elected to proceed with tumor-directed radiation to her metastatic sites followed by systemic chemotherapy. Her therapy included directed radiation to her known metastasis in the supraclavicular, para-aortic, and pelvic nodal regions followed by the combination of six cycles of topotecan and cisplatin chemotherapy.

Approximately 9 months following her diagnosis, the patient noted a new onset persistent cough and CT demonstrated the presence of new mediastinal lymphadenopathy, in addition to suspicious nodal involvement in the left axillary, cervical neck, and left inguinal regions. She was in the process of enrolling in a phase I clinical trial, in a potential attempt to palliate symptoms as they arose, when diagnosed with her pericardial effusion. Figure 3 depicts axial chest CT images with intravenous contrast performed at her current admission and 2 weeks following her pericardial window procedure. Although repeat surgical procedures to manage the effusion were considered, the rapid tumor progression and reaccumulation of effusion suggested a low likelihood of durable relief. The patient elected for palliative care with home hospice and died 1 week after discharge, or 26 days following her pericardial window procedure.

Discussion

Metastasis of cervical cancer to the pericardium is a rare event with limited discussion in the medical literature, especially in terms of making an antemortem diagnosis. Jamshed et al summarized many contemporary approaches to malignant pericardial effusion management in their review of six patients previously reported in the literature. Although different modalities have been described to mitigate the tamponade physiology occurring with pericardial effusion,3–5 the initial goal of all approaches is to restore cardiac output. Moreover, there are a number of options for subsequent management, generally focused upon preventing fluid reaccumulation. Although the optimal modality in recurrent cervical cancer remains unknown, different therapeutic approaches have demonstrated success with pericardial effusions and metastases associated with other malignancies.

Tsang et al reported on one of the largest series evaluating the management of malignant pericardial effusions. Their series covered approximately 20 years and included 275 patients with a confirmed diagnosis of malignancy. Although the median survival for this group of patients was 135 days, the presence of cytology positive for malignant cells and clinical presentation of tamponade were predictive of poorer survival. Although not attempted in our case, tetracycline or doxycycline as a sclerosing agent has been reported in nearly 100 patients with malignant pericardial effusions. Although the median survival was reported at only 98 days, 73% of their patients were reported to have symptomatic control for greater than 30 days.

For patients that undergo a simple hysterectomy for early stage cervical cancer, additional therapy with either a radical parametrectomy or a whole pelvic radiotherapy is often recommended. It remains incumbent upon providers to ensure that potential malignant diagnoses, such as cervical or endometrial cancer, are considered and evaluated in the setting of abnormal genital tract bleeding. Importantly, a diagnosis of either of these preoperatively would change the surgical approach for a patient. Unfortunately, with disease outside of the cervix and surrounding pelvic tissues, these options were not viable in our patient. Furthermore, in the current case, it is unlikely that primary chemoradiotherapy for her locally advanced cervical cancer would have been curative, although may have resulted in some durable disease control for the patient. Standard therapy for patients that present with distant cervical cancer, FIGO Stage IVB, generally consists of palliative chemotherapy, protocol therapy, or supportive

care.9 Commonly utilized regimens include combinations of paclitaxel and cisplatin, and topotecan and cisplatin although recent data question the superiority of one regimen over another.

The option utilized to manage our patient's pericardial effusion was a pericardial window procedure, where a drain path was created from the pericardium to the peritoneal cavity. The drain was removed once drainage subsided and the pericardial sac appeared dry. Alternatively, intrapericardial infusion of sclerosing agents (tetracycline, 5-fluorouracil, bleomycin, cisplatin, talc) may be considered. Intrapericardial instillation of cisplatin has been described as a successful long-term treatment for pericardial metastasis from adenocarcinoma of the parotid gland.6 Finally, external beam radiation has been utilized as a treatment option as well although generally its utilization is less common today than other modalities.

This case depicts an infrequent route of spread of cervical cancer. Although different modalities exist for the treatment of malignant effusion, their role and/or sequence in metastatic cervical cancer and with recurrent effusion remains unclear. Extensive counseling for both the patient and her family is important in order to set up realistic expectations in this clinically challenging scenario.

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Quality of Cancer Survivorship Care in the Military Health System (TRICARE)

The Cancer Journal
Fox JP, Jeffrey DD, Williams TV, Gross CP
January 2013

Purpose

Following the acute phase of treatment, national guidelines recommend cancer survivors have routine contact with health care providers and undergo basic ancillary testing while avoiding high-cost imaging (HCI). We conducted this study to determine how frequently breast, prostate, and colorectal cancer survivors received recommended follow-up care and HCI tests during the survivorship period.

Methods

Using administrative data from TRICARE beneficiaries, we identified a cohort of patients who were treated for breast, prostate, or colorectal cancer between October 2005 and March 2007. These patients were then followed through September 2010. During the 3 years after initial treatment, we determined how frequently survivors received all minimum recommended survivorship care as defined by national guidelines and underwent HCI tests and if these outcomes varied by geographic region.

Results

Overall, 3148 patients underwent treatment for breast (n = 1630), prostate (n = 1173), or colorectal (n = 345) cancer. Sixty-five percent received all minimum recommended care over 3 years (breast = 74.1%, prostate = 65.3%, colorectal = 25.5%). During the 3-year period, 74.1% of breast cancer survivors received a mammogram each year, whereas 69.1% of colorectal cancer survivors had at least 1 colonoscopy. Sixty-four percent had at least 1 HCI study during the 3-year period (positron emission tomography = 10.9%, computer tomography = 48.8%, magnetic resonance imaging = 36.6%) at a cost of $3.5 million. Substantial state-level variation was noted for both outcomes.

Discussion

Some cancer survivors do not receive recommended care following initial treatment while frequently undergoing HCI. The existing geographic variation in quality and imaging utilization suggests that improvements to cancer survivorship care are possible.

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Medical Protocol and Training

Recommendations for Biomonitoring of Emergency Responders: Focus on Occupational Health Investigations and Occupational Health Research

Military Medicine
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January 2013

ABSTRACT

The disaster environment frequently presents rapidly evolving and unpredictable hazardous exposures to emergency responders. Improved estimates of exposure and effect from biomonitoring can be used to assess exposure–response relationships, potential health consequences, and effectiveness of control measures. Disaster settings, however, pose significant challenges for biomonitoring. A decision process for determining when to conduct biomonitoring during and following disasters was developed. Separate but overlapping decision processes were developed for biomonitoring performed as part of occupational health investigations that directly benefit emergency responders in the short term and for biomonitoring intended to support research studies. Two categories of factors critical to the decision process for biomonitoring were identified: Is biomonitoring appropriate for the intended purpose and is biomonitoring feasible under the circumstances of the emergency response? Factors within these categories include information needs, relevance, interpretability, ethics, methodology, and logistics. Biomonitoring of emergency responders can be a valuable tool for exposure and risk assessment. Information needs, relevance, and interpretability will largely determine if biomonitoring is appropriate; logistical factors will largely determine if biomonitoring is feasible. The decision process should be formalized and may benefit from advance planning.

INTRODUCTION

The disaster setting presents many challenges for protecting emergency responders, including prioritizing critical response activities, having limited access to incident leadership, marshaling necessary resources quickly and having timely situational awareness of important occupational safety and health events. The environment and conditions can be dynamic, frequently hazardous, and highly charged with competing demands, political pressures, and often with conflicting response strategies. The dynamic aspect of an emergency response may include fluctuations and changes in hazards and exposures. Protecting the health and safety of the emergency responders throughout all phases of an emergency response (i.e., preparedness, response, mitigation, and recovery) is an important component of any response. Exposure and risk assessment are critical activities in protecting the health and safety of emergency responders. As part of these assessments, questions about the need for biomonitoring often arise in disaster response.

Occupational health investigations in disaster settings focus strictly on the health and safety of the emergency responders and are under the control of the Incident Command. During disasters, the goal is to provide rapid, useful, and actionable information that will have a direct impact on the health and safety of emergency responders involved in response and recovery activities. These investigations are intended to determine the scope and burden of work activities, exposures, and risks, so that prevention can be implemented and determination of short- and long-term risk to emergency responders can be made. Occupational health investigations may involve site-specific investigations to assess individual or group exposure and health effects and may involve descriptive, analytic, applied, or exposure/disease-specific epidemiology. Occupational health investigations differ from clinical care in that health investigations are conducted when there is a concern about a workplace hazard. These investigations may evaluate an exposure or a health concern and are not necessarily conducted by clinicians, a physician–patient relationship is not necessarily established, and clinical care is not necessarily being provided. Biomonitoring may be used to evaluate an exposure or health concern and may or may not be diagnostic in nature. Occupational health investigations are also distinguished from occupational health research in this article.

Occupational health research related to disasters is intended to develop generalizable information[1] that addresses a specified scientific hypothesis or a set of hypotheses during or after a disaster. Hypotheses can be generated from health investigations, but also from data produced by surveillance and health monitoring or from information gaps identified in the published literature. This research may not provide immediate benefit to the emergency responders involved in the response or recovery, but may address important questions pertinent to future emergency response activities or risk assessments in general, such as potential health effects, exposure methodology, or exposure control strategies.

Exposure assessment is a critical component of occupational health investigations and occupational health research studies. Although this article generally focuses on chemical exposures, the framework could be applied to other types of exposure, including biological, physical, radiological, or psychological stressors. Chemicals can be measured in samples collected from various environmental media (i.e., air, water, or surfaces) to predict personal exposure. However, in some cases, the only way to evaluate personal exposure is to identify which chemicals have been absorbed into the body, the magnitude of chemicals absorbed, and their contribution to total body burden. This can sometimes be accomplished through the use of biomarkers. Biomarkers have been defined by the National Academy of Sciences as measurable indicators in a biological system or organism, such as the presence of a chemical or its metabolite within biological specimens, measured alterations in structure or

function, or identifiable genetic variations. Three categories of biomarkers have been identified: exposure, effect, and susceptibility. Some overlap in these categories is possible. For the most part, biomarkers of exposure provide a measure of body burden of a contaminant or its metabolite. Examples of biomarkers of exposure include blood lead, urinary cadmium, and serum dioxin.

Biomarkers of effect (also known as biomarkers of response) measure effects or responses in the body to an exposure. These changes may be early precursors of disease, specific clinical changes, or markers for clinical disease. An example of biomarkers of effect is the decline of blood levels of the enzyme acetyl cholinesterase (AChE) in persons exposed to organophosphate pesticides. The results of biomonitoring of blood AChE levels can be used to determine possible illness and treatment implications. Biomarkers of effect tend to be less specific than exposure markers, as a number of chemicals or agents may cause similar responses. For example, measuring blood AChE levels provides evidence of exposure to organophosphate pesticides, but does not identify the precise pesticide responsible for the decrease in blood enzyme.

Biomarkers of susceptibility indicate when an individual may be at increased or decreased risk for developing a disease after an exposure has occurred. Susceptibility biomarkers may also identify individuals whose body burden may be increased or decreased relative to other individuals because of differences in metabolic or other biological processes. Biomarkers of susceptibility, for example, could include the activity of the Cytochrome P450 2E1 (CYP2E1) enzyme as determined by genotyping studies that modify benzene toxicity. Other factors also affect risk including lifestyle, genetics, health status, and diet.

This article limits the discussion of biomonitoring to the emergency response context. All three categories of biomarkers are likely to be used in disaster research studies. However, for occupational health investigations, some types of biomarkers have more utility than others. For example, susceptibility biomarkers are unlikely to be monitored in an initial emergency response unless there are predeployment evaluations of emergency responders. This type of biomarker has more utility in research studies to determine risk factors for potential health outcomes. Biomarkers of exposure would have the most utility in occupational health investigations as these markers measure body burden, whereas biomarkers of effect would be most useful when associated with a known health outcome.

A number of benefits may arise from conducting biomonitoring in an emergency response.

Although most workplace exposures can be anticipated based on process or job conditions, emergency response often involves unexpected or unpredictable exposures making exposure and risk assessments difficult. Biomonitoring can augment environmental exposure assessment methods, such as personal breathing-zone air monitoring and surface sampling, and may determine the usefulness of these methods as surrogates for capturing the individual burden of exposure. If a substance has a sufficiently long half-life, biomonitoring can be used to estimate cumulative dose after repeated exposures and can help characterize the contribution from multiple exposure routes (e.g., inhalation and dermal). Sampling of environmental media focuses on a single route.

Biomonitoring can be especially useful for assessing dermal exposure because (1) skin sampling methods are not readily available for many chemicals, (2) criteria or standards for comparison are not generally available, and (3) results do not provide information regarding the amount of

chemical absorbed through the skin. Biomonitoring may also be useful in assessing the biological effects from breach or improper use of personal protective equipment (PPE) and may allow for comparing exposure/doses associated with different work practices.

Limitations related to interpretation of results, communication, logistics, and method availability need to be considered. Exposures may not be specific to the incident, so attribution of body burden to the disaster may not always be possible. Because the presence of a chemical in the body does not necessarily indicate harm, results must be interpreted and communicated with care. Implementation of biomonitoring is contingent on successfully anticipating and fulfilling a variety of requirements, such as ensuring the protection of human subjects (including Institutional Review Board [IRB] approval), consideration of ethical issues, and obtaining other organizational approvals. Failure to anticipate these requirements can impair the ability to carry out the project, particularly when collection of biomonitoring specimens is time-sensitive.

The purpose of this article is to provide a decision framework on when to perform biomonitoring in an emergency response, either as part of a health investigation or for research purposes. Both the appropriateness and feasibility of biomonitoring during a disaster are key factors in the decision process and will be discussed in detail.

METHODS

Upon review of the response related to the Deepwater Horizon oil release, the National Institute for Occupational Safety and Health (NIOSH) identified multiple processes that could be improved to better ensure the safety and health of emergency responders, while still maintaining an effective and efficient response. A chief concern was the need for a systematic decision-making process to determine when biomonitoring should be initiated, both within the context of an occupational health investigation and for research initiatives.

In response to this need, the NIOSH director convened a work group consisting of NIOSH scientists experienced with disaster response, biological monitoring, and risk assessment, representing the disciplines of toxicology, occupational medicine, and industrial hygiene. Drawing on direct experience from multiple large emergency/disaster responses, including terrorist attacks of September 11, 2001, anthrax events, severe acute respiratory syndrome, Hurricane Katrina, the H1N1 pandemic, and the Deepwater Horizon oil release, the work group collaborated to devise a comprehensive rationale for determining when to conduct biomonitoring in workers responding to a disaster.

An extensive literature search on biomonitoring during disaster/emergency response was performed in Medline (Ovid), Embase (Ovid), Health and Safety Science Abstracts, TOXLINE, Web of Science and OSH References Collection for articles between 2001 and 2011. Major search terms included, but were not limited to, chemical incident or disaster, emergency response, emergency responder, disaster planning, emergencies, biomonitoring, biomarker, and biological marker.

RESULTS

Use of Biomonitoring for Emergency Response: A Decision Process

Biomonitoring often provides valuable information not available through other means. However, certain factors must be considered when evaluating biomonitoring proposals in the disaster/emergency response setting and the importance of these factors varies depending on the purpose of the biomonitoring. Numerous practical and scientific challenges must be considered when evaluating whether biomonitoring can provide information in an emergency response setting that is unattainable by other means. As noted above, the goal of biomonitoring during an emergency response investigation is to provide actionable information that will have a direct impact on the health and safety of current emergency responders. A decision process was designed to provide occupational health and medical experts with a well-defined, logical framework for determining if biomonitoring should be conducted during an emergency response. The issues or factors within the decision process are categorized under two broad questions: (1) Is biomonitoring appropriate? and (2) Is biomonitoring feasible? Under each question are factors or issues to consider in determining if biomonitoring should be conducted.

Is Biomonitoring Appropriate?

Do Information Gaps Exist That Biomonitoring Can Address?

In disasters, information gaps should first be assessed to determine whether they are amenable to biomonitoring. If the information gap is related to work-site exposure, biomonitoring might provide direct and unambiguous demonstration of exposure, which could only be inferred by alternative monitoring methods. For example, an emergency response worker with considerable dermal exposure to a compound with low vapor pressure should be considered for biomonitoring because other methods of determining exposure will not provide useful exposure information for the individual. Biomonitoring is of particular importance when exposures occur through multiple routes (e.g., dermal and inhalation).

Biomonitoring also could improve decision-making about exposure controls, including the requirements for PPE, as well as remediation strategies. In other instances, biomonitoring may be used to evaluate the efficacy of initial control measures or PPE recommendations. At times, biomonitoring may be the only effective means of determining whether PPE or engineering controls are performing as expected. During the anthrax attacks in 2001, an immunochemical test for anthrax exposure was developed. This biomonitoring test was used to determine if remediation workers who took the anthrax vaccine were immunized and if PPE worn by unvaccinated remediation workers was sufficient.

A key use of biomonitoring is to determine health risks at the individual and group levels. However, the ability to detect chemicals by biomonitoring has outpaced the ability to predict health risks based on their measured concentrations. Where the information gap is related to potential future data interpretation, biomonitoring could provide important baseline exposure or effect information needed to assess future exposure or health data. For example, biomonitoring before exposure and postexposure may be able to establish whether exposure has occurred and whether health monitoring should be conducted postevent to evaluate potential long-term effects.

Will Biomonitoring Provide Information Directly Applicable to Emergency Responders/Remediation Workers Involved in the Ongoing Response?

This second consideration pertains directly to conducting occupational health investigations. It is important to determine whether information derived from biomonitoring would likely have a direct and immediate impact on the health and safety policies and procedures of an ongoing emergency response. This determination must consider whether the proposed biomonitoring activity will primarily support an investigation that will

yield timely information related to current actions to protect emergency responders as opposed to a research study which would assess health impacts and actions to inform future emergency responses.

Given that biomonitoring in health investigations should directly impact emergency responders, it is possible to anticipate some of the health and safety issues likely to develop during a response that could be addressed by biomonitoring. Such issues include:

— Determining if a hazardous exposure (exposure of concern) has occurred or providing assurance if no significant exposures are occurring

— Quantifying exposure from all sources and routes (integrated exposure)

— Assessing the possibility of unanticipated health effects

— Clarifying the results of clinical testing

— Determining the adequacy of PPE and other control measures

— Clarifying whether a health effect may be related to an occupational exposure

— Using data for health monitoring or surveillance

These issues also can directly impact the safety and health policies and procedures for a given event. If a given body burden is associated with health effects, measures may need to be implemented to reduce or monitor exposures. Actions would include engineering controls, changes in work practices, use or changes in PPE, other administrative controls (i.e., temporary removal of worker) or increased frequency of health monitoring and/or health surveillance.

As an example of using biomonitoring during an emergency response, firefighters were called to the scene of a manufacturing facility because of an ill employee and concerns of a gas leak in the building. Environmental monitoring instruments found elevated carbon monoxide (CO) levels, but could not identify the CO source. After evacuation of employees, firefighters quickly assessed the carboxyhemoglobin levels of employees through CO pulse co-oximetry, and questioned them on their principal location in the plant that day. Employee location and carboxyhemoglobin results were mapped out, which then allowed firefighters to identify the CO source and implement mitigation measures.

Will Biomonitoring Provide Interpretable Results?

This third criterion is also most appropriately applied to occupational health investigations, as biomonitoring for research purposes may include biomarkers that are still being explored for their relationship to a health outcome. When conducting biomonitoring during an occupational health investigation, results of the biomonitoring should provide interpretable information relevant to the emergency responders, and have the potential to lead to control measures that could reduce exposure risk and improve emergency responder health.

For most chemicals of concern, health-based biomonitoring criteria do not exist. This leads to the question of interpretability or usefulness of results. A limited number of workplace exposure criteria based on toxicity or on health outcome or exposure levels have been calculated. For example, Biological Exposure Indices have been determined for some chemicals by the American Conference of Governmental Industrial Hygienists. The German Commission has developed biological tolerance values, known as biologischer arbeitsstoff-toleranz-wert. For certain chemicals, such as lead, cadmium, mercury, and CO, regulatory health-based action levels exist and are related to specific urinary or blood values associated with well-defined toxicity endpoints. Under the European Registration, Evaluation and Authorisation and Restriction of Chemicals Program, establishment of derived, no-effect levels are an important component. The concept of Biomonitoring Equivalents that represent safe or acceptable levels has also been recently developed using established reference values and toxicokinetic data. Guidelines on risk communication issues related to Biomonitoring Equivalents have also been developed; these include issues related to confidence and uncertainties associated with the risk assessment. Scheepers et al defined levels of concern to be equivalent to Acute Exposure Guideline Level-2 to ensure that detected exposures were higher than background or occupational settings. In many chemical emergencies, exposures of concern are several fold higher than occupational exposure limits and usually exceed short-term exposure limits or immediately dangerous to life or health values.

Because biological exposure guidelines or standards have been set for so few chemicals, most often during an occupational health investigation no action levels or occupational exposure limit-based biological indices exist. Although the absence of specific standards or criteria increases the uncertainty as to the meaning of biomonitoring results, other approaches can be used to interpret or place biomonitoring results into context. For example, reference values (i.e., levels of certain chemicals within a defined “reference” group) may be helpful in interpreting the measured biomarker levels. Reference values may be obtained from sources such as the Centers for Disease Control and Prevention, National Health and Nutrition Examination Survey Program, and published research studies. A limitation of using reference values is that levels found in a population from a specific geographic location do not necessarily represent levels in the underlying population from which the emergency responders were drawn. In addition, certain chemicals are likely to be detected in biological samples from nearly all people attributable to ubiquitous dietary and/or environmental sources (i.e., background levels). These background levels need to be taken into consideration when interpreting biomonitoring data. Animal and human toxicity values found in the published literature may also be considered when biomonitoring criteria or reference values are unavailable. Often, information about no observed adverse effect levels (NOAELs) or lowest observed adverse effect levels (LOAELs) are available. NOAEL and LOAEL values, along with acute toxicity and pharmacokinetic data, can be used to interpret biological monitoring data.

Conducting biomonitoring in an emergency response setting without biomonitoring interpretation criteria can be a complicating factor requiring expertise in biomonitoring and risk assessment communication. Conducting such risk assessments during the urgency of a response poses the possibility of developing a less detailed appraisal about the quality of the available literature, the applicability of health endpoints, etc., and therefore could be harder to defend in a politically charged atmosphere. Such risk assessments might therefore be preferably conducted in the context of a research study, where more in-depth consideration can be given to the complexities and interpretability of the biomarker in question.

Have Ethical Issues Been Identified, Vetted, and Evaluated?

Ethical issues pertinent to biomonitoring in a research setting are also applicable to biomonitoring in a health investigation. The design of a biomonitoring study needs to take into account participant recruitment and informed consent. Privacy and confidentiality concerns need to be

addressed. Risks and benefits need to be explained. The strategy for data handling, data analysis, interpretation, communication, and dissemination of the biomonitoring results to affected workers, comparison groups, and others are all issues of concern. In an emergency response, additional concerns may arise, such as a desire for all emergency responders to be included in a particular biomonitoring study, when only specific and targeted emergency responders are the focus. For example, tasks that place certain workers at higher potential exposures are selected for biomonitoring instead of those selected at random.

Clinicians who are asked to participate in a biomonitoring program, particular as part of an occupational health investigation, also need to be cognizant of the risks of not adhering to professional standards of care in situations where biomonitoring methods are less well established. Considerations for participation in such biomonitoring activities may include whether the physician will have a physician–patient relationship and will be providing medical care to the patient as part of the overall biomonitoring effort.

Is Biomonitoring Feasible?

Is There is a Validated Method for Biomonitoring?

The availability of a validated method is especially important for occupational health investigations where time is critical. During an emergency response, it is unlikely that sufficient time will be available to develop a biomonitoring method for an occupational health investigation. Some published methods might be quickly put into place in a laboratory setting with little to no modification, assuming that the method has been validated for the intended analytical matrix (blood, urine, etc.). If a biomonitoring method is available, analytical parameters, such as limit of detection, specificity, sensitivity, accuracy, and precision, need to be evaluated in the context of the expected exposure to ensure that the method can detect the chemical at levels observed during the emergency. Often, the levels of exposure or potential interferences may not be known initially, but based on professional judgment, it may be possible to predict whether the selected biomonitoring method will have sufficient sensitivity and specificity for a biomarker of interest. It should be noted that a method being analytically valid does not presuppose that valid clinical information can be derived from the biomonitoring. When validated methods are not available, this may be the appropriate time to consider conducting biomonitoring research for the purpose of method development and validation.

Are There Significant Logistical Issues?

Health investigations and research can have similar logistical issues, although timeframes can differ in terms of funding acquisition, method development, and protocol development. Ideally, preplanning for emergency response activities should include the development of an exposure assessment protocol that considers the possibility of biomonitoring. Since not all exposures can be anticipated, the first step would be to modify the protocol to include the biomarker(s) of interest. The protocol would most likely need IRB approval and perhaps other organizational and Incident Command approvals. It may be possible in preplanning exercises to develop sections of the protocols to decrease the time needed for IRB approval. Political or legal implications may also need to be addressed, which could lead to delays in conducting biomonitoring.

Communicating Biomonitoring Efforts

Biomonitoring of emergency workers will require a risk communication component. Emergency response operations can include individuals with a variety of backgrounds, education levels, and languages. Furthermore, an emergency responder's ability to evaluate or recognize risk may be impaired, especially in stressful life-saving situations. Many principles of effective crisis and emergency risk communication, including simplicity, credibility, and tailoring of messages can be applied to appropriately inform emergency responders about biomonitoring efforts. When developing communications materials, it is important to address a number of issues, such as Why conducting biomonitoring is the correct decision, how investigators are collecting specimens, how investigators are ensuring privacy and confidentiality, how results will be used and by whom, and limitations of the biomonitoring and how those limitations apply to interpreting results and predicting future health outcomes. Communicating with emergency responders early can address their concerns, prevent rumors and misinformation, and improve the overall quality of the investigation. Considering the complexity of factors that affect results, significant attention should be given to the interpretation of findings. Emergency response environments are often chaotic and can sometimes span very large distances. Thus, it is important to develop strategies for disseminating information to emergency responders and maintaining contact with participants throughout the investigation. Pre-existing channels of communication developed as a part of the larger emergency response may provide effective means of distributing information and updates to the workers during the response.

DISCUSSION AND CONCLUSIONS

Our literature search identified few examples addressing specific considerations for biomonitoring in the emergency response setting. Most articles addressed the use of biomonitoring in the conduct of research. Notable examples were publications by the National Research Council and by Manno et al Of the 115 articles identified, only one publication by Scheepers et al attempted to develop a decision matrix for conducting biomonitoring during chemical releases. This article, primarily addressed general populations at risk, described a stepwise procedure that considered exposure, biomarkers and their half-lives, analytical methods, and feasibility of sampling times, but did not focus on the appropriateness of conducting biomonitoring for occupational health investigations directed at emergency responders. Another article described lessons-learned and recommendations from biomonitoring efforts initiated in the first Gulf War, Operation Desert Storm. The National Biodefense Safety Board, an advisory committee to the Assistant Secretary of Preparedness and Response within the U.S. Department of Health and Human Services, recently engaged on the topic of inclusion of scientific investigations as a component of disaster planning, but their report did not specifically address biomonitoring.

The approach in our article differs from the existing literature in that it focuses on biomonitoring of emergency responders and clearly delineates the differences in the decision process between health investigations and research studies. We further describe in detail the logistical and interpretability concerns of performing biomonitoring in the context of a disaster.

Items under each question may be considered in a stepwise manner or concurrently. Addressing these factors will help ensure a careful, measured approach to the conduct of biomonitoring. Conversely, inability to adequately address these factors suggests that biomonitoring needs to be reconsidered, or should not proceed, particularly for the health investigation context. In these situations, the project may alternatively proceed in a research context, with the understanding that the results may not be actionable for current emergency responders.

The use of biomonitoring in health investigations (as opposed to its use in research studies) calls for different approaches, goals, and time frames. To develop an optimal biomonitoring strategy, the formation of a working group by organizations coordinating the conduct of science in disaster response is recommended for both health investigations and research. This working group would operate in the emergency response preplanning stage and during actual emergencies, and would integrate into existing Incident Command Systems. It should include experts in occupational health/medicine, industrial hygiene, toxicology, biomonitoring, epidemiology, chemistry, laboratory science, communication, and other specialty areas, as needed. In the preplanning stage, the work group would develop a framework for biomonitoring protocols and informed consent documents, which would then necessitate only minor modifications to the basic protocol and would help minimize delays in seeking IRB approval. Once an emergency response begins, the work group would then evaluate the various factors with the objective of making a recommendation on whether to proceed with a biomonitoring effort. A recommendation would also be made on whether a potential biomonitoring effort should be conducted as part of a health investigation or research initiative context (or both). The work group will need to re-evaluate the need for biomonitoring as the response proceeds and more information becomes available. Logistical issues, such as those involved with collecting, shipping, and storing specimens could be considered as part of this decision process.

This decision process is designed to be used by occupational health and medical experts when considering biomonitoring during both occupational health investigations and research activities in the context of emergency response. The primary decision on whether to proceed with biomonitoring should begin with the decision on whether to conduct an occupational health investigation or a research study. Then, the factors critical in determining whether biomonitoring should proceed can be assessed based on the given decision process. Several conditions are provided that must be satisfied to determine whether a health investigation or research study is to be initiated. The recommended framework should ensure that biomonitoring will be scientifically sound, needed, and able to be justified in emergency response efforts.

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Shared Decision Making to Improve Care and Reduce Costs

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A sleeper provision of the Affordable Care Act (ACA) encourages greater use of shared decision making in health care. For many health situations in which there's not one clearly superior course of treatment, shared decision making can ensure that medical care better aligns with patients' preferences and values. One way to implement this approach is by using patient decision aids — written materials, videos, or interactive electronic presentations designed to inform patients and their families about care options; each option's outcomes, including benefits and possible side effects; the health care team's skills; and costs. Shared decision making has the potential to provide numerous benefits for patients, clinicians, and the health care system, including increased patient knowledge, less anxiety over the care process, improved health outcomes, reductions in unwarranted variation in care and costs, and greater alignment of care with patients' values.

However, more than 2 years after enactment of the ACA, little has been done to promote shared decision making. We believe that the Centers for Medicare and Medicaid Services (CMS) should begin certifying and implementing patient decision aids, aiming to achieve three important goals: promote an ideal approach to clinician–patient decision making, improve the quality of medical decisions, and reduce costs.

In a 2001 report, Crossing the Quality Chasm, the Institute of Medicine recommended redesigning health care processes according to 10 rules, many of which emphasize shared decision making. One rule, for instance, underlines the importance of the patient as the source of control, envisioning a health care system that encourages shared decision making and accommodates patients' preferences.

Unfortunately, this ideal is inconsistently realized today. The care patients receive doesn't always align with their preferences. For example, in a study of more than 1000 office visits in which more than 3500 medical decisions were made, less than 10% of decisions met the minimum standards for informed decision making. Similarly, a study showed that only 41% of Medicare patients believed that their treatment reflected their preference for palliative care over more aggressive interventions.

There's also significant variation in the utilization of procedures, particularly those for preference-sensitive conditions, which suggests that patients may receive care aligned not with their values and preferences, but with their physicians' payment incentives. Among Medicare patients in more than 300 hospital regions, the rate of joint-replacement procedures for chronic hip arthritis varied by as much as a factor of five, and the use of surgery to treat lower back pain varied by nearly a factor of six. Other studies have found wide regional variation in the treatment of early-stage breast and prostate cancers and in the use of cardiac procedures.

Section 3506 of the ACA aims to facilitate shared decision making. Primarily, it funds an independent entity that would develop consensus-based standards and certify patient decision aids for use by federal health programs and other interested parties. In addition, the secretary of health and human services is empowered to fund, through grants or contracts, the development and evaluation of these tools. Decision aids are meant to be evidence-based and inform patients of the risks and benefits of tests and treatments, their relative effectiveness, and their costs. Health care providers will be eligible for grants to implement these tools and to receive training and technical support for shared decision making at new resource centers. The ACA also authorizes the Center for Medicare and Medicaid Innovation to test shared-decision-making models designed to improve patients' and caregivers' understanding of medical decisions and assist them in making informed care decisions. For approaches that provide savings or improve quality of care, implementation can be mandated throughout Medicare without additional legislation.

Randomized trials consistently demonstrate the effectiveness of patient decision aids. A 2011 Cochrane Collaborative review of 86 studies showed that as compared with patients who received usual care, those who used decision aids had increased knowledge, more accurate risk perceptions, reduced internal conflict about decisions, and a greater likelihood of receiving care aligned with their values. Moreover, fewer patients were undecided or passive in the decision-making process — changes that are essential for patients' adherence to therapies.

Studies also illustrate the potential for wider adoption of shared decision making to reduce costs. Consistently, as many as 20% of patients who participate in shared decision making choose less invasive surgical options and more conservative treatment than do patients who do not use decision aids. In 2008, the Lewin Group estimated that implementing shared decision making for just 11 procedures would yield more than $9

billion in savings nationally over 10 years. In addition, a 2012 study by Group Health in Washington State showed that providing decision aids to patients eligible for hip and knee replacements substantially reduced both surgery rates and costs — with up to 38% fewer surgeries and savings of 12 to 21% over 6 months. The myriad benefits of this approach argue for more rapid implementation of Section 3506 of the ACA.

The Department of Health and Human Services could quickly launch pilot programs for shared decision making while it works to standardize and certify decision aids. The International Patient Decision Aid Standards Collaboration has developed evidence-based guidelines for certification indicating that decision aids should include questions to help patients clarify their values and understand how those values affect their decisions; information about treatment options, presented in a balanced manner and in plain language; and up-to-date data from published studies on the likelihood of achieving the treatment goal with the proposed intervention and on the nature and frequency of side effects and complications. In addition, it would be helpful to include validated, institution-specific data on how often the specified procedure has been performed, the frequency of side effects and complications, and the cost of the procedure and any associated medication and rehabilitation regimens. We believe that decision aids should be written at an eighth-grade level and should be brief.

In our view, it seems most critical to begin with the 20 most frequently performed procedures and to require the use of decision aids in those cases. Many decision aids have already been rigorously evaluated, so CMS could rapidly certify these tools and require their use in the Medicare and Medicaid programs. To give such a requirement teeth, full Medicare reimbursement could be made contingent on having documentation in the patient's file of the proper use of a decision aid for these 20 procedures. Providers who did not document the shared-decision-making process could face a 10% reduction in Medicare payment for claims related to the procedure in year 1, with reductions gradually increasing to 20% over 10 years. This payment scheme is similar to that currently tied to hospital-readmissions metrics.

In addition, the improved quality of care and savings gained through shared decision making can be maximized by integrating this approach into other ACA initiatives. For example, the documented use of patient decision aids could be used as a quality metric in patient-centered medical homes, accountable care organizations, and systems caring for patients eligible for both Medicare and Medicaid. Eligibility criteria for incentives to adopt electronic health record technology might be expanded to include the use of shared decision making and patient decision aids. Moreover, information gathered by the Patient-Centered Outcomes Research Institute (PCORI) could be incorporated into certified decision aids and used to provide physicians and patients with valuable information for making health care decisions. Data about the effectiveness of shared-decision-making techniques could also be collected and disseminated by PCORI for continuous improvement of these approaches.

Unfortunately, implementation of ACA Section 3506 has been slow. More rapid progress on this front would benefit patients and the health care system as a whole.

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Traumatic Event Management in Afghanistan: A Field Report on Combat Applications in Regional Command-South

Military Medicine
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Abstract

This article provides information on the use of Traumatic Event Management (TEM) strategies to debrief combat arms personnel whose units sustained traumatic losses in Afghanistan. The specific focus is on the application of Event-Driven Battlemind Psychological Debriefings to combat units. This article offers the first published account of TEM services employed in southern Afghanistan during intensive surge operations in 2009–2010. This article unfolds in three parts: (1) background to the region in which the debriefings occurred; (2) three case examples with a data summary of types of incidents observed; and (3) discussion of observations, lessons learned, and recommendations for training future clinicians to provide effective debriefings to combat arms personnel.

Introduction

Traumatic Event Management (TEM) is an umbrella term for a flexible set of interventions aimed at supporting troops who experience potentially traumatizing incidents during combat, peacekeeping, garrison, or humanitarian operations.1 Such incidents might include continuous combat operations, deaths of unit members, accidents, environmental catastrophes, and operations resulting in the death of civilians or combatants. TEM is a component of Combat Operational Stress Control (COSC) doctrine and emphasizes stress management for affected individuals and units.2 Among those activities that form the core of TEM are unit needs assessments, command consultation and education, triage, stabilization and restoration procedures, individual and supportive counseling, psychological first aid, and psychological debriefings. The intent of TEM is to encourage post-traumatic growth, an adaptive process whereby individuals exposed to potentially traumatizing events can experience improved relationships, an enhanced sense of hope and appreciation of life, and a deepened sense of personal strength and spiritual development. The most well known of COSC services are psychological debriefings, an intervention in which members of units affected by traumatic events are brought together to discuss an event, become educated on individual and group responses to trauma, and have the opportunity for individual or group follow-up.3

Given past concerns regarding efficacy and even potential harm with debriefing techniques such as critical incident stress debriefs,3,4 the U.S. Army currently advocates the Battlemind Psychological Debriefing model in training COSC personnel. According to Adler et al,5 the Battlemind Debriefing Model was designed for use in three different contexts: (1) in-theater event-driven situations where the interventions follow potentially traumatizing events during deployment, (2) in-theater time-driven debriefings that occur at specified times during the deployment as a means to address the cumulative effects of stress over the course of deployment, and (3) immediate postdeployment debriefings to facilitate transition from combat to home.

Briefly, the components or phases of the Battlemind Debriefing model are: Introduction, Events, Reaction, Self and Buddy Aid, and Battlemind Focus. The order of the phases is sequential, with latitude given to the facilitator in providing either more or less time to a given phase, depending

upon the specific needs of the unit exposed to traumatic event(s). Typically, an Event-Driven Battlemind Psychological Debriefing (EDBPD) (related to #1 in the previous paragraph) is held with a group of 10 to 15 individuals varying anywhere from 45 minutes to 3 hours, contingent upon actual numbers of personnel in attendance and the magnitude of the potentially traumatic event. The intent is to intervene early on with a unit, usually within 48 to 72 hours of an incident to help mitigate the development of serious emotional problems and deal with issues that might affect the group cohesion during future missions. Another important consideration is the need to facilitate mission capability and focus following traumatic incidents, as well as to foster unit reintegration for the members of squads, platoons, and/or companies. The overarching intent of COSC operations is to preserve the fighting force.

It is our contention that the EDBPD model provides an effective tool for supporting troops following traumatic events. Accordingly, this article focuses on the application of EDBPDs to combat areas in southern, central, and western Afghanistan during intensive surge operations in 2009–2010. Previous literature on Battlemind debriefings has focused on Time-Driven and Post-Deployment Battlemind Psychological Debriefings versus EDBPDs for returning Soldiers from Iraq.4,6 As noted in these studies, much of the information regarding debriefings is anecdotal. The Adler et al team6 did employ a randomized procedure where some Soldiers were assigned to a postdeployment debriefing process and others to postdeployment stress education. The postdeployment debriefing yielded positive mental health outcomes on 4-month follow-up for those troops who reported a high number of combat-related experiences in Iraq. This article provides the first published information on how EDBPDs were used in highly kinetic combat environments in Afghanistan, where affected units had no assigned or limited organic behavioral health and combat stress personnel available to them. The authors were Army and Navy Clinical Psychologists who worked in collaboration with each other as part of three separate units (i.e., the Role 3 NATO Hospital, 4th Brigade Combat Team of the 82nd Airborne Division, and the 467th Medical Detachment, Combat Stress Control). What follows is a discussion in three parts: (1) background to the region in which the debriefings occurred; (2) three case examples with a data summary table of types of incidents seen; and (3) a concluding section on observations, lessons learned, and recommendations for training future clinicians to provide effective debriefings to combat arms personnel.

Background to Region

Kandahar, Afghanistan, is the spiritual center of the country and a key economic area with ancient trade routes to Pakistan and Iran.7 The center for coalition operations in southern Afghanistan is Regional Command-South, located on Kandahar Airfield (KAF), a sprawling multinational airbase with representatives from over 15 countries and a population of over 20,000 troops and civilian support personnel at the time this article was written. In November 2009, an additional 30,000 troops were deployed to Afghanistan to support a counterinsurgency strategy and to wrest control of the south and west from Taliban forces, particularly in the economic regions of Kandahar Province and Helmand River Valley in southwestern Afghanistan. For U.S. military personnel, conditions were extremely austere with limited logistical support, especially in the many remote Forward Operating Bases (FOBs) and Combat Outposts (COPs).

Three Examples of EDBPDS

The three event-driven debriefing examples were chosen from our respective deployment experiences to illustrate different contexts in which debriefings occurred, as well as varying degrees of complexity in managing the debriefing sessions themselves. The examples include a relatively

straightforward debriefing session, a session where a participant left during the debriefing process, and a session where the clinician drew upon clinical experiences and resources outside the standard EDBPD model.

Example 1: FOB (A) OCTOBER 2009—A Straightforward Debriefing

Although this example is described here as a “straightforward” or typical example of a debriefing session in theater, it must be remembered that the traumatic incident itself represented a horrific situation for the troops involved, which was outside the range of almost everyone's experience. A motorized (Stryker) battalion suffered the deaths of seven unit members and one Afghan interpreter during an improvised explosive device (IED) and complex ambush attack. Given the number of fatalities, the battalion requested that the KAF Role 3 Mental Health and Combat Stress Control (CSC) Team augment the Behavioral Health Team organic to the unit. The CSC team was flown to the FOB the next day.

Once on the ground, the CSC Team met with the Battalion Surgeon and the unit's Behavioral Health (BH) Officer, who were already on site. Further communication with the unit revealed that members of the affected unit did not return to the FOB until the previous night, after being at the blast site for 12 hours. Rather than attempt to immediately schedule any meetings, it was recommended that the unit rest for a day before engagement. The CSC team subsequently met with nine members of the platoon during the scheduled session the following evening. The unit's BH Officer served as the primary facilitator. Attendance was voluntary by unit members. The standard EDBPD protocol was followed beginning with a description of the event from each member's perspective, discussion of their reactions to the incident and loss of their fellow Soldiers, an outline of self and buddy care, and options for further support. One striking perceptual phenomenon noted by almost all members was that, regardless of their vehicle's position in the convoy, the sound of the explosion made them think the blast was smaller than it turned out to be. Consequently, as the smoke and dust cleared, team members were unprepared for the level of carnage and vehicle destruction caused by the blast. At the close of the 75-minute session, two unit members stayed behind requesting additional support. The BH Technicians met individually with these Soldiers for an additional 20 to 30 minutes. CSC team members reviewed their observations from the debriefing session, identifying Soldiers needing further follow-up. Overall, the unit members engaged in the EDBPD process and felt it increased their unit cohesion by hearing others' perspectives and discussing their experiences. The individual follow-up sessions also appeared to be beneficial as the Soldiers involved returned to full duty. Results of session and subsequent follow-ups were briefed to the battalion commander the next day.

Example 2: FOB (B) JANUARY 2010—A Session Where a Distraught Participant Leaves the Debriefing

While conducting a dismounted patrol through the Arghandab River Valley en route to inspect an abandoned school believed to be a weapons cache, several Soldiers were struck by a remote-controlled detonated daisy chain of seven IEDs alongside a mud wall. The Company Commander and Explosive Ordnance Disposal (EOD) Technician were killed, while the platoon leader sustained a traumatic above-the-knee amputation and the medic, a mild concussion. Two days later, a request was placed and the BH Team flew out to the company COP. Those in the company who were not present at the time of the Commander's death were provided individual support and follow-up over 3 consecutive days leading up to their team members' memorial service. For the attached squad that was on-site of the IED, a 1-hour EDBPD was provided by the BH Officer and Technician. Twelve people originally presented for the group and were informed of the nature and intent of the session. Six of those who presented were subsequently excused as only those at the actual event were invited to remain. The standard EDBPD model was followed.

Partway through the debriefing, one Solider became visibly distraught and left the session. That Soldier was provided individual follow-up immediately after the group. He indicated that he could not tolerate the visual images that the group discussion generated as he apparently felt responsible for the passing of the Company Commander whom he had attempted to treat. This encounter proved to be highly beneficial, as it not only allowed the BH Officer to note the status of the Soldier for further monitoring, but also laid the groundwork for a working relationship, as this particular Soldier later required individual behavioral health services before redeployment for an unrelated event.

The remaining Soldiers were effective in factually describing the event and then transitioning to the emotional impact they experienced in treating the extensive injuries of their Platoon Leader, the EOD Technician, and the Company Commander. Several Soldiers used the opportunity to voice frustrations with their felt helplessness, guilt for not being able to do more, and even offered some humor when recounting comical statements made by their Platoon Leader at the time of his injury. During the concluding psychoeducational piece, the Soldiers inquired into the status of those surviving and asked questions about expected outcomes and advice on how to approach and interact with their comrades upon eventual redeployment. The participants were then invited to return to the COP for the memorial service and follow-up with the chaplain for spiritual support or follow-up during the BH Team's routine battlespace circulation a few weeks later.

Example 3: FOB (C) APRIL 2010—A Challenging Session Requiring a Change in Protocol

The FOB CSC Team was mobilized to support a unit that had lost three members in a complex IED and ambush attack. The affected battalion was within 2 months of the end of their year-long deployment and had already sustained the highest number of deaths and wounded in action within their brigade. Although the CSC Team received a positive response from the unit regarding an offer of support, the debriefing itself followed a problematic course from the outset. The first problem occurred with miscommunication within the unit regarding those who should be invited to the debriefing session. The initial plan discussed by the CSC Team with the Commander was to have only the five Soldiers who were on-site at the time of the incident appear for the debriefing session. When word was passed to the platoon, the message was received that all 26 members of the platoon were “required” to attend. A second problem arose in that the venue location was changed without notice to the relevant leadership. As a result, a number of Soldiers were angry and displeased that attendance had been deemed mandatory. Seating was arranged in rows and did not accommodate all in attendance.

The level of discomfort and dissatisfaction by the troops was palpable at the start of the session. During the Event Phase, only two Soldiers were willing to reconstruct events. Almost all Soldiers responded “I was pulling security” or “I'm good” (meaning, “I don't wish to speak”). Pursuing any questions regarding event reconstruction proved of little value. Sensing the need to respond to the current situation, the CSC Team Leader shifted to the Kuhlmann Debriefing Protocol.8 The Kuhlmann Model calls for the group to offer specific means to memorialize or pay tribute to those who have died, as well as a very brief mention of their personal and varied responses to grief. This modality change opened the discussion to a striking and memorable set of recollections and began a shift to a level of lightheartedness as Soldiers reminisced about their fallen comrades. The final stages of the debriefing involving self and buddy aid appeared to engage few members. The CSC team remained on scene for 10 to 15 minutes to offer support, but participants declined follow-up at that time. Interestingly, some of the most hostile and resistant participants sought individual support from the CSC Team in the weeks that followed. These Soldiers remained engaged in individual psychotherapeutic interactions for the duration of their respective Operation Enduring Freedom deployments.

Data Summary of Incidents Seen

The information that follows is based on EDBPDs that occurred between August 2009 and March 2010 in southern and western Afghanistan during a time of surge operations. Collectively, the authors participated in approximately 50% of all the EDBPDs conducted in the region during that time frame. The lead author, as Behavioral Health Consultant to Regional Command-South, participated in coordinating an additional 30 to 40% of the psychological debriefings in the region. We believe that our experience draws from a representative sample of debriefings within the region (Table I).

As is evident from the summary table, requests for debriefing support originated from FOBs throughout the region. Units requested TEM services in the aftermath of numerous catastrophic incidents, including IED and rocket attacks, vehicle accidents, drowning, and, in one case, suicide. The largest number of requests for services resulted after specific events, rather than from requests for support at periodic times during deployments. Given the frequency of combat-related events and the need to attend to day-to-day care of the troops, there was little time to deliver debriefings at specified intervals during the deployment such as Month 4 or Month 8, as per Time-Driven Psychological Debriefing guidance. Specific outcome data from these interventions are not available as the nature of these debriefings and the context in which they were performed was not conducive to that level of evaluation and research. However, several conclusions can be drawn from these experiences as discussed later.

Observations, Lessons Learned, and Recommendations

Normal Reactions to Abnormal Events

For the most part, units affected by potentially traumatic events appeared to be relatively cohesive and engaged in steps to return to the mission. Even in cases where there was significant anger directed at Command and leadership for perceived failings, the affected units generally expressed a willingness to “stay in the fight.” One author (Patricia Hammond), however, found one company that had sustained substantial losses during the course of their combat tour to have recurrent problems with two Soldiers who repeatedly refused to patrol during the last 2 months of the unit's deployment. This subsequently generated conflict within the unit as they prepared to redeploy. The range and intensity of views and emotions expressed within the EDBPDs were otherwise viewed by the facilitators as within expected and “normal” bounds, given the extraordinary circumstances surrounding these combat debriefings. For several Soldiers observed throughout the deployment cycle, this normalization of combat experiences in theater proved crucial as the mentality was then applied to preparation for redeployment and helping Soldiers reintegrate with their families upon return stateside.

The Need for a Flexible Approach

A “cookie-cutter approach” does not work in a dynamic and ever-changing battlespace. Just as no two traumatic events were alike, no two debriefings were prepared or delivered in the same manner. Rather, all debriefings required an individualized approach based on the requests and needs of the Command, Soldiers, unit atmosphere, timing, location, transportation, combat event, etc. The need for this targeted approach became increasingly evident for one BH Officer as over a half-dozen EDBPDs were conducted with two different companies because of the significant number of casualties and losses sustained. Additionally, psychological debriefing facilitators need a solid grasp of the debriefing

process and a wide range of clinical experience to manage their own feelings during the debriefing sessions, especially considering the inherent nature of dual relationships in military and deployed settings. Similarly, an ability to tolerate a high degree of affect, particularly anger, is critical to making the process work. Military medical doctrine, although helpful in trying to standardize a systematic overall approach to CSC and psychological debriefings, does not fully consider and address the more existential and humanistic aspects related to combat exposure. The clinician's ability to individually relate to and interact with the unit on a personal level can exponentially increase (or can deter from) the efficacy of psychological debriefings and TEM overall. Incorporating familiarity with the Soldiers, or even “paying tribute” as described earlier in the Kuhlmann Debriefing Protocol, can make a significant difference.

Helping Soldiers Deal With a Sense of Helplessness

Learned helplessness appeared to be a common theme—in terms of the certainty of constant deployments, limited ability to manage home-front stressors, inherent inequalities with the rank structure, frustration with the mission and rules of engagement, and even the number and nature of current insurgency tactics. This tendency was especially apparent in companies that had experienced a high degree of combat exposure in a relatively brief time. By fall 2009, a common perception held by the population that the authors served was that the enemy possessed the psychological momentum and unit members had a decreasing chance of returning home safely. As losses continued into the following spring, despite strategic efforts in neighboring regions, such as Helmand Province, unit morale was degraded by a sense of helplessness in confronting the enemy. Emotions related to this perception and external “locus of control” were evident throughout the debriefings conducted through summer 2010. Frustration and anger were frequently voiced in response to the Soldiers' seeming inability to engage the enemy following IEDs and perceived duplicity of local nationals who were thought to know the location of these IEDs. In other instances, Soldiers described a sense of mistrust of leaders in guarding the safety of unit members on missions. As casualty rates rose, some Soldiers expressed their perception that their higher leadership was more concerned about the safety of local nationals over that of their own Soldiers. Although specific acts of misconduct or intent to commit such acts were not identified in the sessions, the conditions to potentiate such offenses do exist, especially among troops with histories of poor coping skills. Per standard procedures, if a Soldier voiced homicidal ideation with a specific intent to harm others, that Soldier would be taken off mission and scheduled for further evaluation.

The Need to Engage Units Outside the TEM Experience

Based on the authors' experiences downrange, it appears crucial for CSC and BH Teams to interact with units outside of potentially traumatic events. This means that CSC and BH assets must remain mobile and become acquainted with Commands and Soldiers alike. Without the buy in of both, clinicians not only lose credibility, but also run the risk of combat stress and behavioral health personnel being identified as “the people who only show up when something bad happens.” Such a perception can undermine the utility of any interventions the CSC and BH Teams might provide. Although outcome research with TEM and psychological debriefings is lacking, it is unlikely that a single debrief will necessarily prevent the development of post-traumatic stress disorder (PTSD) or other psychiatric illnesses. This is especially true considering that history of childhood trauma is a better predictor of combat-related PTSD rather than the combat itself.9 Combat stress doctrine holds that unit cohesion is one of the best predictors of resiliency to combat stress.10 It seems that clinician time is most valuable and best spent ensuring that interventions and interactions throughout the TEM process are specifically geared toward building and strengthening those bonds.

The Need to Revise Doctrine in Light of Multiple Events

Current COSC doctrine is limited in providing guidance to team members in supporting units that experience multiple catastrophic incidents within a short time frame. Most combat stress debriefing training focuses on discrete incidents, not the cumulative effect of multiple incidents that may occur even within the same week. Although we found the EDBPD process to be a useful tool for many units, COSC personnel need to understand the limitations of what can be accomplished through the use of these procedures. In several cases, facilitators were asked by Command to gauge the ability of units to go “back on mission,” based on the TEM process. In those situations, Commands were informed that the TEM process was not a method for determining the fighting spirit or capability of a unit but could help the Command identify individuals who might require further monitoring or follow-up. COSC personnel need to understand their professional limitations in assessing the capacity of units versus individuals to return to the fight following traumatic incidents, especially considering the brief nature and group setting of EDBPDs.

Adequately Preparing Units for the TEM Experience

As clearly identified in military doctrine,2,10 affected units need food and rest in the immediate hours after a potentially traumatic event. Scheduled EDBPDs were often delayed to allow the unit leadership time to evaluate the Soldiers' more critical and basic needs. Such leader engagement helped to facilitate the debriefings. One particular Platoon Sergeant set aside a table for unit members to sit together for a meal the day after an incident to facilitate the re-establishment of camaraderie and esprit de corps. Similarly, the ability to change into clean, dry uniforms may also help meet recovery needs so Soldiers are not recalling the incident wearing blood-stained uniforms and equipment.

The Value of TEM Services

By observing troops who have faced extreme conditions and potentially traumatic events in a debriefing format, clinicians are afforded a unique window of opportunity for perceiving and listening to how troops talk about their experiences. Such experiences assist clinicians in gauging what is normal and expected under various conditions, particularly as it relates to traumatic events and the rigors of combat. Providing a forum for Soldiers to openly talk about their anger, pain, and fear with the support of both clinicians and Command is essential. Debriefings gave clinicians an inside look at Soldiers' abilities to cope and manage stress. The debriefings allowed us to track trends and inform Brigade Surgeons and Command on the status and general well-being of troops. Debriefings also facilitated follow-up with troops in the ensuing days and months on through redeployment. As such, EDBPDs play a vital role in-theater in the care of our combat troops.

More work must be undertaken to refine the content and structure of the debriefing process to ensure quality care experiences for our troops. As to empirically validated benefits of and potential for Battlemind Debriefings to help prevent the development of PTSD, we are awaiting more data from large-scale research trials. In the absence of any other standardized alternatives to EDBPDs, continued research and the ongoing option to employ such procedures in the field is critical. Initial data could potentially be collected at the unit level by organic BH Teams in tracking Soldiers at the time of debrief and upon postdeployment health assessment, as compared to others in the unit who reported combat exposure, but declined or who were not available to participate in an EDBPD. On a larger scale, self-reported outcome data could be obtained via focus groups and surveys

as part of the biennial Mental Health Advisory Team visits. Subsequent research will hopefully evaluate and enhance the effectiveness of this tool with evidence-based lessons disseminated and implemented across the enterprise.

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Ultrasound in the Austere Environment: A Review of the History, Indications, and Specifications

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Abstract

In the last 10 years, the use of ultrasound has expanded because of its portability, safety, real-time image display, and rapid data collection. Simultaneously, more people are going into the backcountry for enjoyment and employment. Increased deployment for the military and demand for remote medicine services have led to innovative use and study of ultrasound in extreme and austere environments. Ultrasound is effective to rapidly assess patients during triage and evacuation decision making. It is clinically useful for assessment of pneumothorax, pericardial effusion, blunt abdominal trauma, musculoskeletal trauma, high-altitude pulmonary edema, ocular injury, and obstetrics, whereas acute mountain sickness and stroke are perhaps still best evaluated on clinical grounds. Ultrasound performs well in the diverse environments of space, swamp, jungle, mountain, and desert. Although some training is necessary to capture and interpret images, real-time evaluation with video streaming is expected to get easier and cheaper as global communications improve. Although ultrasound is not useful in every situation, it can be a worthwhile tool in the austere or deployed environment.

Introduction

Increased U.S. military operations tempo has increased demand for medical providers to “do more with less” in austere and deployed environments. Clinicians often find themselves in uncomfortable locations treating patients with minimal and makeshift supplies. Since laboratory and radiology services are often very limited in these situations, clinical judgment becomes more important when deciding which patients need medical evacuation. However, published studies point out the ease and utility by which ultrasound can be employed in austere settings. This review will detail the evidence that ultrasound is useful in a rapidly increasing number of situations.

History and Overview

SONAR, the first use of ultrasound, was developed during World War I, and ultrasound was found to have medical uses in the 1940s. Ultrasound uses cyclical, high-frequency sound waves that are well above the threshold of human hearing (normally 20,000 Hz) created by an electrical current into a ceramic transducer thus producing a piezoelectric effect that creates a sound wave. Lower range frequencies, in the 2 to 7 MHz range, have high penetration but low resolution. These frequencies are often best for deep locations such as the abdomen, pelvis, and heart.

Higher frequencies, 8 to 12 MHz, offer low penetration but give impressive resolution. These frequencies are often used for musculoskeletal examinations, “small parts” (i.e., eyes), and procedures such as central lines, injections, and biopsies. Frequency and contour of the probe determine the picture that the clinician sees on the ultrasound (Fig. 1).

Because of the different nature of examinations, uses for the probes, and types of probes, users of ultrasound in the austere environment at a minimum need two probes: the 10 to 12 MHz straight linear array probe for high resolution and either a low penetration curvilinear array or phased array microconvex and 5 to 7 MHz intracavity probe for deeper penetration. Linear array probes use a series of “crystals” to take pictures in a straight (or curved) line by using all of the crystals at relatively the same time.

Compared to the phased array probe which oscillates which crystals are used in a pattern chosen by the machine for certain resolution and depth, this allows the probe head to be smaller and get into tighter places (between ribs, etc.). During times of necessity, certain probes may be used for other than their standard uses—in a series of combat care events, the U.S. Army used a small curved 5 to 7 MHz intracavity probe as a small parts probe for skin/soft tissues with good effect by changing the gain levels on the ultrasound machine. Although one probe can perform “double duty,” the resolution will be inferior to a dedicated probe. When a third probe can be afforded, a transvaginal probe may be useful for care of women in the expeditionary setting.

Ultrasound technology was formerly only available to radiologists but has now become more accessible to adequately trained providers. Financial incentives, greater patient satisfaction, and improved diagnostic and treatment capability have driven the change to primary care and emergency medicine specialties routinely using ultrasound in “point of care” settings. Bedside ultrasound can be useful since it has no ionizing radiation; compared to other imaging modalities, it is often very cost-effective in the clinical setting.

Utility of Ultrasound in the Austere Environment

Even with the propagation of ultrasound in the clinic and emergency room setting, some question whether ultrasound matters and how it applies to clinical care in the austere setting. Some authors state that a good clinical examination can render an expensive ultrasound unnecessary. However, as cited in multiple studies below, evidence supporting ultrasound as a viable diagnostic and decision support tool in the austere setting is convincing.

Complex triage decisions are required when determining whether a patient can be treated onsite or should be evacuated. Clinicians strive to avoid two extremes when making evacuation decision—both a high-risk, expensive evacuation for a problem that turns out to be low risk and a slower, but possibly safer, evacuation for a high-risk, immediate problem are to be avoided. Simultaneously, clinicians must consider what supplies and manpower are available for consumption if continued care is chosen over evacuation. Previous examples are cases where clinicians have successfully ruled out testicular torsion with a Doppler ultrasound saving a dangerous aeromedical evacuation and have ruled in cholelithiasis which required immediate evacuation for surgery. Ultrasound can help make informed decisions and has assisted in the triage of real patients.

Although some argue that triage decisions should be made on clinical grounds, classic textbook presenting symptoms are often not actual presenting symptoms. A comparative case study regarding Focused Assessment with Sonography for Trauma (FAST) examinations of two

patients illustrates this principle. Both patients suffered multiple penetrating trauma to the thorax and were taken to the same Level I trauma center for evaluation. “Patient 1” had unstable vitals and what appeared to be life-threatening injuries whereas “Patient 2” had stable vitals and what appeared to be nonlife threatening injuries. However, a FAST examination of “Patient 2” found a collection of blood in Morrison's pouch, the splenorenal recess, and the pelvis, whereas “Patient 1” had no intra-abdominal fluid. This information changed the initial clinical assessment that “Patient 1” needed emergent surgery, and instead, “Patient 2” was deemed the more injured. Small field hospitals, on-ship clinics, and remote area clinics now use FAST examinations routinely to improve triage ability—often avoiding evacuation to higher level care and saving precious resources in “resource strapped” environments.

Ultrasound has been used in mass casualty triage outside the hospital in both the 1988 Armenia earthquake and the 2008 Wenchuan earthquake. Ultrasound can perform an accurate trauma evaluation in under 4 minutes—important when there are thousands of casualties. In a remote location in the Amazon, lengthy, and possibly dangerous, transfer was avoided in 28% of the cases where ultrasound was used. The team was able to effectively rule out gallstones and ectopic pregnancy as the cause of abdominal pain which “yielded a considerable savings in resources.” This study found that bedside ultrasound improved the diagnostic certainty in 72% of cases by narrowing the differential diagnosis. This group found the technology so useful that it has now been used in >20 temporary expeditionary clinics manned by volunteer physicians. Not only did the differential narrow, but in 17 of 25 patients, the certainty of the diagnoses improved. The physicians using this technology felt that it helped them save scarce resources and time.

A French study evaluated 302 scans on 169 patients from prehospital ambulance response and found that in 67% of cases, it increased diagnostic certainty. The average examination time was 6 minutes, and the study found varied pathology such as pericardial effusions, pleural effusions, and vascular lesions, which were then confirmed by standard of care imaging once the patient arrived at the hospital. Based on these studies and others, the Emergency Medicine community is continuing research investigating the feasibility of moving ultrasound into the field to guide treatment by first responders or even nonclinical personnel.

Indications

Trauma

The FAST examination is common in the hospital setting. This is a quick, 2 to 4 minute assessment performed on trauma victims in the Emergency Room. The examination assesses 4 areas—pericardium, right upper quadrant, left upper quadrant, and the pelvis around the bladder. The goal of this examination is to observe for free fluid after blunt trauma, which may indicate hemorrhage. This study has been found to be sensitive (83.3%) and very specific (99.7%).

It is conceivable that the FAST examination could be used for risk stratification and evacuation decisions in austere environments since it has good sensitivity. In a hospital setting, a normotensive patient should be rechecked again in 6 hours after a negative FAST scan. However since the sensitivity is not 100%, a physician in the austere environment may not wait 6 hours on a medical evacuation because the FAST was negative. Conversely, with its outstanding specificity, a positive FAST should spur clinicians to argue for a higher risk, more rapid transport even in patients

with stable vital signs. Additionally, this examination can easily be performed almost anywhere—even during aeromedical rapid transport with approximately the same sensitivity and specificity as in the hospital. Of course, cost, weight of the machine, predeployment training, and the evacuation environment should be considered before bringing the ultrasound on a mission.

Pericardial Effusion

In a review of studies in three prehospital settings, ultrasound cardiac examinations were “adequate” in approximately 94% of cases and diagnosed pericardial effusion with 100% sensitivity and specificity. In Emergency Department imaging, cardiac ultrasound has increased survival nearly two-fold in penetrating cardiac injury with the actual survival of the nonecho group versus the echo group being 57% and 100%, respectively (number needed to treat for prevention of a single mortality was 2.2). Of course, in cases of protracted evacuation, it is unlikely that this will greatly affect survival rates, but may encourage a clinician to evacuate a stable pericardial effusion rapidly once they have confirmed the diagnosis (Fig. 2). In cases of cardiac tamponade, an ultrasound guided procedure with a long needle could theoretically be better than the same lifesaving procedure done blind. In the austere environment, pericardiocentesis can be performed since the 30 mL syringe is ubiquitous and the 18-gauge spinal needle is normally carried in packs for relief of tension pneumothorax (PTX), and the success rate improves with ultrasound.

Pneumothorax

Ultrasound can be used to exclude or diagnose PTX. A 2001 case report of an 18-year-old skier who fell forward onto his chest detailed how, on the mountain, ultrasound was used to rule out a PTX. PTX is diagnosed by the absence of normal lung sliding along the pleura under ultrasound. As little as 150 mL of air in normal gravity and only 50 mL in microgravity can be seen on the anterior portion of the chest. Recent meta-analysis of 20 studies shows that ultrasound is more sensitive and as specific than anteroposterior chest radiography (88% and 99%, respectively, for ultrasound versus 52% and 100%, respectively, for chest radiography). Although clinicians without ultrasound may choose to place a thoracostomy tube before air evacuation, there is both risk with this procedure and loss of critical supplies.

PTX can decompensate during air evacuation in unpressurized aircraft—patients could be evaluated preflight for a PTX given the clinical scenario and “ruled out.” Pre- and mid-flight evaluation can also be used to assess the patient and either place the thoracostomy tube or delay placing a chest tube if the patient's examination is stable. Since PTX and hemothorax are known causes of preventable death, ultrasound can be a useful modality to evaluate those who do not clinically “declare themselves.”

Musculoskeletal

Normally, musculoskeletal imaging involves large X-ray machines or magnetic resonance imaging, but there is an increasing evidence base to support the use of ultrasound in the outpatient clinical setting. Portable ultrasonography is currently used by the U.S. military to evaluate musculoskeletal trauma in forward-deployed locations. Ultrasound is known to be very effective when evaluating for long bone fractures—sensitivity for midshaft fractures approach 100% in one study. In a study of 20 nonultrasound-trained EMT's, they were given 2 minutes of ultrasound training and were then able to evaluate long bone fractures in a controlled environment with a final sensitivity of 97.5% (95% CI: 94.1–100, $p < 0.05$) and specificity of 95% (95% CI: 85.4–100, $p < 0.05$). As with most targeted single area ultrasounds, the evaluations were able to be

completed in <5 minutes. Additionally, ultrasound has been successfully used to guide reduction of fractures without using standard radiographs. Quick evaluation with ultrasound could eliminate the need for an evacuation by ruling out a fracture immediately. Of course, there are limitations to ultrasound for fracture evaluation as this modality is best for superficial long bone fractures and can have problems seeing deeper, nondisplaced, or incomplete fractures. However, assessment of complicated fractures can allow for an appropriate evacuation destination to be chosen to eliminate sending the wrong injury to the wrong hospital.

Beyond fracture recognition and diagnosis, ultrasound has promise for use in remote locations to evaluate for abscesses and foreign objects. Although it could be argued that abscesses can be diagnosed on clinical grounds, most clinicians have had experience with an incision and drainage of an abscess that was surprisingly large and needed extensive packing. Training models can help providers recognize an abscess with ultrasound that can be safely drained with minimal/no packing and allow appropriate disposition in an austere environment. Foreign bodies can also be identified successfully by ultrasound in forward operating bases. Although in an early phase of development, animal model data using sea urchin spines indicates ultrasound may be useful in ruling out intra-articular foreign body—sensitivity of 100% (95% CI: 46.3–100) and specificity of 75% (95% CI: 21.9–98.7).

High-Altitude Pulmonary Edema

High-altitude pulmonary edema (HAPE) is pulmonary edema that develops in climbers at high altitudes. Since its symptoms are often vague and nonspecific, some have used ultrasound to assist with the diagnosis of HAPE. Ultrasound can be used to attempt to find the “comet tail” pattern found where there is increased microreflections of sound waves by increased pulmonary edema (Fig. 3). These comet tails have been shown to correlate well with both clinical symptoms and oxygen saturations in climbers—for each change in the comet tail pattern by 1 point, based on the scoring system used in the study, the oxygen saturations decreased by 0.67% (95% CI: 0.41 to 0.93, $p < 0.001$). Of course, since they seem to correlate so well with ultrasound findings, clinicians can use oxygen saturations directly and ultrasound may not be necessary. HAPE can be distinguished from left ventricular failure in either trained hands or via telemedicine by assessing the pulmonary wedge pressure. Those with HAPE can be allowed to descend, and then once symptoms resolve, slowly ascend versus those with decompensated left ventricular failure who should be immediately evacuated.

Based on data from one intensive care unit study involving ultrasound in pulmonary diseases following the Bedside Lung Ultrasound in Emergency (BLUE) protocol, an algorithm evaluating lung sliding and the specific category of the ultrasound picture, ultrasound yielded the proper diagnosis in 90.5% of the cases. This allows the providers to differentiate between pulmonary edema (97% specificity, 89% sensitivity) versus PTX (100% specificity, 88% sensitivity) versus pneumonia (94% specificity, 89% sensitivity). Limitations of this study include the high level of experience of these providers and the elimination of 15% of the initial patients enrolled from the final statistics based on either rare, unknown, or multiple diagnosis. Therefore, this data will be less useful in the austere setting, although further research may yield translatable results.

Acute Mountain Sickness

Acute mountain sickness (AMS) is a syndrome that includes a headache in conjunction with fatigue, dizziness, lassitude, poor sleep, or gastrointestinal symptoms. AMS is thought to be caused by increased intracranial pressure (ICP) with associated edema or vasodilation. Increases in optic nerve sheath diameter (ONSD) are associated with increased ICP, but experts debate the exact cutoff (5.0 to 5.8 mm). In two field studies at altitude, increasing ONSD was associated with increasing AMS scores at altitude ($p < 0.001$ for both studies). Although these were proof of concept studies, the data could be useful in the field to help differentiate AMS from other conditions such as intoxications, viral illnesses, or poisonings which may mimic AMS but are not associated with increased ICP. Also, high altitude cerebral edema (HACE) which is the deadly end point of AMS, could, in theory, be ruled out with normal ONSD and thus change evacuation priorities (Fig. 4).

Eye Injury and Pathology

Ultrasound does an impressive job imaging the globe, and this examination is simple enough to even be done by nonclinicians in a telemedicine scenario as seen in a series of space shuttle experiments which found that an individual with limited ultrasonography skill can still visualize all anatomical aspects of the eye. Additionally, the military has used eye ultrasound in austere settings to diagnose both foreign bodies and retinal detachments. Although ultrasound can be very accurate in diagnosing eye injury, clinical diagnosis will likely be more useful than imaging in almost all cases. Rapid diagnosis, pain control, an eyeshield, and evacuation as needed are the key to preventing loss of eyesight. Ultrasound would be somewhat useful to confirm a globe penetration or retinal detachment and then evacuate to a specific hospital with an ophthalmologist.

Stroke

Cerebral vascular accidents (CVA) or stroke can be diagnosed with the right ultrasound equipment. In a German case series of 25 patients in a prehospital setting (patient homes or medical transport), a trained physician (in Germany physicians ride with the emergency response service) visualized and measured flow in the middle cerebral artery in 20/25 patients showing that using trained physicians to diagnose CVA is “feasible” in nonhospital settings. Another case report identified a 49-year-old climber who was diagnosed, and theoretically, treated, with ultrasound. Transcranial Doppler was available in that case, and a middle cerebral infarct was diagnosed. Clinicians started aspirin and left the ultrasound in place for 12 hours, in which initial limited data shows may actually be therapeutic for stroke victims. The ultrasound machine and probe must be capable of transcranial Doppler, which can be confirmed after discussion with the ultrasound supply company. CVA is a rare condition on expeditions, so the use of an ultrasound for its diagnosis may be more appropriate as a “bonus” rather than the primary reason to have this machine in austere settings.

Obstetrics

Although obstetrical ultrasound examination is common in Obstetrical and Family Medicine clinics in the United States, the utility of it in the deployed setting is questionable as a result of low rates of pregnancy. Local nationals are usually either full term when the diagnostic ability of ultrasound is of little use or, in early first trimester, when they are being worked up for abdominal pain with a positive pregnancy test. In the latter situation, lack of the appropriate probe will likely limit the utility of ultrasound since a transabdominal probe is not sensitive enough to rule out ectopic pregnancy. Although a clinician may want to rule out this life-threatening condition, unless a transvaginal probe is available, the patient

should be immediately evacuated if ectopic pregnancy is suspected. As a transvaginal probe has very few uses, unlike other probes, it is less likely to be found in austere settings given the extra weight and cost. However, for those in austere clinic settings seeing indigenous populations, acquisition of a transvaginal probe may be justified.

Specific Types and Qualities of Ultrasound Machines

There are many types of ultrasound machines, and the exact type needed depends on the mission, supplies, and expected injuries. Table Idetails various ultrasound machines that are considered portable, but still versatile. Another stumbling block, beyond cost, is how to charge the unit on a remote mission. Although some small field locations have grid or generator power, some locations will need to use solar charging. Additionally, rapid response search and rescue or emergency personnel with a home base can also detach their units and use them on battery reserve for various times.

These machines are often very rugged and can survive in multiple environments. They have been used by NASA in low-earth orbit—which involved both high- and low-gravity environments. The U.S. military uses these machines in dusty, hot, cold, humid, and arid environments all around the world with little difficulty. Some of these areas are very austere and include tent conditions with unreliable power, but these machines are still trusted as reliable and useful in these caustic environments. Their use has spread to both indoor and outdoor dirty conditions during disaster relief and medical missions. Ultrasound has also been used in unpressurized aeromedical evacuation in many situations and studies. Generally, the probe is considered the most fragile part given the crystal array, and care should be taken to ensure proper storage in a shockproof case for transportation.

The choice to purchase an ultrasound will be directly related to its utility for each mission. Factors such as training, budget, patient population, resources, clinic location, and evacuation abilities must be taken into account when deciding on which, if any, ultrasound machine should be purchased for an either a mission or static clinic. As technology improves, machines get smaller and more portable while the price tends to decrease. Refurbished machines are available for significant savings.

Training

Naturally, any technology is useless without someone to interpret the data. Some have wondered if wilderness medicine providers have adequate training to use ultrasound effectively in austere settings. Increasing numbers of clinicians are trained to use ultrasound for point-of-care assessment in the clinic and Emergency Department. It is often part of residency training in Primary Care, General Surgery, and Emergency Medicine. Some would even say that ultrasound has replaced physical examination skills in a younger generation of physicians.

As with most procedures, there are training recommendations for the appropriate number of ultrasound that a clinician requires to be considered adequately trained—the American College of Radiology and American Institute of Ultrasound in Medicine recommend 300 to 500 cases and 3 months of training. However, some data suggests that 200 cases is the “lowest limit” but not even sufficient for some radiologists. As with many procedures in medicine, there is disagreement about competency requirements between specialty societies. Nonradiology societies such as the Society for Academic Emergency Medicine and the American Academy of Family Physicians argue for much lower numbers based on

competency performing the specific point-of-care ultrasound procedures instead of minimum numbers since targeted examinations can be focused.

Streaming/Remote Viewing

If specialized training is not an option for a clinician, or if the patient is a difficult case, then video streaming can be utilized to allow remote evaluation by a radiologist. This technology has been used multiple times during evaluations by NASA, where nonmedical personnel use ultrasound with specific instructions and this information is beamed real time down to a provider on the ground. Nonmedical personnel did require appropriate training to get the correct views, but this training takes 2 to 3 hours and can be reinforced with a simple guide showing the proper technique. Streaming has also been used in austere settings such as Mt. Everest (2009) where, in a proof of concept study, the ultrasound was connected to a data conversion device then a laptop computer for streaming.Voice Over Internet Protocol was then used by the radiologist to communicate with the nonradiologist at the point of care. Most commercial ultrasounds have USB connection options, and data streaming can be used through most computers with the appropriate software. Of course, there is extra cost, weight and power consumption for the computer to process the images, and an Internet connection is needed to send the images. Additionally, weather may interfere with satellite systems, but more areas are using cell phone technology or hardwired connections that are not as susceptible to weather.

“The Future”

As ultrasound begins to play a role in the austere environment, the technology continues to improve with faster processing power and more features. The future of ultrasound will most likely utilize software in a smart phone. A device such as this would allow a micro-USB probe to attach to the smart phone and allow the user to carry their own ultrasound machine everywhere they go (yes, we are entering the world of the Star Trek tricorder). Current USB probes cost approximately $2,000, but these probes will likely be $500 within the near future.

Conclusion

In approximately 10 years, ultrasound has gone from a modality normally scheduled in the Radiology Department to one now routinely performed in the office. Ultrasound is now feasible and increasingly common in the austere setting since it improves diagnostic certainty and ability to triage injuries in a poor logistics situation. It has been used in multiple environments and may assist a lone physician with little supplies who has to decide between slow and safe transportation versus a rapid, but more dangerous, approach. Ultrasound has become faster, cheaper, more portable, more rugged, and more versatile. There appears to be a future in austere and deployed medicine for ultrasound.

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Nutrition and Fitness

Caffeine Content of Dietary Supplements Consumed on Military Bases

Journal of Internal Med
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7 Jan 2013

Excessive caffeine consumption, particularly when combined with other stimulants, may increase the risk of hypokalemia, rhabdomyolysis, and other heat-related injuries among athletes and military personnel. Caffeine is consumed in a wide range of popular items including coffee, teas, sodas, energy drinks, energy gels, chocolate, gums, and over-the-counter medications. Dietary supplements, which are commonly consumed by military personnel, are a poorly characterized source of caffeine. Only with accurate information about the quantity of caffeine in dietary supplements can consumers and clinicians be assured of safe use. As part of an ongoing multidisciplinary collaboration to promote dietary supplement safety, we analyzed some of the most popular supplements sold on military bases to determine the accuracy of information available to military personnel and their health care providers regarding caffeine content in dietary supplements.

METHODS

We identified the most popular dietary supplements sold as capsules (excluding drinks and gels) on military installations labeled as containing either (1) caffeine or (2) 1 or more herbal ingredient known to naturally contain caffeine but without “caffeine” listed on the label. Supplements were purchased at a large, local retail store selling dietary supplements. The quantity of caffeine per serving in the supplements was determined by high-pressure liquid chromatography with UV (HPLC-UV) absorbance after solvent extraction. If the caffeine level was below the limit of quantitation by the HPLC-UV method, liquid chromatography with tandem mass spectrometry detection was used. The results obtained were compared with the caffeine content listed on the product label. All analyses were performed by NSF International.

RESULTS

Thirty-one supplements met our inclusion criteria. Twenty products listed caffeine on the label, and 9 of these products' labels (45%) listed an accurate amount of caffeine (within 10% more or less than the amount listed on the label). Caffeine amounts listed on the label of 5 of the 20 products (25%) varied widely from chromatographically determined levels, with ranges from 27% to 113% of the labeled quantity. Of the 20 products, 6 (30%) listed caffeine as an ingredient without providing an amount on the label. All 6 of these products contained high amounts of caffeine, ranging from 210 to 310 mg per serving.

Eleven supplement labels listed an herbal ingredient that naturally includes caffeine but did not list “caffeine” on the label. Green tea leaf extract was listed on all 11 labels, with 3 labels also including a second caffeine-containing ingredient (black tea leaf [n = 1], white tea leaf extract [n = 1], and kola nut [n = 1]). Our analyses revealed that these products contained no to minimal amounts of caffeine (range, 0-3 mg of caffeine per serving).

COMMENT

The law regulating the manufacturing and sales of dietary supplements in the United States has loopholes that allow manufacturers to avoid listing the quantity of caffeine on the label. Our chemical analyses of the caffeine content in dietary supplements popular on military bases found that less than half (9 of 20 [45%]) of the analyzed supplements' labels provided clinically useful information regarding caffeine content. Of the 20 product labels listing caffeine, 5 (25%) failed to meet the minimal legal requirements in that they listed a “per serving” amount of caffeine that was inconsistent with what our analyses detected. In addition, 6 of the 20 product labels (30%) were compliant with legal standards, yet failed to provide clinically useful information about caffeine content even though they each contained more than 200 mg of caffeine per serving. For comparison, soft drinks are prohibited by law to contain more than 71 mg of caffeine per 12 fl oz.

A limitation of our study was that we tested only 1 sample of each supplement. Future research would need to determine if our findings are representative and if caffeine content varies from one sample to another. However, our findings are consistent with prior research demonstrating that commercially available dietary supplement labels do not provide sufficient information in respect to caffeine content.

Given the lenient legal framework and inaccurate labels, military personnel are unable to determine if a supplement can be safely combined with other products or foods containing caffeine. This is of increasing concern, as caffeine intake in the form of energy drinks has significantly increased over the past decade, and a recent Centers for Disease Control and Prevention study found that 45% of service members consume energy drinks on a daily basis. In addition, physician reports of adverse reactions are a cornerstone of monitoring supplement safety in the United States, but even after careful review of the label, clinicians are unable to determine if an adverse reaction may be associated with the caffeine contained in an individual supplement. To ensure consumer safety, accurate information on caffeine content should be provided on all dietary supplement labels.

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Effects of Fructose vs Glucose on Regional Cerebral Blood Flow in Brain Regions Involved With Appetite and Reward Pathways

Journal of the American Medical Association
Kathleen A. Page, MD; Owen Chan, PhD; Jagriti Arora, MS; Renata Belfort-DeAguiar, MD, PhD; James Dzuira, PhD; Brian Roehmholdt, MD, PhD; Gary W. Cline, PhD; Sarita Naik, MD; Rajita Sinha, PhD; R. Todd Constable, PhD; Robert S. Sherwin, MD
2 January 2013

Abstract

Importance

Increases in fructose consumption have paralleled the increasing prevalence of obesity, and high-fructose diets are thought to promote weight gain and insulin resistance. Fructose ingestion produces smaller increases in circulating satiety hormones compared with glucose ingestion, and central administration of fructose provokes feeding in rodents, whereas centrally administered glucose promotes satiety.

Objective

To study neurophysiological factors that might underlie associations between fructose consumption and weight gain.

Design, Setting, and Participants

Twenty healthy adult volunteers underwent 2 magnetic resonance imaging sessions at Yale University in conjunction with fructose or glucose drink ingestion in a blinded, random-order, crossover design.

Main Outcome Measures

Relative changes in hypothalamic regional cerebral blood flow (CBF) after glucose or fructose ingestion. Secondary outcomes included whole-brain analyses to explore regional CBF changes, functional connectivity analysis to investigate correlations between the hypothalamus and other brain region responses, and hormone responses to fructose and glucose ingestion.

Results

There was a significantly greater reduction in hypothalamic CBF after glucose vs fructose ingestion (−5.45 vs 2.84 mL/g per minute, respectively; mean difference, 8.3 mL/g per minute [95% CI of mean difference, 1.87-14.70]; P = .01). Glucose ingestion (compared with baseline) increased functional connectivity between the hypothalamus and the thalamus and striatum. Fructose increased connectivity between the hypothalamus and thalamus but not the striatum. Regional CBF within the hypothalamus, thalamus, insula, anterior cingulate, and striatum (appetite and reward regions) was reduced after glucose ingestion compared with baseline (P < .05 significance threshold, family-wise error [FWE] whole-brain corrected). In contrast, fructose reduced regional CBF in the thalamus, hippocampus, posterior cingulate cortex, fusiform, and visual cortex (P < .05 significance threshold, FWE whole-brain corrected). In whole-brain voxel-level analyses, there were no significant differences between direct comparisons of fructose vs glucose sessions following correction for multiple comparisons. Fructose vs glucose ingestion resulted in lower peak levels of serum glucose (mean difference, 41.0 mg/dL [95% CI, 27.7-54.5]; P < .001), insulin (mean difference, 49.6 μU/mL [95% CI, 38.2-61.1]; P < .001), and glucagon-like polypeptide 1 (mean difference, 2.1 pmol/L [95% CI, 0.9-3.2]; P = .01).

Conclusion and Relevance

In a series of exploratory analyses, consumption of fructose compared with glucose resulted in a distinct pattern of regional CBF and a smaller increase in systemic glucose, insulin, and glucagon-like polypeptide 1 levels.

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Fructose Ingestion and Cerebral, Metabolic, and Satiety Responses

Journal of the American Medical Association
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2 January 2013

Fructose found in sucrose and high-fructose corn syrup, both of which contain roughly equal amounts of glucose, has been the subject of intense debate. Products containing fructose are preferred by consumers and cooks over those containing only glucose, owing to the intrinsically greater sweetness of fructose and its ability to improve the appearance and texture of baked goods. As a result, sucrose and high-fructose corn syrup are added not just to sodas, energy drinks, and sports drinks favored by adolescents and adults but also to juice drinks consumed by infants and toddlers and to snacks, processed meats, sauces, and many other foods consumed by people of all ages.

It is not surprising, then, that the consumption of sugar and high-fructose corn syrup in the United States has substantially increased in the last few decades. Paralleling this increase has been an increase in obesity, especially among children and adolescents, for whom milk intake has reciprocally declined. Has increased sugar intake caused the obesity epidemic? The stakes in this debate are high and extend from governmental policy on farm subsidies and health care costs, to the marketplace involving food manufacturers, to school revenues from beverage machines, to mom-and-pop stores selling baked goods.

Teasing out the individual contribution of a single nutrient on obesity is difficult, but there are reasons to believe this might be possible for fructose. Prospective cohort studies link increased intake of sugar-sweetened beverages with weight gain in adults. A recent meta-analysis of feeding studies showed that participants consuming ad libitum high-fructose diets gained significantly more weight than participants consuming control diets. Data from animal studies consistently show that compared with glucose, fructose added to the diet or injected directly into homeostatic appetite control centers of the hypothalamus increases food intake and body weight.

In this issue of JAMA, Page and colleagues report their findings from a proof-of-concept study demonstrating that animal studies of the brain effects of fructose on appetite promotion are relevant to humans. Proof-of-concept studies use experimental conditions that provide maximal contrast between the intervention and control conditions so as to increase the likelihood of finding differences. Subsequent studies would then refine the experimental conditions to detect more subtle differences. Using a magnetic resonance imaging technique, arterial spin labeling, the authors quantify regional cerebral blood flow as a surrogate for brain activity in a group of healthy, young, normal-weight study participants before and after drinking a 75-g preparation of either pure glucose or fructose. In studies focusing on the hypothalamus, arterial spin labeling has

demonstrated several advantages over the more traditional blood oxygen level–dependent (BOLD) functional magnetic resonance imaging method in that it provides more precise localization and is less susceptible to artifactual image degradation from surrounding bony sinuses.

The major new finding reported by Page et al is that the hypothalamic brain signal generated in response to fructose ingestion was statistically different from the response following glucose ingestion. The directionality of the difference is not as important as the fact that a difference was found and is accompanied by an increased sensation of fullness and satiety after glucose, but not fructose, consumption. These findings support the conceptual framework that when the human brain is exposed to fructose, neurobiological pathways involved in appetite regulation are modulated, thereby promoting increased food intake.

Not to be overlooked in the report were several brain regions outside of the hypothalamus in which the response to the fructose or glucose ingestions was assessed by both arterial spin labeling and functional connectivity analysis using BOLD measurements. Functional connectivity analysis explores which parts of the brain communicate with a given “seed” region, in this case the hypothalamus. This was accomplished by testing the strength of the correlations in BOLD signal patterns between brain regions. Subcortical regions, including the thalamus and striatum, showed differences for both regional cerebral blood flow and connectivity patterns. The striatum, as with the hypothalamus, did not deactivate during fructose ingestion, which may cause decreased inhibitory responses during fructose ingestion relative to glucose ingestion. By containing “reward” pathways (dopaminergic neurons implicated in addictive behaviors), striatal sites may be involved in the “hedonic” aspects of food intake regulation often ascribed to the greater perceived sweetness of fructose compared with glucose.

Because reduced insulin secretion is claimed as a benefit of fructose consumption relative to glucose, it is ironic that greater secretion of insulin after glucose ingestion correlated with reduced striatal signal, although this is in keeping with the known ability of insulin to reduce food intake in humans. In addition, cortical structures, including the rostral anterior cingulate and the anterior insula, showed distinct activation patterns during the dietary manipulations. These cortical regions have been broadly implicated in higher-order control functions beyond that of appetite behaviors.

When results of studies manipulating a dietary element show adverse effects on food intake leading to increased body weight, a common counterargument is that it is the excess calories that are important, not the food. Simply put: just eat less. The reality, however, is that hunger and fullness are major determinants of how much humans eat, just as thirst determines how much humans drink. These sensations cannot simply be willed away or ignored. If the addition of a food group is a primary determinant of the weight gain through enhancing appetite, then whether that food contributes to comorbidity directly or indirectly through effects of increased calorie intake becomes moot. The remedy remains eating less, but the means involve reducing the food element, if possible.

To more definitively resolve the role of fructose in obesity, studies are needed that include obese persons and those at risk for developing obesity. Fructose should be consumed as an added sugar, reflecting real-world conditions, and control conditions should include alternatives such as water, milk, and foods free of added sugars. Even then, the study population will need to be large enough and have long enough follow-up (>1 year) to detect potentially small changes in food intake and body weight, especially in susceptible subgroups. But the implications of the study by Page et al, as well as the mounting evidence from epidemiologic, metabolic feeding, and animal studies, are that the advances in food processing

and economic forces leading to increased intake of added sugar and accompanying fructose in US society are indeed extending the supersizing concept to the population's collective waistlines.

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Obesity

Does Body Mass Index Adequately Convey a Patient's Mortality Risk?

Journal of American Medicine
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2 Jan 2013

What adult weight best advances health, minimizes the risk of chronic disease, and promotes longevity? This question has engaged the interest of the public, health care professionals, and a wide range of clinical investigators. The consequences of answering this question have profound health, social, and economic implications for individuals, communities, and the population as a whole.

A Metropolitan Life Insurance Company (MLIC) statistician revealed an association between longevity and body weight in 1942. Lifespan was longest when body weight was maintained at the same level as 25-year-old adults with similar height and frame size. The initial 1942 MLIC ideal body weight tables were later revised to desirable weight tables in 1959 and again in 1983 to height and weight tables. Obesity was considered present when a person's weight exceeded his or her desirable weight by 20%.

This approach was popular among researchers. However, the MLIC tables were complex, had technical limitations, and were not easily applied when evaluating patients in the clinic or when screening individuals in field settings. Because body weight increases with height, there is a need to establish normal body weight as a function of height. This is accomplished by the body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), which increases with greater adiposity. In 1985, a National Institutes of Health consensus panel defined overweight-obesity as a BMI of 27.8 or greater for men and 27.3 or greater for women. The BMIs at these levels are approximately 20% above the MLIC desirable weights. The panel recommended weight loss for people whose BMIs exceeded these thresholds. In 1997, a World Health Organization Consultation on obesity defined preobesity (overweight) as a BMI of 25 or greater and class (grade) 1 obesity as a BMI of 30 or greater, class 2 as a BMI of 35 or greater, and class 3 as a BMI of 40 or greater. One year later, a National Heart, Lung, and Blood Institute (NHLBI) expert panel recommended a similar BMI-based definition of overweight and obesity. Total mortality has a U-shaped relationship with BMI. Mortality rates sharply increase at BMIs of less than 18.5 and of greater than 30.

In this issue of *JAMA*, Flegal and colleagues report their findings from a systematic review and meta-analysis of associations between standard NHLBI BMI categories for overweight and obesity and all-cause mortality. Using rigorous study selection criteria and statistical methods, and

based on a sample of more than 2.88 million individuals with more than 270 000 deaths, they confirmed significantly increased all-cause mortality hazard ratios (HRs) relative to normal weight (defined as a BMI of 18.5-<25) for overall obesity (grades 1, 2, and 3 combined; HR, 1.18 [95% CI, 1.12-1.25]) and grades 2 and 3 obesity (HR, 1.29 [95% CI, 1.18-1.41]). Higher all-cause mortality was not observed in individuals with grade 1 obesity. Mortality was significantly lower among those who were overweight (HR, 0.94 [95% CI, 0.91-0.96]) compared with normal weight individuals. The findings remained consistent even after adjusting for smoking status, preexisting disease, or weight and height reporting method (self or measured).

The present investigation extends a 2005 study by Flegal et al based on the National Health and Nutrition Examination Survey that did not find an increased mortality risk in overweight persons. Among others with similar findings, McGee et al found no increase in all-cause mortality for overweight males (relative risk, 0.965 [95% CI, 0.922-1.009]) and females (relative risk, 0.968 [95% CI, 0.925-0.987]) in a 2005 meta-analysis including 388 622 individuals with 60 374 deaths. Orpana et al estimated the relationship between all-cause mortality and BMI in a nationally representative sample of 11 326 Canadian adults and found a relative mortality risk of 0.76 (95% CI, 0.58-0.99) in overweight nonsmokers.

Based on these observations, are the concerns about overweight as currently defined unfounded? Answering this question requires consideration of BMI as a health risk phenotype. Body mass index accounts for about two-thirds of the between-individual variation in total adiposity. Body mass index does not account for sex, race, age, and fitness differences in fat mass even at the same body weight. Race and age both influence the associations among disease risk, mortality, and BMI. Moreover, fat distribution varies widely even among individuals at the same level of adiposity, with an abdominal fat pattern conveying the greatest health risks. The NHLBI clinical guidelines recognize this limitation of BMI, and waist circumference is recommended as an additional surrogate marker of the health risks associated with adiposity and adipose tissue distribution.

Body mass index is known to be an imperfect predictor of metabolic risk. Some individuals with normal BMI have an overweight-obesity metabolic pattern. Others with high BMIs appear to have a healthy metabolic pattern. Factors such as cardiorespiratory fitness are also independent predictors of total mortality in some groups after controlling for BMI, waist circumference, and percentage of body fat. A relatively large fat mass can mask small muscle mass, which is a condition referred to as sarcopenic obesity. Sole use of BMI as a health risk phenotype aggregates people with substantial differences in nutritional status, disability, disease, and mortality risk together into similar BMI categories. Identification of at-risk individuals for overweight and grade 1 obesity is best captured by considering traditional risk factors, including blood pressure, blood lipid levels, and fasting blood glucose level, in addition to BMI, waist circumference, or both as recommended in the NHLBI report. Newer markers such as those representing systemic inflammation may also extend risk prediction beyond BMI.

Apart from an imperfect relationship between BMI and phenotype, are there explanations why overweight may be associated with a lower mortality risk? Physicians are increasingly aggressive in managing risk factors among patients with overweight or obesity. Substantial declines in cardiovascular disease risk factors have been reported among persons with obesity, more so than in those with normal weight. New pharmacological therapies and invasive treatments for existing disease may prolong survival and, when combined with public health measures, may account for the weakening of associations between obesity and mortality observed over time. Overweight and grade 1 obesity might lead to greater morbidity that is not captured when evaluating associations between all-cause mortality and BMI.

What appears to be a reduced or very low all-cause mortality risk in overweight people may represent an artifact of applying a wide range of BMIs in the normal weight reference category established by the NHLBI. In most studies, the lowest all-cause mortality is observed between a BMI of 22 and 25. Persons with a BMI between 18.5 and 22 have higher mortality than those with a BMI between 22 and 25. Placing these persons in a single group raises the mortality rate for the normal weight group. The average resulting from combining persons in the lowest mortality category (BMI of 22-25) with those who have greater mortality (BMI of 18.5-22) might explain why the NHLBI category of normal weight has an observed mortality similar to class 1 obesity (BMI of 30-<35).

Can overweight as defined by BMI actually have a protective association with mortality? The presence of a wasting disease, heart disease, diabetes, renal dialysis, or older age are all associated with an inverse relationship between BMI and mortality rate, an observation termed the obesity paradox or reverse epidemiology. The optimal BMI linked with lowest mortality in patients with chronic disease may be within the overweight and obesity range. Even in the absence of chronic disease, small excess amounts of adipose tissue may provide needed energy reserves during acute catabolic illnesses, have beneficial mechanical effects with some types of traumatic injuries, and convey other salutary effects that need to be investigated in light of the studies by Flegal et al and others.

The study by Flegal et al confirms that obese individuals with a BMI of 35 or greater are at increased risk of mortality, as are their underweight counterparts with a BMI less than 18.5. The large BMI range between these extremes includes persons with differing adiposity, adipose tissue distribution, muscularity, nutritional status, and disease risk factors. Not all patients classified as being overweight or having grade 1 obesity, particularly those with chronic diseases, can be assumed to require weight loss treatment. Establishing BMI is only the first step toward a more comprehensive risk evaluation.

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Obesity: many hands to make light(er) work

The Lancet
12 Jan 2013

Westminster City Council in London, UK, recently offered the provocative proposal that benefit or welfare payments could be “varied to reward or incentivise” people who were prescribed exercise classes, as a public health measure for those deemed to be overweight or obese. This idea would be counterproductive if it were not so evidently impractical. Yet the report in which this suggestion is embedded, *A Dose of Localism—the Role of Councils in Public Health*, is interesting in that it attempts to contribute some new thinking to health promotion by local authorities in Britain, in a climate of severe financial pressures.

At the national level, the Coalition Government's responsibility deal seeks to bring commercial partners together with public sector stakeholders in a bid to craft pragmatic policies for judicious food and alcohol consumption, as well as promotion of exercise. Beginning on Jan 7, Change4Life has launched a prominent advertising campaign to highlight unhealthy ingredients contained in popular foods and drinks. Junior Health Minister

Anna Soubry says that the “continuing success of Change4Life” will contribute to addressing the fact that “England has one of the highest rates of obesity in Europe, with over 60% of adults and a third of 10 and 11 year olds overweight or obese”. On the other side of the ideological divide, shadow health secretary Andy Burnham argues that the Coalition's approach, which involves collaboration with arguably culpable food and drink companies amongst others, is misguided; he has urged legal limits for sugar, salt, and fat in food aimed at children, and the opposition Labour party is shortly to publish a policy review document on “children, food and obesity”.

Behind the political histrionics there is a serious issue with obesity in Britain. Indeed, people are gaining weight in developed and developing countries alike, and the consequences in terms of rising incidence of non-communicable diseases and escalating demands on health systems will be extremely damaging both individually and collectively. In a report, *Action on Obesity: Comprehensive Care for All*, released by the Royal College of Physicians (RCP) on Jan 1, 2013, a blueprint is set out for how the UK's National Health Service (NHS) needs to adapt its approach to the obesity problem. The report quotes an annual estimated cost of £5 billion for dealing with the health-care burden of obesity, and projects this to double by 2050; however, the total societal costs will be much greater.

Current NHS services for obesity are said to be “patchy”, with a lack of integration of professionals and pathways for treatment of different disorders that are associated with obesity, including colon cancer, diabetes, and coronary heart disease. The report perceives a need for multidisciplinary teams to address severe and complex cases of obesity, as in oncology for instance—such teams could bring together physicians, surgeons, and psychiatrists along with dietitians and professionals in physical exercise to share training and expertise in effective services, with a goal of streamlined treatment of obesity.

Perhaps most damningly, current training in management of obesity for health-care professionals is described by the RCP as “inadequate”. One recommendation is that obesity (or bariatric) medicine be established as a subspecialty for doctors in the UK, which would engender specialist knowledge and training and allow individuals to lead or contribute to improved care in local centres of excellence. The report acknowledges that general practitioners should have a “pivotal” role in prevention and management of obesity; however, their training to date is described as “minimal and often poorly coordinated”. On a brighter note, what might improved medical management of obesity cost? Although not attempting to provide detailed projections of the cost of providing joined-up care, the RCP report does note that some obesity treatments—including interventions such as bariatric surgery—are cost effective.

The *Lancet* Obesity Series in 2011 clearly articulated the complexity of obesity control and prevention, and called for leadership and strong public health measures to improve the food and built environments. It argued that a systems approach is needed with multiple sectors involved. Obesity is a physiological response to an abnormal environment. Sadly, the RCP report is a missed opportunity to link a clinical and health sector response with effective public health programmes. The report can only be a part of the holistic and committed approach that is needed to counter obesity effectively, comprising comprehensive public health programmes to forecast, monitor, and prevent obesity worldwide.

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Effect of an Accelerometer on Body Weight and Fitness in Overweight and Obese Active Duty Soldiers

Military Medicine
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January 2013

ABSTRACT

This study evaluated whether using a web-linked accelerometer, plus mandatory physical training, is associated with various weight- and fitness-related outcomes in overweight/obese active duty soldiers. Soldiers who failed the height/weight standards of the Army Physical Fitness Test (APFT) were randomized to use a Polar FA20 accelerometer device (polar accelerometer group [PA], *n* = 15) or usual care (UC, *n* = 13) for 6 months. Both groups received 1.5 hours of lifestyle instruction. We collected data at baseline, 2, 4, and 6 months, and evaluated group differences in temporal changes in study outcomes. At 6 months, 1/28 subjects (UC) passed the APFT height/weight standards. There were no group differences in changes in weight (PA: −0.1 kg vs. UC: +0.3 kg; *p* = 0.9), body fat (PA: −0.9% vs. UC: −1.1%; *p* = 0.9), systolic blood pressure (PA: +1.3 mm Hg vs. UC: −2.1 mm Hg; *p* = 0.2), diastolic blood pressure (PA: +3.8 mm Hg vs. UC: −2.4 mm Hg; *p* = 0.3), or resting heart rate in beats per minute (bpm) (PA: +7.8 bpm vs. UC: +0.1 bpm; *p* = 0.2). These results suggest that using an accelerometer with web-based feedback capabilities plus mandatory physical training does not assist in significant weight loss or ability to pass the APFT height/weight standards among overweight/obese soldiers.

INTRODUCTION

The prevalence of obesity in the United States is about 33.8% and worldwide obesity (body mass index [BMI] ≥ 30 kg/m^2) has more than doubled since 1980 (World Health Organization, http://www.who.int/mediacentre/factsheets/fs311/en/index.html). It is estimated that by 2048, all adults in the United States could be overweight (BMI ≥ 25 kg/m^2) and therefore at risk of developing related chronic diseases such as type 2 diabetes mellitus, hypertension, and heart disease. The military population has paralleled the general population in this risk profile with over 60% of service members being overweight or obese. According to a recent publication by the Armed Forces Health Surveillance Center, the percentage of active duty members who needed medical attention because of overweight or obesity tripled from 1.6% in 1998 (*n* = 25,766) to 5.3% in 2010 (*n* = 86,186). They further reported that over the same period of time, the median duration of military service after an initial overweight-related diagnosis was 3 years 6 months, which was 1 year 3 months less than matched controls.

Overweight and obesity are significant military medical concerns because they are associated with decreased physical fitness and both acute and chronic adverse health effects. They also contribute to significant financial burden, decreased operational effectiveness, and reduced eligibility to serve. Since 1992, 24,000 U.S. Army soldiers have been discharged for failure to comply with Army Regulation 600-9 for physical fitness.

Since pharmacologic weight-loss interventions are not approved for use in active duty soldiers, alternate methods such as diet, exercise, and counseling are key factors in therapy. Internet-based interventions serve as an acceptable delivery method, but evidence suggests that programs must go beyond providing advice and information alone. A review of Internet use for weight loss suggests that successful online programs include a structured approach to modifying energy balance, the use of cognitive-behavioral strategies such as self-monitoring, and individualized feedback and support. A recent publication in the New England Journal of Medicine evaluated weight-loss intervention methods. Appel et al studied 415 obese patients with at least 1 other cardiovascular risk factor. Over a 24-month period, patients receiving remote weight-loss support via telephone, a study-specific web site, and e-mail lost 4.6 kg in weight, and patients receiving both remote and in-person support during group and individual sessions lost 5.1 kg. Both intervention groups lost significantly more weight than a control group using self-directed weight-loss methods (−0.8 kg), but there was no significant difference in change in weight from baseline between the 2 intervention groups.

The use of accelerometers and web-based automated systems focused specifically on changing physical activity has been studied infrequently in the past. A study of 265 civilians, who were given an accelerometer as part of a web-based automated behavior system, found a high rate of compliance and an average 2.6-kg reduction in weight over 12 weeks. A previous study done by the same group found that the web-based program and accelerometer produced an average increase of 2 hours and 18 minutes of moderate physical activity per week, with a greater loss of body fat when compared to the control group (wearing the accelerometer but without access to the web program which provides feedback). Currently, interventions focused specifically on changing physical activity behavior are in their infancy. A recent review of web-based weight-loss interventions in adults found only 9 randomized, controlled studies published between 2001 and 2009. Conclusions were that online weight-loss programs with self-reporting showed greatest retention rates but studies with an in-person component in addition were the only ones that met weight-loss goals of at least 5%. Attrition was high and engagement was low across most studies as evidenced by minimal use of the Internet resources. When incentives were used, log-in frequency increased, but this did not necessarily predict greater weight loss.

Finding practical interventions, which effectively target weight management and physical inactivity, would be of great value both to the soldier and to the military. We therefore sought to investigate the effect of a minimally time intensive, nonpharmacologic intervention (an accelerometer and associated interactive website) on improving weight and body fat content of overweight and obese active duty soldiers. We hypothesized that active duty soldiers who fail the height/weight standards of the Army Physical Fitness Test (APFT), if given an accelerometer device, will be able to improve their weight status and other fitness metrics after using this device for 6 months.

METHODS

Subjects

Subjects were recruited from a pool of active duty soldiers who trained within the Walter Reed Health Care System (Washington, DC, Metropolitan Area). Subjects were eligible to participate if they were active duty Army soldiers, aged 18 years or older, and had recently failed the height/weight standards of the most recent APFT. Subjects were excluded if they had an Army physical fitness profile precluding participation in the APFT and/or were pregnant. No monetary compensation was given for participation; but, if subjects were randomized to the usual care (UC) group, they

were given the opportunity to use the accelerometer for 3 months after completion of the study. All subjects were offered an opportunity to be evaluated for secondary causes of obesity by an endocrinologist at the completion of the study.

Design

This was a prospective, open-label, randomized controlled trial. The Principal Investigator was excluded from recruitment to minimize the potential influence of rank on subject enrollment. The trial was approved by the Walter Reed Army Medical Center Institutional Review Board (Protocol no. 350703), and all subjects provided written informed consent. Recruitment occurred between October 2009 and October 2011.

Subjects were randomized to one of two arms using block randomization techniques in SAS (SAS Institute, Cary, North Carolina)—an intervention group that received a Polar FA20 accelerometer (polar accelerometer group [PA], Polar Electro, Lake Success, New York) and a UC group. The study enrolled 28 subjects. This number was short of the original sample size proposed because of difficulty with subject recruitment. However, a sample of this size was sufficient to test our hypothesis regarding weight loss, assuming that UC subjects lose an average of 5 pounds (SD = 2.5 pounds), PA subjects lose an average of 10 pounds (SD = 5.0 pounds), power = 0.80, $\alpha = 0.05$, and two-sided tests comparing means would be conducted.

Of the 28 subjects randomized initially, reasons for loss to follow-up were 1 pregnancy, 1 Army physical fitness profile, 1 permanent change of station, 1 expiration of term of service, and 1 drop out for an unknown reason. Data from 42 follow-up visits were missing because of inability to contact the subject. Of the 20 subjects whose data were used in analysis, follow-up rates were 17/20 (85%) at 2 months, 8/20 (40%) at 4 months, and 10/20 (50%) at 6 months.

Protocol

The PA group received a Polar FA20 accelerometer (Polar Electro) and an associated Flowlink hardware component to allow recording and interaction with the Polar Personal Trainer website (www.polarpersonaltrainer.com [provides subjects data and feedback as described below but was not used by the investigators to guide intervention]). The Polar FA20 product is worn as a wristwatch that uses an accelerometer technology and patented filtering and signal processing methods to determine when the user is active. Active time is divided into health-enhancing and fitness-enhancing activity. Calories, distance, and active steps are only accumulated when active time is detected. The wristwatch is synchronized with the password-protected website with a press of a button and approximation with the Flowlink device. Users are able to track activity levels online over time and modify exercise routines as desired. The intervention group was able to contact the study team at any time regarding technical issues concerning the device. The UC group proceeded with usual care consisting of self-directed exercise and/or U.S. Army mandated physical training.

At baseline, all subjects received 1.5 hours of standardized health instruction, given by an exercise physiologist, stressing the importance of exercise on healthy physiology, eliminating excuses, and examples of exercise programs. All subjects also had access to nutrition counseling via self-referral, but this was not mandatory. After initial recruitment, no further health or exercise counseling was provided and online records of the Polar Personal Trainer website were not reviewed by the investigators.

Measures

Data collection occurred via in-person visits and APFT records. Subjects were asked to make 2-, 4-, and 6-month follow-up visits with the associate investigators and were sent e-mail reminders for each visit. Age and sex were collected at baseline. The outcomes, weight, blood pressure (BP), heart rate measured in beats per minute (bpm), and body fat measurements per U.S. Army protocol (Army Regulation 600-9; using neck, waist, and hip circumference), were collected at baseline, 2, 4, and 6 months. Height and the subjective physical activity levels using the International Physical Activity Questionnaire (IPAQ) were collected at baseline and 6 months. The IPAQ long form collected data on the duration and frequency of walking, and moderate-intensity and vigorous-intensity activity in the domains of work, transportation, domestic chores and gardening, and leisure time. IPAQ scores were calculated using the summation of the duration (in minutes) and frequency (days), and categorized as high (≥3000 Metabolic Equivalent of Task [MET]-minutes/week), moderate (≥600 MET-minutes/week), or low (<600 MET-minutes/week) activity level.

Statistical Analysis

The analyses first compared baseline characteristics of the PA and UC groups using *t*-tests and χ^2 tests. Next, we calculated "change-from-baseline" scores for the outcome measures by subtracting the baseline value from the follow-up value. We calculated change-from-baseline scores using the 6-month values only because of missing data for the interim measurements. Then, the analyses examined group differences in changes-from-baseline using *t*-tests. Because the sample was small, we conducted nonparametric tests of changes-from-baseline as well to validate the results of the *t*-tests. Where appropriate, such as with weight and waist circumference, we conducted separate analyses for men and women. All statistical analyses used SAS 9.2 (SAS Institute).

RESULTS

Baseline Characteristics

Of the 28 randomized subjects, 53.8% were male, average weight was 96.2 kg (SD = 18.9 kg), average body fat was 36.4% (SD = 9.4%), and average BMI was 36.8 kg/m^2 (SD = 21.6 kg/m^2). Average age of the subjects was higher in the PA group compared to the UC group (35 vs. 28.7 years, respectively; $p = 0.03$). Females in the PA group had greater waist circumference (93.4 cm vs. 85.7 cm, $p = 0.04$) and body fat (45.3% vs. 38.5%, $p = 0.04$) than females in the UC group. The overall group differences in body fat are attributable to this gender group difference. Baseline mean total IPAQ scores in MET-minutes/week were 8334.7 in the PA group and 13296.8 in the UC group, both of which correlated with high activity levels, and this was not significantly different.

Change in Weight

After randomization, analysis was completed in 11 subjects in the UC group and 9 subjects in the PA group. At 6 months, the mean change in weight from baseline was +0.3 kg in the UC group and −0.1 kg in the PA group ($p = 0.88$). When divided by weight-change categories, 5/11 (45%) lost greater than 1 kg in the UC group vs. 4/9 (44%) in the PA group. There was no change in weight (less than 1 kg change) in 1/11 (9%) UC

subjects vs. 3/9 (33%) PA subjects. There was greater than 1 kg weight gain in 5/11 (45%) UC subjects and 2/9 (22%) PA subjects. There was no statistically significant difference in mean change in weight at 6 months between groups, even when analyzed by categories of weight change. Only 1/20 subjects, who was in the UC group, passed the AFPT height/weight standards at 6 months.

Change in Fatness and Fitness

The mean change in body fat percent was −1.1% in the UC group and −0.9% in the PA group ($p = 0.92$). The mean changes in neck circumference, waist circumference, and female hip circumference between the UC and PA groups were, respectively, +0.2 cm vs. +0.4 cm ($p = 0.87$), −1.2 cm vs. −3.0 cm ($p = 0.38$), and −0.5 cm vs. −0.7 cm ($p = 0.94$). Mean changes in resting heart rate and BP also were not significantly different between groups.

Comparison of baseline and 6-month IPAQ scores could only be assessed in 9 subjects who completed the survey at the completion of the study. In the UC group, 3 subjects decreased activity level and 1 did not change activity level. In the PA group, 3 subjects increased activity level and 1 subject decreased activity level. Mean change in total physical activity level in the PA group was −474.7 MET-minutes/week and in the UC group was −5645.6 MET-minutes/week ($p = 0.45$).

DISCUSSION

The use of mobile electronic devices that track physical activity parameters is rising in popularity likely attributable to its ability to provide timely feedback on weight-loss goals. Devices with web-based feedback have especially become user-friendly, interactive tools that can give additional information about progress and potential improvement over time. This study evaluated whether U.S. Army soldiers, when given a wristwatch style accelerometer with web-based feedback capability for 6 months, would have more weight loss, body fat loss, and higher rates of passing the APFT height/weight standards compared to controls subject to UC. Besides baseline health counseling provided to all study subjects, there was no additional weight-loss support provided by any of the investigators and use of the devices was not monitored. Although this study was limited by the number of subjects, access to the accelerometer did not seem to have any effect on mean weight loss, body fat loss, or ability to pass the APFT height/weight standards. Mean neck, waist, and hip circumferences did not decrease significantly in either intervention group and there was no effect on mean BP or heart rate, or on subjective physical activity scored by the IPAQ.

The limited data were a result of low initial recruitment and high dropout rate. Attrition rates were 39% at the 2-month visit, 71% at the 4-month visit, and 64% at the 6-month visit. Recruitment occurred over 2 years and was found to be difficult despite attendance by the associate investigators at both the biannual APFT and the Army Weight Control Program meetings. Overweight soldiers are usually required to attend remedial physical fitness sessions plus Army Weight Control Program meetings, and these commitments in addition to their usual duties could have been deemed as cumbersome without any incentive provided. In general, soldiers live a structured lifestyle that is created for them rather than by them, and it was our initial hypothesis that access to a device that could assist with self-directed weight loss without incurring an additional time commitment would be preferred and utilized. Self-motivation would of course be a strong component in being successful. From the

experience of conducting this study and the results, we now believe it was actually the “absence” of an exogenous support system that led to a lack of improvement in physical activity and weight-loss parameters.

These results, together with findings from previous research, suggest that the addition of continued person-to-person contact throughout the study for social support, education, and weight-loss strategies would potentially improve outcomes. In addition to the results of the Appel et al[10] study described earlier, another recent article emphasized the benefits of enhanced weight-loss counseling when compared with even basic weight-loss education. Wadden et al randomized 390 obese adults to 3 different groups: UC with quarterly weight-management education with a primary care provider, brief lifestyle counseling which included quarterly visits plus monthly sessions with a lifestyle coach, or enhanced lifestyle counseling defined as brief lifestyle counseling as above plus meal replacements or weight-loss medication. They found that subjects in the enhanced lifestyle counseling group lost significantly more weight on average than the UC group and this benefit remained even after subjects given sibutramine were excluded.

A previously mentioned review on web-based weight-loss interventions found wide variability in weight-loss outcomes among several studies from no weight loss to an average loss of 7.6 kg. Several studies reviewed showed a positive association between log-in frequency and weight loss. Because of study method differences, it has been historically difficult to extrapolate a preferred intervention, and high attrition rates with minimal use of the Internet resources have been described. Among studies cited, the highest attrition rate found was 41%, and this has been associated with less education and less initial weight loss. As in our study, low retention tends to affect the power and ability to detect a weight-loss difference.

Despite all but one subject failing the APFT height/weight standards, as well as persistent overweight and obesity, subjective physical activity scores on both the baseline and 6-month IPAQ were mostly in the “high” range. Since we did not review physical activity history on the Polar FA20 accelerometer website, we cannot disprove these findings; but, we found this discordance interesting and recommend that future studies focus on comparison of subjective and objective measures of physical activity in the military population.

CONCLUSION

The results of this study implicate a need for more aggressive methods of weight-loss assistance in the military population. Even in an environment where physical fitness is given the utmost importance and priority, attempts at using a noninvasive technique, though potentially time consuming, were unfruitful. Both recruitment and retention were barriers to high-quality data. Future studies in the military setting would benefit from a focus on behavior modification strategies in addition to web-based programs. Possible methods include interactive education on exercise techniques and accelerometer use with continued feedback provided either in-person or via web-contacts, baseline goal-setting with incentives provided at each stage achieved, a concomitant diet modification plan, and longer follow-up with a weight-maintenance phase.

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Association of All-Cause Mortality With Overweight and Obesity Using Standard Body Mass Index Categories

Journal of the American Medical Association
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2 January, 2013

Abstract

Importance

Estimates of the relative mortality risks associated with normal weight, overweight, and obesity may help to inform decision making in the clinical setting.

Objective

To perform a systematic review of reported hazard ratios (HRs) of all-cause mortality for overweight and obesity relative to normal weight in the general population.

Data Sources

PubMed and EMBASE electronic databases were searched through September 30, 2012, without language restrictions.

Study Selection

Articles that reported HRs for all-cause mortality using standard body mass index (BMI) categories from prospective studies of general populations of adults were selected by consensus among multiple reviewers. Studies were excluded that used nonstandard categories or that were limited to adolescents or to those with specific medical conditions or to those undergoing specific procedures. PubMed searches yielded 7034 articles, of which 141 (2.0%) were eligible. An EMBASE search yielded 2 additional articles. After eliminating overlap, 97 studies were retained for analysis, providing a combined sample size of more than 2.88 million individuals and more than 270 000 deaths.

Data Extraction

Data were extracted by 1 reviewer and then reviewed by 3 independent reviewers. We selected the most complex model available for the full sample and used a variety of sensitivity analyses to address issues of possible overadjustment (adjusted for factors in causal pathway) or underadjustment (not adjusted for at least age, sex, and smoking).

Results

Random-effects summary all-cause mortality HRs for overweight (BMI of 25-<30), obesity (BMI of ≥30), grade 1 obesity (BMI of 30-<35), and grades 2 and 3 obesity (BMI of ≥35) were calculated relative to normal weight (BMI of 18.5-<25). The summary HRs were 0.94 (95% CI, 0.91-0.96) for overweight, 1.18 (95% CI, 1.12-1.25) for obesity (all grades combined), 0.95 (95% CI, 0.88-1.01) for grade 1 obesity, and 1.29 (95% CI, 1.18-1.41) for grades 2 and 3 obesity. These findings persisted when limited to studies with measured weight and height that were considered to be adequately adjusted. The HRs tended to be higher when weight and height were self-reported rather than measured.

Conclusions and Relevance

Relative to normal weight, both obesity (all grades) and grades 2 and 3 obesity were associated with significantly higher all-cause mortality. Grade 1 obesity overall was not associated with higher mortality, and overweight was associated with significantly lower all-cause mortality. The use of predefined standard BMI groupings can facilitate between-study comparisons.

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Increased Adolescent Overweight and Obesity Documentation Through a Simple Electronic Medical Record Intervention

Military Medicine
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January 2013

ABSTRACT

Objective: The purpose of this project was to improve provider documentation of adolescent overweight and obesity through body mass index percentile (BMI%) documentation in the military's electronic medical record (EMR). Methods: Using the FOCUS-PDCA (Find-Organize-Clarify-Understand-Select-Plan-Do-Check-Act) model, we developed an intervention to improve rates of diagnosis of overweight/obesity in our adolescent medicine clinic. Medical technicians documented the patient's BMI% and growth chart in the EMR. Pre- and postintervention chart reviews of approximately 300 consecutive patient encounters compared the rates of overweight/obesity with provider-documented diagnosis. Results: A total of 333 pre- and 328 postintervention clinic encounters were reviewed. The rate of obesity calculated was similar between pre- and postintervention groups (30% vs. 31%). Correct diagnosis increased from 40% to 64% after the intervention. Females and patients seen by resident physicians were less likely to receive a correct diagnosis at baseline, but these differences were mitigated in the postintervention group. In multivariate analyses, only the intervention and provider type were predictive of an improvement in correct diagnosis. Conclusion: BMI% documentation in our EMR was an effective way to improve documentation of overweight/obese adolescent patients and may be particularly helpful for resident physicians.

INTRODUCTION

One-third of children are overweight or obese; the prevalence of obesity in the United States has more than tripled (from 5% to 17%) among children and adolescents over the past 30 years. Seventy percent of obese teenagers become obese adults, and childhood overweight/obesity has an estimated direct medical cost of $3 billion per year.

In addition to numerous well-described comorbidities, pediatric and adolescent overweight/obesity has a direct impact on both military readiness and resource utilization. It is estimated that one-third of all 17- to 24-year olds are too overweight to serve in the military, and since 1995, there has been a 70% increase in failed entry physicals because of being overweight. Combined active duty costs (medical care, lost training, attrition) and dependent/retiree costs related to overweight/obesity are more than $1.25 billion per year.

Screening for pediatric and adolescent overweight/obesity through body mass index (BMI) percentile is currently recommended by the American Academy of Pediatrics, the American Medical Association, and the U.S. Preventative Services Task Force and is a National Committee for Quality Assurance Healthcare Effectiveness Data and Information Set measure.

Current documentation rates for pediatric and adolescent overweight/obesity are low. Only 26% to 40% obese children and adolescents, presenting for routine well-child visits in military treatment facilities, were documented as obese. In another study of over 60,000 patients presenting for routine well-child visits, only 34% of overweight/obese patients were documented as overweight/obese.

Improved documentation of overweight/obesity through electronic medical record (EMR) prompts has been previously demonstrated. Armed Forces Health Longitudinal Application 3.3, the current version of the military's EMR, automatically documents BMI value without percentiles; documentation of BMI percentile requires an additional step. In the studies of EMRs with similar limitations, pediatric and adolescent overweight/obesity documentation improved between 8% and 49% with the addition of automatic BMI percentile calculations, chart prompts, and provider education initiatives.

The purpose of this project was to improve provider documentation of adolescent overweight and obesity through BMI percentile prompting in the military's EMR.

METHODS

Using the FOCUS-PDCA model, this project is a pre- and postintervention quality improvement project. The project was conducted in the adolescent medicine clinic of a large academic military medical center that included staff providers (general pediatricians, nurse practitioners, and adolescent medicine physicians), adolescent medicine fellows, and first- and second-year residents (general pediatricians, internists, and transitional year residents) from military and civilian training programs. The clinic primarily serves as a primary care clinic for dependents of active duty service members or retirees. The clinic provides primary care services for active duty service members and consultative care for both active duty service members and dependents. All adolescent patients, from 12 to 19 years of age, who presented for well-adolescent, acute care and

specialty care appointments during the project period were eligible for inclusion in this process improvement project. The EMR in use at the time of the project was Armed Forces Health Longitudinal Application 3.3.

Baseline (preintervention) data were collected on consecutive patients eligible for inclusion over an approximately 1-month time period. Data collected included age, gender, BMI percentile (manually calculated if not documented), documentation of overweight/obese, and provider type (staff, fellow, resident). Overweight was defined as a BMI percentile ≥85% and obesity as a BMI percentile ≥95% for age and gender, per the recommendations of American Academy of Pediatrics. Adolescent overweight/obesity documentation was considered correct if the primary provider documented the appropriate diagnosis in those identified as overweight or obese by chart review. Data were collected until 100 overweight and/or obese charts were identified (333 total charts reviewed).

The intervention performed was inclusion of BMI percentile and BMI growth curve by the medical screener (medical technician, medic, or nurse). This required one additional, automated step within the EMR during the screening process. A small poster defining adolescent overweight and obesity was placed in each examination room, and clinic preceptors (staff providers and adolescent medicine fellows) were advised of the project.

Postintervention data were collected over another approximately 1-month time period until another 100 overweight and/or obese charts were identified (328 total charts reviewed) for consecutive eligible patients. Data type collected were the same as that of the preintervention group.

SPSS version 19 was used for the analysis. χ^2 test was used for categorical data; independent samples *t*-tests were used for continuous data; and logistic regression was used to evaluate the effect of the intervention independent of the demographic variables. This project was approved as a quality improvement project by the institutional review board at the San Antonio Military Medical Center.

RESULTS

The actual rate of overweight and obesity calculated was similar between pre- and postintervention groups (30% vs. 30.5%; $p > 0.05$). The mean age in the pre- and postintervention groups was similar, as were age by grouping, sex, BMI percentile, and provider type.

The BMI percentile and BMI growth curve were recorded in 93% of postintervention charts reviewed and compared to 7% of preintervention charts reviewed. Overall, documentation of a correct diagnosis of overweight or obesity increased in the postintervention group (40% vs. 64%; $p < 0.01$). At baseline, female patients were less likely to receive a correct diagnosis documented compared to males (30% vs. 52%; $p < 0.05$) as were those seen by residents compared to fellows and staff (16% vs. 67% and 58%; $p < 0.01$). These differences did not persist in the postintervention group. Correct diagnosis documentation rates increased among all provider types ($p < 0.01$), but residents appeared to show the most improvement (16% vs. 56%). In multivariate analyses, only intervention status and provider type were predictive of a correct diagnosis being documented in the chart.

DISCUSSION

Our project successfully demonstrated that chart prompting with BMI percentiles and BMI growth curves in the military's EMR can increase the documentation rates of adolescent overweight/obesity diagnoses in our adolescent medicine clinic. Females and patients seen by resident physicians were less likely to receive a correct diagnosis at baseline, but this was not identified in the postintervention group.

Adolescent overweight and obesity rates in our population were similar to those of the general adolescent population. Baseline rates of correct diagnosis were also similar to those previously reported in comparable settings. The large percentage of patients seen by specific provider types was indicative of the training nature of our clinic; the proportion of patients seen by specific provider types between the pre- and postintervention group was not statistically significant.

Similar to previous studies, our project found that chart prompting with BMI percentile within EMRs consistently improves documentation of pediatric and adolescent overweight/obesity diagnosis. The apparent disparity by gender in overweight and obesity documentation rates found in our population at baseline was not reported in previous studies. The differences observed may indicate provider hesitancy in discussing weight-related health concerns in female adolescents, but further research is required to fully understand this observation.

We also found that the level of training was a significant factor, even when controlling for other demographic variables. Resident physicians failed to consistently document the correct diagnosis. It also appears that our intervention changed their practice. Given that resident physicians evaluate many of our patients, chart prompting with BMI percentile in our EMR has become the standard within our clinic.

There are several limitations to our project. First, most direct patient care is provided by resident physicians and adolescent medicine extenders. The primary patient care mission of our adolescent medicine-trained staff and fellows is supervisory. Resident physicians and adolescent medicine extenders may function differently than providers in other adolescent medicine clinics. However, the documentation rates for obesity seen in our clinic are similar to the rates seen in previous studies. Second, the patients attending our clinic may differ demographically from the general population, but our rates of obesity are very similar to previous studies. Third, our project included all clinic encounter types; patients seen for acute or specialty care reasons may not warrant immediate discussion of overweight/obesity, e.g., asthma exacerbations, or suicidality. Still, research suggests that one-third of adolescents do not have any preventative care (well-child) visits from the ages of 13 to 17 years, and 40% only had one such visit, suggesting that all visit types may warrant addressing overweight/obesity when it is present.

Additional research and process improvement projects are required to continue to improve adolescent overweight/obesity care. Even with our intervention, one-third of overweight/obese adolescents were missed. Also, improved diagnosis does not necessarily imply improved patient outcomes, but it does provide a framework for secondary and tertiary prevention. Additional research is needed to translate improved recognition of overweight and obesity into improved patient outcomes.

Chart prompting with BMI percentile in the military EMR provided a simple, effective means of increasing documentation of appropriate diagnoses of adolescent overweight and obesity in our clinic. Other military clinics serving adolescents should consider implementation of this process to improve provider recognition and documentation of overweight and obesity among adolescents.

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The U.S. Air Force Diabetes and Obesity Research Working Group: A Model for Building Military-Specific Clinical Research Infrastructure

Military Medicine
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January 2013

The diabetes and obesity epidemic is sweeping through our nation. The Centers for Disease Control and Prevention estimates that 26 million Americans now have diabetes and 79 million have prediabetes. If current trends continue through 2050, one in three Americans will have diabetes, predominantly attributable to the rise in obesity. When a patient is diagnosed with diabetes, that individual's lifetime medical costs more than double.

The military is not immune from these national trends. The Tobacco, Obesity, and Alcohol (TOBESAHOL) study estimated that obesity/overweight-related illnesses account for $1.1 billion and diabetes accounts for $300 million among TRICARE Prime beneficiaries. Beyond the heavy cost implications, these conditions also have direct impact on military readiness. Although policy changes in recent years have allowed members with diabetes to continue serving on active duty, their ability to participate in operational missions is typically limited. Military population health figures indicate that approximately 1,000 active duty Air Force members have diabetes, and 3,000 have prediabetes.

These numbers are the result of an underlying, unhealthy lifestyle among Airmen. The 2010 Air Force Healthy Airman Report (accessible only by military personnel) states that only 54% of Airmen have a healthy weight. Less than 5% of Airmen consume 5 servings of fruits and vegetables daily, far below the nine U.S. Food and Drug Administration-recommended daily servings. Accordingly, there is a sharp rise in the prevalence of diabetes after retirement when these habits continue without the enforcement of military fitness standards. There are an estimated 49,000 Air Force Medical Service (AFMS) adult beneficiaries with diabetes and well over 100,000 with prediabetes. It is clear that unhealthy lifestyle practices during the active duty years lead to obesity, which ultimately contribute to the increasing rates of diabetes and prediabetes in later years.

Given the magnitude of the problem and the reality of limited resources, research is necessary to determine the best methodologies to prevent diabetes and to manage the disease cost effectively. Unfortunately, there has traditionally been limited infrastructure in place to facilitate this research. Military medical researchers are challenged by multiple duties to include deployments, assignment changes, clinical duties, and teaching responsibilities. The current mode of staffing specialty medical departments is based primarily upon clinical productivity and wartime support, rather than research requirements. Therefore, the ability of an active duty clinician to effectively conduct research is limited. In view of these limitations, it is necessary to have a mechanism to organize research priorities, define appropriate research projects, and efficiently utilize available research resources.

In recognition of the need for expanded AFMS diabetes and obesity research, the Air Force Surgeon General's research division (AFMSA/SG9) hosted an initial meeting in 2009 with potential investigators from six Air Force medical centers (Andrews, Keesler, Lackland, Nellis, Travis, and

Wright-Patterson Air Force Bases). There was great interest among the investigators, and the need for dedicated research staff to assist in building a viable program was identified. In response, AFMSA/SG9 awarded a contract that provided diabetes research coordinators at each of the medical centers for 3 years. In February 2010, the group of investigators and coordinators met to generate the Air Force Diabetes Research Development Document (RDD). The purpose of this document was to establish research priorities relevant to the Air Force mission, against which future projects would be organized. The priorities included (1) primary prevention of diabetes, (2) technologies to bridge current resource gaps in outpatient diabetes care, (3) models of care to improve efficacy of outpatient diabetes care, (4) inpatient diabetes care, (5) biomarkers to better define diabetes populations, and (6) safety/operational concerns.

The group subsequently determined the need to formally establish itself as the Diabetes and Obesity Research Working Group (DORWG) with an official charter in November 2010. Membership of the group included clinicians, scientists, and research coordinators from the six participating medical centers. Chair and Vice Chair positions were assigned for 1-year rotating terms. The DORWG mission was defined to promote and conduct research for prevention, identification, education, and treatment of diabetes and obesity in all military beneficiaries. General goals for the group were to direct and conduct diabetes and obesity research within the Air Force, serve as subject matter experts for Air Force leadership, contribute to overall Graduate Medical Education research efforts, and improve awareness of diabetes and obesity research. The charter defined that meeting research priorities would be accomplished by both intramural and extramural research efforts, through collaboration with a variety of research partners and funding sources. The charter also established a regular communication schedule, to include monthly teleconference meetings and quarterly face-to-face meetings at rotating sites.

To meet the RDD research priorities and charter goals, the DORWG developed a strategic plan that defined long-range objectives and strategies. The foremost strategic objective of the DORWG was to promote Air Force diabetes and obesity research. Brainstorming research projects and categorizing them according to RDD priorities enabled the group to address the most important Air Force needs. It also allowed researchers to visualize which areas were not being addressed and where to focus future research efforts. To date, over 30 new research projects related to diabetes and obesity have been established in line with the DORWG-identified priorities. One multisite trial was approved for funding and began actively enrolling patients to evaluate the use of a personalized diabetes risk score in a comprehensive lifestyle modification program. Two additional multisite studies were subsequently selected for funding: one evaluating the prevalence of metabolic syndrome among recently retired military members, and another examining the impact of a nonpharmacologic supplement to prevent the development of diabetes. Numerous other local studies were developed and initiated that only required minimal local funding. The total number of AFMS beneficiaries participating in the diabetes research studies at the six sites will soon exceed 2,000 subjects. Research findings have already been presented at the 2011 AFMS Research Symposium and the 2012 American Diabetes Association annual meeting. As studies conclude and the program matures, many more presentations are anticipated, along with publications in peer-reviewed medical journals.

Another strategic objective was to increase participation of potential Air Force researchers in the DORWG. The involvement of the working group participants is critical to ensure an organized approach to research efforts and the needed time commitment for the development of plans and reports. Several aspects of the DORWG charter were specifically designed to increase the number of participants. For example, officer terms of service were limited to one year, ensuring greater leadership involvement from a variety of individuals. Quarterly face-to-face meetings were planned at different sites to increase visibility and interest at those locations among those who might not otherwise participate. Over the coming

year, the DORWG is expanding its meeting sites to locations with Air Force family medicine residency programs. All of these efforts foster a growing vision for research across the AFMS. As a result, the number of AFMS clinicians actively engaged in diabetes and obesity research projects has increased from a handful to more than 20.

Overall, the establishment of the DORWG model has proven to be important for many reasons. First, it creates a platform for defining research priorities against which all projects are organized. Within these priorities, it creates the ability for participants to brainstorm research concepts, upon which specific projects are developed. It encourages multibase collaboration on projects, enabling a greater pool of research subjects to answer questions of key research interest. With the promotion of collaboration between bases, it reduces the potential for duplication of effort. It also allows for different bases to pursue different research questions, but in a coordinated fashion. The DORWG facilitates communication of a unified message to AFMS leadership regarding the importance and urgency for diabetes and obesity research, as well as priorities within this arena. It is far more powerful for researchers within a particular discipline to speak as one voice, rather than having individual researchers seeking support on their own. On a practical level, the presence of the group inspires potentially reluctant researchers to participate in research that they may not have otherwise been able to conduct. Finally, although the DORWG remains the only entity of its kind in the AFMS research community, it serves as a model for other AFMS research disciplines to likewise organize research priorities and concepts. It is the sincere hope of the DORWG membership that other research communities can benefit from our experience.

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Physiological Injuries and Surgery

The 510(k) Ancestry of a Metal-on-Metal Hip Implant

New England Journal of Medicine
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10 Jan 2013

Many medical devices that pose great safety risks to Americans, including metal-on-metal hip implants, currently enter the U.S. market through a Food and Drug Administration (FDA) regulatory pathway that is not intended for evaluating safety and effectiveness. This pathway, called the 510(k) process, instead involves evaluation of “substantial equivalence” to previously cleared devices, many of which have never been assessed for safety and effectiveness and some of which are no longer in use because of poor clinical performance.

The Medical Device Amendments of 1976 created three classes of devices: class I included low-risk devices, such as toothbrushes; class II contained moderate-risk devices, such as infusion pumps; and class III included high-risk devices and those awaiting proper classification, such as metal-on-metal hip implants. These classes roughly corresponded to the level of premarketing review required. Thus, class I and II devices underwent review for substantial equivalence to devices already on the market, also called preamendment devices (although subsequent legislation granted exemptions). Class III devices were meant to undergo the more rigorous premarket approval (PMA), the only pathway that

requires clinical data. However, class III devices were allowed to receive review for substantial equivalence temporarily, until the FDA down-classified these devices or promulgated regulations requiring PMA. Congress had always intended class III devices to undergo PMA, and in 1990, it directed the agency to establish a schedule to finish the transition to PMAs for all devices that were to remain in class III.

As of December 19, 2012, however, the FDA still had not completed this transition to PMA for high-risk devices, although it had stated its intention to clear proposed rules for all remaining class III preamendment devices by December 31, 2012. Currently, 19 different types of class III devices, including metal-on-metal hip implants, are allowed to reach patients through 510(k) clearance. Because of this loophole, companies that market these devices are often legally able to obtain clearance without demonstrating safety and effectiveness through clinical studies, but by claiming substantial equivalence to earlier “predicate devices” — or pieces of those devices — which may also have been found substantially equivalent to even earlier devices, and so on, all the way back to preamendment devices. Because many predicates have never been assessed for safety and effectiveness, an FDA finding of substantial equivalence does not mean that a new device is safe and effective; it means only that the device is deemed no less safe and no less effective than a predicate. Even voluntarily recalled devices can serve as predicates, as long as the FDA did not formally remove these devices from the market or a court did not find them adulterated or misbranded.

One prominent type of class III device that remains eligible for 510(k) clearance is metal-on-metal hip implants, such as the DePuy ASR XL Acetabular Cup System, which received FDA clearance in July 2008 without a clinical study. The Australian Orthopaedic Association National Joint Replacement Registry initially reported in September 2008 that this device required revision surgery at a high rate, and in 2010 the National Joint Registry (NJR) for England and Wales reported a 5-year revision rate of approximately 13%, which was more than four times the registry's reported 5-year revision rate for all hip-replacement prostheses combined. DePuy voluntarily recalled the ASR XL in Australia in 2009, citing “declining demand” as a reason, and then worldwide in 2010 because of the high revision rate reported by the NJR.

Using FDA documents obtained from the agency's database and Freedom of Information Office, we traced the ancestry of the ASR XL back more than five decades, through a total of 95 different devices (including femoral stems), including 15 different femoral heads and sleeves and 52 different acetabular components.

The 510(k) clearance for the ASR XL focused on three characteristics: the porous bone ingrowth surface, metal-on-metal articulation, and large femoral head sizes (57 to 63 mm), which were larger than those of the predicate total hip prostheses. These three characteristics were uniquely combined in the ASR XL but were evaluated for “substantial equivalence” by comparing select characteristics to different predicate devices, none of which contained all of these characteristics (i.e., they were “split predicates”).

The porous bone ingrowth surface was not specific to the type of articulation; thus, in most cases, the predicates were not metal-on-metal and were substantially different in design from the ASR XL. None of the predicates in the ancestry had the same combination of characteristics as the ASR XL acetabular component.

Clearance of the large metal-on-metal articulation was based on a much smaller group of predicates, some of which differed substantially in design from the ASR XL or had poor clinical performance. Ultimately, clearance was based on the claim that these predicate devices were

substantially equivalent to three prostheses that were used before 1976: the McKee–Farrar, Ring, and Sivash metal-on-metal total hip prostheses. It is important to note that these three devices were discontinued long ago (and well before clearance of the ASR XL) because their risk of revision was so much higher than that of other hip prostheses.

One metal-on-metal hip in use at the time of the application and whose use was well supported by clinical evidence was the original Metasul hip. However, this hip differed substantially in design from the ASR XL in two major ways. The cup was not solid metal, but instead consisted of a metal shell and a metal articular surface inlay with a polyethylene "sandwich" between the two. A second difference was head size: the Metasul had much smaller heads (≤32 mm) than the ASR XL.

The use of larger heads was an important characteristic of the ASR XL. The clearance for the large metal heads with sleeves was based in part on predicates that were not used in total hip replacement but were designed for use in *partial* hip replacement, in which the large metal heads articulate with the natural articular cartilage of the acetabulum, not with a metal cup.

This ancestry reveals serious flaws in the 510(k) procedure for metal-on-metal hips, which resulted in clearance of a new device that was never shown to be safe and effective. A clinical trial might have identified the high revision rate of the ASR, which became evident after 9 months when it was compared with all other total conventional hip prostheses in the Australian Joint Registry (9-month-to-1-year hazard ratio, adjusted for age and sex, 2.62 [95% confidence interval, 1.67 to 4.11]) and which precipitously worsened over time.

As thousands of Americans are painfully learning, there are unknown risks with devices that enter the market without clinical data showing safety and effectiveness, and implanted body parts cannot be recalled as easily as defective auto parts. The recently passed Medical Device User Fee and Modernization Act contains a provision that should make it easier for the FDA to close the loophole for the remaining 19 class III devices by allowing the agency to reclassify devices by order rather than through regulation. There would be value in an FDA-sanctioned registry.

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Pulsed Radio Frequency Energy Therapy Use for Pain Relief Following Surgery for Tendinopathy-Associated Chronic Pain: Two Case Reports

Military Medicine
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January 2013

ABSTRACT

Chronic tendon pain from overuse is a common condition, with limited options for ongoing pain management. Two cases are presented in which pulsed radio frequency energy (PRFE) therapy was used for pain relief following surgical intervention for chronic tendinopathy–associated pain,

unresponsive to conventional therapies. Both patients showed a dramatic reduction in pain following PRFE therapy after 2 to 3 weeks of treatment, and at the 7-month (case 1) and 6-month (case 2) follow-up visits, both patients reported that pain had not returned. Recent molecular evidence suggests a possible mechanism underlying PRFE-mediated pain relief. Further study into this promising technology is warranted.

INTRODUCTION

Chronic tendon pain from overuse is common and challenging for clinicians. Such conditions are often the result of sports-related or occupational activities in which the tendon is exposed to intense, repetitive, or long-duration activity. Excessive tendon loading is thought to be a primary factor promoting tendon degeneration, and mechanical strain is thought to result in altered cell activity within the tendon. Intrinsic and extrinsic factors implicated in tendinopathy include prolonged or intense use, frequent microtrauma, obesity, age, and certain anatomical factors. Additionally, genetic predisposition may contribute in some cases. Histologically, tendinopathy often show degeneration and/or disorganization of collagen bundles, altered tenocyte morphology, increased cellularity, and in many cases an absence of inflammation, though it has been suggested based on studies in animal models that inflammatory changes may occur early before outward signs of tissue injury.

Tendinopathy can be a difficult condition to treat, and although many treatment options are available, there remains a lack of high-quality, evidence-based efficacy data available for many tendinopathy treatments. Conservative measures used to treat tendinopathy include ice, relative rest, orthotics and braces, and, in the case of foot and ankle tendinopathy, elevation.

There is evidence to support the use of eccentric strengthening for some tendinopathy and stretching. Oral and/or local nonsteroidal anti-inflammatory drugs (NSAIDs) may provide short-term pain relief for certain types of tendinopathy; however, there is little support for their long-term use. Similarly, although data suggest local corticosteroid injections may provide relief from acute-phase tendinopathy-associated pain, data are lacking regarding long-term benefits. For patients who fail conservative therapy, surgery is also an option; however, it is invasive and does not relieve pain in all cases.

In clinical practice, many physical modalities are under study for the management of tendon disorders and resulting pain. Here, we describe pain relief in 2 patients following surgery for tendinopathy-associated chronic pain using pulsed radio frequency energy (PRFE) therapy, a biophysical treatment modality that involves delivery of nonionizing radio frequency energy to soft tissue to provide pain relief, and indicated for the adjunctive, palliative treatment of postoperative pain and edema in superficial soft tissue.

Results from in vitro studies, as well as recent clinical findings, indicate that PRFE can trigger a biological cascade of events in human skin cells and wounded tissue that results in the expression of factors that function in soft tissue repair and pain signaling. In animal studies, PRFE has been found to have an effect on collagen deposition and an increase in tendon tensile strength. Clinically, PRFE therapy has been used to provide relief for pain of various etiologies, including postoperative pain and pain associated with ankle sprains and inversion injuries, heel neuroma, hand and finger injuries, neck pain and whiplash, algoneurodystrophy, and cutaneous wound pain. PRFE therapy has also been associated with a reduced consumption of analgesics and a shorter hospital stay following foot surgery. In addition, a recent meta-analysis of 25 controlled trials involving

over 1,300 patients treated with PRFE demonstrated statistically significant benefit in the treatment of pain, edema, and wound healing, with p values of <0.0001.

Here, 2 cases of tendinopathy-associated chronic pain are reported. In both cases, PRFE therapy was prescribed after conventional therapies and surgical intervention failed to provide pain relief. In each case, pain relief occurred soon after initiation of PRFE treatment, and with long-lasting effects.

CASE 1

A 27-year-old male presented with a 4-year history of left fifth metatarsal pain (level 4 out of 10; Wong–Baker FACES pain scale) with increasing inability to work. The original injury occurred during military service when the patient fell while running. He was diagnosed with probable tendon or ligament rupture and fracture of the fourth and fifth metatarsals. Treatment included a removable cast/walking boot, casting, and physical therapy. Despite these interventions, pain had persisted. The patient also suffered from headaches, which were treated with topiramate followed by gabapentin.

Over the preceding 2 years, the patient had failed NSAIDs, injections (lidocaine plain 2% 1 cc with Kenalog-40 1 cc and Marcaine 0.25% plain), immobilization, physical therapy, and orthotics. The pain became shooting in character and progressively worsened, particularly with prolonged periods of standing and walking. At presentation, he favored his right foot upon standing and an ankle brace provided minimal relief.

Magnetic resonance imaging was ordered to confirm tendinopathy and nerve conduction velocity/electromyography for the tarsal tunnel syndrome. The Anesthesia Pain Clinic diagnosed nerve entrapment, and he underwent tarsal tunnel release with Kidner procedure to remove an accessory navicular bone. The surgery is used to decompress the tarsal tunnel area. The curvilinear incision is made behind the ankle to identify the posterior tibial nerve separating it from the accompanying artery and vein along the tunnel. The Kidner procedure is used to remove prominence of accessory navicular to reduce compression of surrounding soft tissues.In a similar manner, the tarsal tunnel release accompanied with the Kidner procedure is a combined effort to accomplish a decompression of soft tissue. Postoperatively, the patient's pain level was 8 out of 10 (Wong–Baker FACES pain scale) with tingling sensation. Nonweight bearing with casting and crutch walking was initiated. Oxycodone and/or acetaminophen (325 mg) (2 tablets every 6 hours) were prescribed for pain.

At postoperative week 2, the patient's pain level remained at 8 out of 10 with diminished tingling. He was placed in a removable cast/walking boot, which he subsequently discontinued because of back pain. The patient progressed to crutches, and over the next month, the pain remained consistent, with oxycodone and acetaminophen required every 6 hours routinely. At 6.5 weeks postsurgery, the patient's pain remained at a level of 6 out of 10 and still required opioids for relief. PRFE therapy (Provant Therapy System; Regenesis Biomedical, Scottsdale, Arizona) was initiated for pain. Provant is a portable, noninvasive medical device that delivers PRFE via a spiral antenna placed adjacent to the treatment area. The device generates pulses that are 42 μs long, 1,000 times per second, creating an electromagnetic field that bathes the treatment area and generates the therapeutic effect. The electromagnetic field has an electrical field strength of 591 V/m and a magnetic field strength of 6.4 A/m at a distance of 5 cm from the treatment applicator. The dosage is preset and self-regulated, to ensure consistent and therapeutic dosing. Therapy can

be administered directly through clothing and bandages. Treatment is generally self-administered in the home without nursing supervision and performed twice daily for 30 minutes. The device shut off automatically at the end of the 30-minute treatment, and unlike TENS and electrical stimulation devices, the treatment is noncontact and does not involve electrodes or administration of direct current. Unlike other pulsed electromagnetic field devices designed for bone stimulation, which operate at very low frequencies (1–300 Hz), the device operates at the Federal Communications Commission designated shortwave frequency of 27.12 MHz. In both cases described here, PRFE therapy was self-administered in the home by placing the treatment applicator over the site of pain for 30 minutes twice a day in accordance with the manufacturer's instructions. In general, PRFE treatment is imperceptible to the patient.

Following the first week of PRFE therapy, the patient reported less pain with pain medication needs decreased to episodic use at night for severe pain. The patient also began to use compression stockings to decrease edema and lidocaine gel on occasion. With 3 weeks of PRFE, the patient's pain was almost completely resolved. The patient progressed to wearing sneakers and sandals and continued with physical therapy for balance training, full-weight bearing, and muscle strengthening.

At 6 weeks following initiation of PRFE, the patient used oxycodone and acetaminophen occasionally at night for severe pain and was able to walk some distance before feeling tired. PRFE therapy was discontinued at 7.5 weeks. The patient reported that pain had not returned after 7 months postsurgery.

CASE 2

A 34-year-old male patient presented with a 2.5-year history of left ankle pain and was diagnosed with peroneal tendinopathy with lateral ankle instability. The patient twisted his ankle in a fall resulting in swelling and bruising of the lateral ankle. He underwent physical therapy for 3 months with minimal improvement. After a year of persistent lateral ankle swelling, the patient received a cortisone injection, which provided pain relief for approximately 1 month. Swelling and pain with activity continued. The pain became “shooting,” radiating from his foot to his knee, averaging 3 out of 10, with flares to 6 to 7 out of 10 (Wong–Baker FACES pain scale). He received minimal relief from conventional therapies, which included ibuprofen 3 to 4 times a week, medical massage, ice, warm water, changing shoes, an ankle brace, and weight loss. Radiography indicated marked widening of the lateral aspect of the talotibial joint space under inversion stress consistent with ligamentous injury on the lateral aspect of the ankle. A Brostrom procedure, repair of the anterior talofibular ligament, as well as a peroneal tendon repair, was performed. Postoperatively, the patient was casted and pain management consisted of ibuprofen (600 mg) every 6 hours and 2 tablets of oxycodone (5 mg)/acetaminophen (325 mg) every 6 hours. Relief was inadequate with pain upon standing starting within 5 to 10 minutes. Occasional tingling and burning sensations were noted. Trials of acetaminophen and codeine and gabapentin for neuritic pain were ineffective. Crutches, a removable cast/walking boot, and compression stockings completed the postoperative regimen. By postoperative week 9, the patient was unable to stand more than 10 minutes without pain, tingling, or burning. PRFE therapy was started.

The patient used Provant twice daily for 30 minutes in accordance with the manufacturer's instructions. Within 2 weeks, the pain was almost completely resolved, requiring only occasional NSAIDs. Opioids were discontinued. The removable cast/walking boot and crutches were

continued. Three weeks later, the patient returned to clinic in sneakers and without pain. The patient's pain had not returned as of 6 months postsurgery.

DISCUSSION

In these 2 cases, PRFE therapy was used for pain relief following surgical intervention for chronic tendinopathy–associated pain that was unresponsive to conventional therapies. In both cases, pain relief occurred within weeks following the initiation of PRFE therapy. Since the therapy was initiated after surgical intervention, it is difficult to determine whether pain relief resulted from PRFE, surgical treatment of the tendinopathy, or the combination. In addition, a common limitation of individual case reports is that treatment outcomes are not compared to a control population and are limited by small sample size.

With that said, the outcomes reported here are in agreement with numerous other clinical studies that report successful postoperative pain relief using PRFE, and there is evidence to suggest that PRFE modulates molecular factors involved in pain signaling, including factors associated with postoperative pain. New in vitro research indicates that PRFE may stimulate the production of endogenous opioids by epithelial keratinocytes, interrupting pain sensation via the endothelin-1 pathway. Elevated levels of mRNA transcripts for endorphins, enkephalins, dynorphins, and endothelin-1 receptors have been identified following the exposure of cultured human keratinocytes to PRFE (J. Moffett, personal communication).

It is interesting to note that many of the molecular factors associated with tendinopathy appear to be modulated by PRFE. At the molecular level, strain can affect the expression and secretion of various factors by tendon cells, including those normally involved in tendon homeostasis and repair. It is thought that repeated overuse may lead to an imbalance in the molecular microenvironment of the tendon, shifting from one that is primarily regenerative to a degenerative one. PRFE may be helpful in restoring this balance, given the observed effect of PRFE on factors which may contribute to tendinopathic pain signaling and tendon repair (such as matrix metalloproteinases [MMPs] and cytokines involved in cell signaling pathways).

CONCLUSIONS

Physical modalities have long been used to treat tendinopathy, and modern molecular science is evolving to explain how physical modalities may help to reduce pain. These 2 cases demonstrate a marked improvement in chronic pain following PRFE therapy after conventional treatment options had failed. Experimental evidence suggests overlap between molecular factors modulated by PRFE, and those associated with pain signaling and tendinopathy, providing possible insight into its therapeutic effectiveness. Further study of this promising technology is warranted.

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The Addition of Body Armor Diminishes Dynamic Postural Stability in Military Soldiers

Military Medicine

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ABSTRACT

Poor postural stability has been identified as a risk factor for lower extremity musculoskeletal injury. The additional weight of body armor carried by Soldiers alters static postural stability and may predispose Soldiers to lower extremity musculoskeletal injuries. However, static postural stability tasks poorly replicate the dynamic military environment, which places considerable stress on the postural control system during tactical training and combat. Therefore, the purpose of this study was to examine the effects of body armor on dynamic postural stability during single-leg jump landings. Thirty-six 101st Airborne Division (Air Assault) Soldiers performed single-leg jump landings in the anterior direction with and without wearing body armor. The dynamic postural stability index and the individual stability indices (medial–lateral stability index, anterior–posterior stability index, and vertical stability index) were calculated for each condition. Paired sample *t*-tests were performed to determine differences between conditions. Significant differences existed for the medial–lateral stability index, anterior–posterior stability index, vertical stability index, and dynamic postural stability index ($p < 0.05$). The addition of body armor resulted in diminished dynamic postural stability, which may result in increased lower extremity injuries. Training programs should address the altered dynamic postural stability while wearing body armor in attempts to promote adaptations that will result in safer performance during dynamic tasks.

INTRODUCTION

Postural stability has been defined by Riemann et al as the process of coordinating corrective movement strategies and movements at the selected joints to remain in postural equilibrium. Dynamic postural stability is the ability to maintain the base of support when the base of support is moving or when an external perturbation is applied to the body. Postural stability has been identified as a risk factor for ankle and knee injuries in athletic populations and is likely a risk factor for injury in the military. Soldiers are often required to carry heavy loads while deployed and on tactical operations for long distances and over-rugged terrrains. The loads Soldiers carry are determined by the mission requirements and for protective purposes with the minimum load consisting of body armor, which accounts for approximately 43% of a Soldier's fighting load; the average rifleman's fighting load is approximately 29 kg. The effects of load carriage on physiological function and gait have been established. However, the effect of load carriage on postural stability is largely unknown and has only incorporated static testing conditions. Static testing conditions fail to replicate the dynamic military environment, which places significant demands on postural control encountered during tactical training and missions.

Ankle and knee injuries are a common occurrence in military personnel and are associated with high medical costs, lost time from duty, and impact military readiness. Ankle and knee injuries account for 10.9% to 15.1% and 10.2% to 12.0%, respectively, of all musculoskeletal injuries in military personnel. Additionally, the lower extremity is the most common anatomical location of hospitalized injuries in the military. Furthermore, ankle and knee injuries were among the most common anatomical locations for nonbattle air evacuations during Operations Iraqi Freedom and

Enduring Freedom. Despite the frequent occurrence of ankle and knee injuries in the military, the risk factors for these injuries are largely unknown in this population.

Decreased postural stability has been prospectively identified as a risk factor for ankle and leg injuries. Altered postural stability has also been observed following knee, and low back injuries. The effects of load carriage on postural stability in Soldiers are limited and have only assessed static testing conditions, which fail to imitate military activities. Schiffman et al assessed the effects of three different loads (6, 16, and 40 kg) on static postural stability and observed linear increases in center of pressure excursions with increases in load. Moreover, May et al demonstrated decreased balance scores while carrying a load equal to 30% of body weight during the modified sensory organizational test. Although the effect of load carriage appears to be detrimental to static postural stability, its effect on dynamic postural stability is largely unknown and warrants investigation.

A direct connection between load carriage and risk of injury has not been established, but recent epidemiological evidence indicates that the Soldier does perceive it to be a risk factor for injury. Additionally, recent epidemiological evidence demonstrates an increase in ankle and knee injuries in Afghanistan compared to Iraq. This study supports the personal observations of the Division Surgeons of the Army 101st Airborne Division (Air Assault) while in both theaters. The reported and observed increase is likely attributable to the challenging terrain that is difficult to traverse under normal conditions and even more demanding while carrying the load necessary for tactical missions. It is suggested that load carriage over long durations may result in injury, especially to the ankle and knee. The most common self-reported region being uncomfortable during loaded field marching were the foot and ankle. Additionally, it was documented that 24% of infantry Soldiers who participated in loaded road marching suffered an overuse injury. The addition of carrying an unaccustomed load while deployed is suggested to increase ankle and knee injuries, which may be because of the detrimental effects load carriage has on postural stability.

Altered or diminished postural stability has been demonstrated to be a risk factor for lower leg injuries. Military personnel carry and wear additional weight for tactical and protective purposes. This additional weight likely has impact on dynamic postural stability. The degree of this altered postural stability is unknown. The overall purpose of this study was to examine the effects of personal body armor on dynamic postural stability as measured by the dynamic postural stability index (DPSI). We hypothesized that the addition of body armor would significantly decrease the Soldier's dynamic postural stability as indicated by an increase in the DPSI. If our hypothesis is correct, the results will demonstrate that the minimal amount of weight Soldiers carry is detrimental to postural stability and should be addressed in physical training programs.

METHODS

Participants

Thirty-six subjects (male = 32, female = 4) were recruited from the Army 101st Airborne Division (Air Assault) to participate in this study. To participate, subjects must have been 18 to 45 years old from the 101st, with no history of concussion or mild head injury in the previous year, no upper extremity, lower extremity, or back musculoskeletal pathology in the past 3 months that could affect the ability to perform the required tests, no history of neurologic or balance disorders, and not taking any medications that could disrupt balance or proprioception. Additionally, all subjects

were cleared for active duty without any recent prescribed duty restrictions. Approval for this study was obtained from the University of Pittsburgh's Institutional Review Board, Eisenhower Army Medical Center, Clinical Investigation Regulatory Office, and the Human Research Protection Office as part of an ongoing research project focusing on injury prevention and performance optimization in the 101st Airborne Division (Air Assault). All testing was conducted at our Human Performance Research Laboratory, Fort Campbell, Kentucky, a remote research facility operated by the Neuromuscular Research Laboratory, University of Pittsburgh.

Instrumentation

A force plate (Kistler 9286A, Amherst, New York) was used to collect the ground reaction force data (1200 Hz) during the single-leg jump landing task to assess dynamic postural stability. Force plate data were passed through an amplifier and analog to digital board (DT3010, Digital Translation, Marlboro, Massachusetts) and stored on a personal computer.

Load Carriage Condition

The load carriage condition was comprised of standard U.S. Army clothing (boots, socks, T-shirt, and shorts) and equipment (body armor). Each subject wore their own personal body armor, the average weight of the body armor and the body armor as percentage of body weight. The body armor was chosen as it is the minimum load Soldiers carry while on missions and during tactical training.

Procedures

Subjects reported to a research laboratory for a single test session. Dynamic postural stability was assessed using a single-leg jump landing in the anterior direction, which has demonstrated good intersession reliability (ICC 3, k), 0.86. The single-leg jump landing task was only conducted on the dominant limb. Limb dominance was defined as the limb the subject would use to kick a ball maximally. The jump distance was normalized to the subject's body height and the jump height was standardized at 30 cm.

Subjects were positioned 40% of their body height away from the edge of a force plate and a 30 cm hurdle was placed at the midpoint between the starting position and the force plate. Subjects were instructed to jump in the anterior direction using a two-footed jump over the hurdle and to land on the force plate with only the dominant leg, stabilize as quickly as possible, place their hands on their hips once stabilized, and remain still for 10 s while looking forward. Upper extremity movement was unrestricted during the jump; however, once subjects were stabilized they were asked to quickly place their hands on their hips. Subjects were allowed three practice trials for each condition to become familiar with the single-leg jump landing task. Following the practice trials, subjects completed the test trials. A 1-minute rest period was provided between trials to prevent fatigue.

Trials were discarded and repeated if subjects failed to jump over or came in contact with the hurdle, fell upon landing or if the nondominant leg came in contact with the dominant leg or the ground around the force plate. All subjects were able to complete the task. All of the subjects performed the task without body armor first. A total of three successful trials were collected for each condition (no-load and load) and used for data analysis.

Data Reduction

A custom MATLAB (v7.0.4, Natick, Massachusetts) script file was used to process the ground reaction force data for calculating the DPSI. Ground reaction force data were passed through a zero-lag fourth order low pass Butterworth filter with a frequency cutoff of 20 Hz.

The DPSI is a composite of the anterior–posterior, medial–lateral, and vertical ground reaction forces and also provides stability indices for the anterior–posterior (APSI), medial–lateral (MLSI), and vertical (VSI) directions. The DPSI was calculated using the first 3 s of the ground reaction forces immediately following initial contact identified as the instant the vertical ground reaction force exceeded 5% body weight. This method of calculating DPSI has demonstrated good test–retest reliability (ICC 3, 1), 0.96. Higher stability indices and DPSI scores represent worse dynamic postural stability. Each subject had a total of three trials, which were averaged and used for final analysis.

Statistical Analysis

Paired sample *t*-tests were performed for the dependent variables to determine if there was a significant difference between no-load carriage and load carriage conditions. All statistical analyses were performed using SPSS (v13.0, SPSS, Chicago, Illinois). An α level of 0.05 was set a priori to determine significance for all statistical analyses.

DISCUSSION

Decreased postural stability has been identified as a risk factor for ankle and knee injuries in athletic populations. The equipment Soldiers carry for personal protection and tactical purposes places considerable weight on the Soldiers' bodies, with the minimal load consisting of body armor. Load carriage negatively affects physiological function, gait, and static postural stability; however, its effect on dynamic postural stability has yet to be explored. The purpose of this study was to investigate the influence of body armor on dynamic postural stability. The results of this study indicate that the addition of body armor diminishes dynamic postural stability. Specifically, increases were noted in the MLSI, APSI, VSI, and DPSI confirming our hypothesis. The decrease in dynamic postural stability while wearing body armor may increase the risk of sustaining a lower extremity musculoskeletal injury and negatively impacting military readiness and mission success. Careful consideration should be given to developing training programs that incorporate balance training and the addition of body armor to induce adaptations that will likely mitigate the negative effects of body armor on dynamic postural stability.

The addition of body armor reduced dynamic postural stability. Ground reaction forces have consistently been shown to increase with the addition of a load, which was evidenced by higher MLSI, APSI, and VSI scores in the current study. Similarly, peak vertical ground reaction forces significantly increased during two-legged drop landings with the addition of body armor, helmet, and rifle. Additionally, carrying a load results in an increase in body sway resulting in less stability, which may explain the increase in ground reaction forces observed in this study. Furthermore, it has been established that carrying a load results in a forward lean thereby, placing a subject closer to their limits of stability, which may result in an increase in ground reaction forces.

Poor postural stability has been prospectively identified as a risk factor for ankle and leg injuries. In this study, the addition of body armor resulted in Soldiers landing with greater ground reaction forces in the APSI, MLSI, VSI. Landing with greater peak vertical ground reaction forces has been identified as a risk factor for anterior cruciate ligament injury. A 10% increase was observed with the addition of body armor for the MLSI and APSI scores, whereas a 7% increase was observed for the VSI and DPSI scores. Increases in the MLSI may have important considerations for lateral ankle sprains as they occur in the frontal plane and individuals with chronic ankle instability have increased MLSI scores compared to healthy controls. The relationship between load carriage and injury rates has yet to be established; however, preliminary survey data indicate that the majority of the Soldiers who were injured under loaded conditions believe that carrying a load contributed to their injury. The potential cause for an increase in musculoskeletal injuries may be as a result of diminished dynamic postural stability while carrying a load. The load utilized in this study was the minimum load a Soldier would carry. As loads approach those of tactical operations, decrements in dynamic postural stability are likely to increase.

A variety of postural stability training programs have been developed. These programs have demonstrated the ability to improve postural stability and reduce musculoskeletal injuries. Currently, postural stability training is not incorporated into daily Army physical training; however, it is included in newer military training programs. The Eagle Tactical Athlete Program has been implemented at the 101st Airborne Division (Air Assault). This program is an 8-week periodized training regimen that incorporates postural stability and physical training while wearing body armor that improved Soldier's postural stability. Additionally, proper landing technique may be important to reduce the effects of body armor on dynamic postural stability. Proper landing technique programs have been successfully developed to reduce anterior cruciate ligament injury in female athletes. Our previous research has demonstrated that hip flexion angle at initial contact are important predictors of DPSI during single-leg jump landings. Specifically, a greater hip flexion angle resulted in lower DPSI scores indicating better dynamic postural stability. Additionally, greater knee flexion at initial contact and greater knee flexion throughout the landing results in a greater dissipation of ground reaction forces. Furthermore, earlier onset of muscle activation improves reaction to the landing surface and reduces the time to transition from a dynamic to a static state resulting in a successful jump landing.

In this study, the average weight of the body armor was 12.5 kg, which was approximately 15.5% of subjects' body mass. This load was selected as it is the minimum amount of equipment Soldiers wear for protective purposes. It has been established that load carriage considerably alters physiological function, gait, static postural stability, knee kinematics during drop landings, and potentially contributes to musculoskeletal injuries. Carrying additional weight has been part of Army physical training, but has traditionally been limited to field marches. However, during deployment, Soldiers may be required to carry loads in excess of 100 pounds. Physical training programs that incorporate postural stability training and additional weight may mitigate the negative effects additional weight has on dynamic postural stability. Careful consideration should be given to the incorporation of additional weight into training programs as an increase in musculoskeletal injury rates has been reported.

We acknowledge that this study has several limitations. First, the weight of the body armor varied between subjects as each subject wore their own personal body armor. The weight of body armor can vary between individual Soldiers based on their needs and preferences. Incorporating a standardized body armor weight could have potentially negatively affected Soldier performance during the dynamic postural stability tasks as Soldiers may not have been accustomed to the body armor weight. The influence of different body armor weights would likely have the greatest effect on the VSI, which is most susceptible to variations in weight. Second, the order of the two testing conditions was not randomized. It is

possible that a learning effect could have influenced the dynamic postural stability measures during the load condition because it followed the no-load condition. In an attempt to mitigate this effect, a minimum of three practice trials were provided for each condition. More practice trails were allowed, as needed, until subjects felt comfortable with the test procedures. Since subjects were provided time to become familiarized with the single-leg jump landing task during both conditions, it is unlikely that the order of the two testing conditions would provide further alteration of performance. It is possible that subjects adopted a different landing strategy during the load condition compared to the no-load condition; since kinematic and electromyography data were not collected during this study, we cannot comment if landing strategy changed. Last, it is possible that subjects became fatigued during the course of this study and could have influenced the results. Subjects were provided with a 1-minute rest period between trials and between conditions, which should have prevented fatigue. Additionally, since subjects wore their own personal body armor, they should be accustomed to the load.

Future research should explore the influence of carrying additional weight on injury rates in the military during deployment and nondeployment. Additionally, future research should examine the effects of carrying additional weight during other dynamic postural stability tasks that replicate the military environment as well as incorporating various loads that are reflective of the loads Soldiers carry during combat and tactical missions. Furthermore, a prospective study is needed to demonstrate that dynamic postural stability is a risk factor for lower extremity injuries in the military.

CONCLUSION

The addition of a minimum load such as body armor results in diminished dynamic postural stability as evidenced by increases in MLSI, APSI, VSI, and DPSI. Altered dynamic postural stability may result in an increase in lower extremity musculoskeletal injuries. Because of the deleterious effects body armor has on dynamic postural stability, future research is warranted to develop physical training programs to promote adaptations that will result in safer performance during load-bearing dynamic tasks while not increasing musculoskeletal injury rates.

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Silent Aspiration and Recovery From Dysphagia in a Case of Bickerstaff Brainstem Encephalitis

Military Medicine
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Abstract

Bickerstaff brainstem encephalitis (BBE) is a rare inflammatory demyelinating disease with rapid progression typically followed by complete recovery. Reports of dysphagia in this population are limited and general. The purpose of this article is to heighten awareness of the potential for silent aspiration in patients with BBE. This article details the nature of dysphagia during the recovery phase of BBE and includes findings from serial videofluoroscopic swallowing evaluations. In addition, it shows the impact of cognitive impairment on the ability to eat safely. Early

instrumental swallowing evaluation, close monitoring, and conservative management are essential to ensure safety in patients recovering from BBE.

Introduction

Bickerstaff brainstem encephalitis (BBE) is a rare demyelinating disease of the central nervous system, first described by Bickerstaff. Median age of onset approaches 40 years, and it predominates in males (1.8:1 combined). BBE typically follows an acute flulike infection, followed by progressive onset of ataxia, symmetrical external ophthalmoplegia, hyperreflexia, hemisensory loss, dysesthesia, weakness, and disturbed consciousness that frequently progresses to coma. Recovery is usually complete over the course of several months. Because of common autoantibodies, neuroimaging, and neuropsychological findings, BBE is considered to form a continuous spectrum with Miller–Fisher syndrome, both of which are thought to be variants of Guillain–Barré syndrome (GBS). Distinguishing features of BBE are impaired consciousness and a greater likelihood of normal reflexes. Currently, there is no standard medical treatment. Clinicians provide frontline supportive care until the condition remits. Medical treatments include corticosteroids, plasmapheresis, intravenous immunoglobulin (IVIG), and methylprednisolone.

Altered consciousness, bulbar impairment and prolonged intubation are common aspects of BBE and its treatment and are strongly associated with dysphagia. In Bickerstaff's original series of eight patients, six of the seven surviving patients had complete bulbar paralysis with concomitant dysarthria and dysphagia at some stage of the illness. Despite this initial report, there are no known published cases of instrumental swallowing evaluations in BBE. There are a number of reports of bulbar palsy, facial weakness, dysarthria, and altered consciousness in this population (Table I). These conditions are strongly associated with dysphagia, yet only a few of these cases are reported to have dysphagia.

This article presents the progress of one patient with BBE and emphasizes careful observation and instrumental examination of swallowing function as well as management decisions to optimize patient safety. Summaries of cognitive status (Rancho Los Amigos Cognitive Scale-Revised), swallowing safety indicator (Penetration–Aspiration Scale), primary findings, and treatment recommendations from each instrumental swallowing examination are listed in Table II. Brief notes about overall motor and cognitive functioning provide information regarding the course of general recovery in relation to progress with swallowing.

Case Report

E.B., a 31-year-old, highly physically fit, active duty male, experienced an episode of altered mental status, ophthalmoplegia, dysphagia, quadriparesis, ataxia, hyperreflexia, and urinary retention, approximately 2 weeks following a febrile gastrointestinal illness while on a mission in Uganda. There was no history of prior illness or injury, ingestion of local food or drink, and exposure to sick locals. Initial treatment included metronidazole, loperamide, and an unspecified additional antibiotic. E.B. appeared to recover and returned to his home in Italy. Within 10 days of his return, E.B. experienced new onset of fever, rigors, urinary retention, diplopia, and leg weakness. He was hospitalized and within 24 hours developed cranial nerve VI and VII palsies, dysphonia, ascending weakness, ataxic gait, loss of sensation in extremities, and ultimately confusion and somnolence. Magnetic resonance imaging (MRI) revealed multifocal lesions in the brainstem, thalami, cerebral peduncles, left frontal lobe,

and cervical spine from C2 to C5. Electroencephalography did not show focal discharges, but did reveal slowing, most significantly in the left frontal lobe.

Cerebrospinal fluid analysis showed elevated white blood cells to 26 with a lymphocytic predominance, no red blood cells, protein of 150, normal glucose, and no organisms. Test results were negative for herpes simplex virus and other common viruses including human immunodeficiency virus. Based upon the history of the preceding initial gastrointestinal illness, the evidence of dymyelinating injury on MRI, and the absence of bacteria or virus in the cerebral spinal fluid, initial diagnosis was acute demyelinating encephalomyelitis. E.B. was treated with plasmapheresis, IVIG, and IV corticosteroids, and, despite negative bacterial or viral findings, acyclovir and broad-spectrum antibiotics. Two days following intubation, E.B. regained consciousness but remained on mechanical ventilation with non-oral nutrition and hydration support. Percutaneous tracheostomy was performed 18 days post-initial hospitalization (DPIH). At that time, he was successfully extubated and underwent a videofluoroscopic swallowing (VFS) study. According to a verbal report of results, the VFS revealed inability to protect the airway during swallowing.

Twenty-one DPIH, E.B. was transferred to a hospital in Germany. During this period, he had continued weakness in all extremities and experienced altered mental status, most notably memory dysfunction and significant impulsivity and emotional lability. Cervical spine MRI showed continued areas of contrast enhancement, although there were no intracranial enhancing lesions. The results of electromyographic studies were essentially normal, with no evidence of axonopathy or block. The results of serology tests were positive for C. jejuni antibodies, but were negative for GQ1B antibodies or other infectious and autoimmune conditions.

On the basis of the history of progressive quadraparesis, ataxia, ophthalmoplegia, dysphagia, and hyperreflexia, as well as cerebrospinal fluid albuminocytologic dissociation, the pattern of predominantly brainstem and thalamic demyelination, and supportive features of a positive test for C. jejuni, diagnosis was adjusted to BBE. E.B. did well on continued steroid regimen without further use of IVIG or plasmapheresis.

Speech pathology and otolaryngology evaluations were ordered on admission to Walter Reed Army Medical Center (WRAMC) (23 DPIH) as E.B. had been and remained aphonic. The following evening, E.B.'s tracheostomy tube was downsized (size 8 cuffed to size 6 cuffless), and a Passy–Muir speaking valve was successfully placed 2 days later (26 DPIH). E.B. was then able to communicate verbally by whispering. At this time, extremity strength was improving, especially in the upper extremities, although atrophy in the legs and hands (distal > proximal) was noted.

Also on DPIH 26, a VFS was conducted to fully assess E.B.'s swallowing function. The results of the VFS revealed severe pharyngeal dysphagia characterized by premature spillage of the bolus to the pyriform sinuses, decreased pharyngeal contraction, and delayed onset of the swallow response with thin liquids. Decreased laryngeal elevation and closure resulted in varying degrees of aspiration on all trials of thin liquids. E.B. did not respond to or show any awareness of aspirated material (silent aspiration). Aspiration of thin liquids was not eliminated with postural changes. E.B. eliminated aspiration of small boluses of nectar-thick liquids using a chin-tuck posture; however, this material still penetrated the laryngeal vestibule. Given the patient's fragile medical condition and continued altered mental status, a conservative approach was taken. The initial diet recommendation was to remain nil per os (NPO) with the exception of ice chips.

On DPIH 27, the speech-language pathologist (SLP) instructed and prescribed a daily protocol of Masako maneuvers (interdental tongue position during nonnutritive swallowing; 3 sets of 5 repetitions 3 times daily) to improve pharyngeal contraction. Continued physical weakness and difficulty following directions despite cues from the SLP rendered additional exercises and maneuvers impractical and unsuccessful.

On DPIH 31, E.B. produced a significantly stronger volitional cough and limited voiced sounds. A second VFS was performed on DPIH 33. No aspiration was evidenced during this study, but deep laryngeal penetration without a physical response occurred with thin liquids. This penetration was eliminated with nectar-thick liquids and a chin-tuck maneuver. Mild residue remained in the valleculae and pyriform sinuses following liquid, pudding, and soft-solid trials. However, E.B. indicated awareness of these residuals and cleared them with a self-initiated double swallow and liquid wash. Recommendations included a mechanical soft diet with nectar-thick liquids, chin-tuck maneuver with every swallow, and alternation of liquids and solids. Retrograde memory returned, but short-term memory and attention problems remained.

The following day (DPIH 34), E.B.'s nasojejunal feeding tube was removed and he continued with the daily Masako exercise regimen and modified diet with chin-tuck posture. Compliance was compromised by cognitive deficits, including reduced awareness and self-monitoring. Signs of respiratory distress, including changes in skin coloration, perspiration, and coughing, appeared several minutes after meals. Dietary and postural recommendations were strictly reviewed, emphasized, and reiterated to all caregivers.

A third VFS was conducted on DPIH 39. Silent aspiration occurred with thin liquids. Nectar-thick liquids were swallowed safely without a chin-tuck posture, although mild post-swallow pharyngeal residue was noted. Recommendations were to continue a mechanical soft diet with nectar-thick liquids and to alternate food and liquids during meals. On DPIH 47, a fourth and final VFS at WRAMC revealed grossly normal swallowing function. E.B. was placed on a regular diet with alternating foods and liquids, and was discharged from swallowing and speech management services. At this time, he could ambulate with minimal assistance for short distances and plans were in place to transfer him to an acute rehabilitation facility.

Comment

This case of BBE involved severely impaired sensory and motor function of axial structures as well as the extremities. Although dysphagia is mentioned in the literature as a complication of BBE, descriptions are lacking. This case documents the time course of recovery from BBE with an emphasis on dysphagia, supported by weekly VFS evaluations. This appears to be the first documented case of dysphagia with silent aspiration in BBE. Silent aspiration, or aspiration without any indication of immediate awareness, is especially dangerous because clinicians and patients alike may be unaware of its presence. This case highlights that silent aspiration occurs during the recovery phase of the disease (in this case, about 1 month after initial hospitalization) while other functional deficits are improving, and medical practitioners might typically allow patients to begin an oral diet. Aspiration pneumonia is preventable if dysphagia is detected early and if patients and caregivers take recommended precautions. Cognitive impairment further complicates clinical management, because patients who are unaware or unconcerned about deficits are likely to be noncompliant or inconsistent in following management recommendations. This patient appeared to ignore recommendations once he was placed on a restricted diet (DPIH 33), which became clear when the SLP visited him after a meal and noted profuse perspiration, sallow skin color, and weak coughing. His wife confirmed that this reaction was common after every meal. It is likely that this patient was able to tolerate a significant

degree of aspirated material because he was young and highly fit, given his military readiness. Careful monitoring of swallowing function with fluoroscopic imaging and of his behavior while eating and drinking were critical to his eventual recovery.

Sensory impairment of the laryngopharynx is presumed to underlie silent aspiration. Motor impairment can also increase the risk of aspiration because of reduced laryngeal elevation, leading to inadequate airway protection as well as residue after swallowing. Health care providers must be aware of these sensory and motor risks, and take extra precautions to protect the pulmonary systems of patients with BBE until adequate recovery has occurred.

Immediate signs of aspiration typically include coughing, gagging, or other signs of distress. In the absence of these, the clinician may ask a patient to phonate after swallowing to detect the sounds of liquid in the larynx. However, in a severe case of BBE like the one presented here, the patient is unable to phonate, rendering such tests meaningless. Observing a patient for several minutes after eating or drinking may reveal other clinical signs, such as perspiration, change in oxygenation (skin or nail color), and delayed coughing. Clinicians should remain at bedside after feeding for an adequate amount of time to assess these features, and caregivers should be trained in the observation of these signs.

In conclusion, oropharyngeal dysphagia appears to be an underreported sequela of BBE. Although dysphagia may be assumed during the progressive phase of disease, clinicians must take care to recognize and manage conservatively the ongoing impact of dysphagia during recovery. Dysphagia accompanied by silent aspiration may lead to aspiration pneumonia, which is a potentially dire, yet avoidable complication of BBE.

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Portable Spirometry in the Deployed Setting

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Abstract

Recent studies suggest an increased risk of respiratory complaints associated with deployment. The objective measurement of lung function provided by portable spirometry is likely to improve the ability of military providers to diagnose and treat lung disease. A portable spirometer was taken to southern Afghanistan on a recent deployment and used at both a level I aid station and a level II medical facility, which were colocated on a forward operating base in the Kandahar Province. In addition to being helpful managing asthma, the spirometer also facilitated identification of nonobstructive causes of dyspnea. The following cases provide proof of concept that portable spirometry can add to the limited armamentarium of military providers practicing in the austere deployment environment.

Introduction

Respiratory disorders are among the most common disease nonbattle illnesses reported among deployed service members. In addition to common infectious respiratory ailments that can quickly spread among individuals living in close quarters, there are a number of relatively unique exposure risks encountered in the current theaters of operations. Smoke from burn pits, particulate matter from sandstorms, and diesel exhaust from vehicles and generators are some of the environmental exposures encountered by deployed individuals that are suspected to be capable of exacerbating or causing respiratory complaints.

Burn pits have been employed as a means of solid waste disposal throughout the U.S. Central Command area of operations. A number of studies have implicated burn pits as a possible causative factor for new-onset respiratory symptoms among deployed service members. An epidemiologic study conducted by the Armed Forces Health Surveillance Center and Naval Health Research Center found that exposure within a 5-mile radius of a burn pit was not associated with an increased risk for newly reported or recurring respiratory symptoms. This does not preclude the possibility that an individual with a specific exposure history or genetic predisposition might develop respiratory symptoms from exposure to burn pits.

Although burn pits have been the most highly publicized environmental risk factor, other potential triggers of acute and chronic respiratory complaints in theater include particulate matter and exhaust fumes. Sandstorms are common in Iraq and Afghanistan and have been associated with an increased risk of hospital admission for both asthma and heart disease. Exhaust from military vehicles, aircraft, and diesel generators also poses a threat to those with prolonged exposure. In particular, diesel exhaust that is commonly used in military vehicles and generators has been shown to increase the risk of pulmonary disease in vitro as well as in vivo.

Spirometers used in the hospital setting are typically bulky and require periodic calibration, but recent technological advances have resulted in portable spirometers that are self-calibrating and relatively inexpensive. The EasyOne (ndd Medical Technologies; Andover, Massachusetts) is one such spirometer that was recently used on a forward operating base in southern Afghanistan. The two medical treatment facilities (MTFs) on this base included both a level I battalion aid station and a level II MTF. The staff at these facilities included physicians specialized in allergy and immunology who were able to provide training on proper techniques in the use of spirometry. The following cases illustrate how a portable spirometer can be a useful diagnostic and management tool for deployed medical providers practicing in an austere environment with limited resources.

Case Reports

Case No. 1—Asthma

A 21-year-old Afghan male who worked for U.S. Forces as an interpreter presented to the level II MTF complaining of shortness of breath and nonproductive cough for 2 days. He had a history of childhood asthma, but denied any problems over past 5 years. He was afebrile, with 1 day of nasal congestion. Vital signs showed a respiratory rate of 26 with normal pulse, blood pressure, and oxygen saturation (97%) on room air. Physical examination was remarkable for mild respiratory distress, with increased work of breathing but no intercostal retractions. He had diffuse, bilateral expiratory wheezing on auscultation; no rales or rhonchi. Spirometry was performed pre- and post-administration of albuterol and is illustrated in Figure 1.

Using portable spirometry, the physician was able to obtain a better sense of the severity of the patient's airway obstruction and the degree of reversibility following administration of a short-acting beta agonist. The spirometric loops demonstrate a classic picture of airway obstruction. Although the predicted values used are not based on males from the Middle East, spirometry allowed for comparison of values pre- and postbronchodilation, showing a significant degree of reversibility.

According to the 2009 National Health Interview Survey Data compiled by the Centers for Disease Control and Prevention, the lifetime prevalence of asthma in the United States in adults age 18 and older is 13.3%. Across the subdivisions of age, the highest reported prevalence was in the 20 to 24 year old age group (17.8%). According to the 2006 Office of the Under Secretary of Defense for Personnel and Readiness executive summary of the military population, 87% of new enlisted recruits in 2006 were between the ages of 18 and 24 years old, and 47% of the active duty enlisted force fell into this age group.

Military standards of medical fitness for induction, enlistment, appointment, and retention on active duty, as well as policies pertaining to medical waivers, physical profiling, and medical fitness standards for deployment, recognize the varying degrees of severity of asthma and impairment. Given the prevalence of asthma in the adult population, it is not surprising that asthma is one of the most common medical conditions for which medical waivers are considered and granted.

Between sandstorms, burn pits, and viral illnesses, the deployed environment is an unpredictable one, with many stimulants that could trigger an asthma exacerbation more severely than an individual had experienced in Garrison. This presents a unique challenge to military providers when deployed, particularly with regard to available tools for assessing clinical status and response to medications both acutely and long term.

Key management issues related to asthma are severity, control, and responsiveness to treatment and other interventions (smoking cessation, weight loss). The National Heart, Lung and Blood Institute Expert Panel Report on the guidelines for asthma management and diagnosis recommends that spirometry measurements before and after short-acting bronchodilators should be undertaken any time the diagnosis of asthma is being considered. The spirometry measurements most helpful in asthma are forced expiratory volume in 1 second (FEV1) and forced vital capacity. Reversibility in FEV1 of ≥12% and ≥200 mL from prebronchodilator value support an asthma diagnosis.

In case no. 1, spirometry proved useful for initial assessment, as well as follow-up response to medications. Spirometry is the preferred method for the measurement of airflow obstruction and reversibility, and is superior to peak expiratory flow meter, which can underestimate the degree of airflow limitation and has a wide variability of predicted values based on the manufacturer. Fuhlbrigge et al showed that low FEV1 is associated with increased risk of severe asthma exacerbations. Therefore, the ability to objectively assess pulmonary function with spirometry in theater is likely to improve the ability of military providers to diagnose and manage patients with asthma.

Case No. 2—Masquerader of Asthma

A 60-year-old U.S. contractor presented to a level I MTF complaining of intermittent breathing difficulty over the previous 2 weeks. He had no history of asthma or any known lung disease and was a nonsmoker, but was taking medication for gastreoesophageal reflux disease (GERD). His symptoms occurred exclusively during the day, were not associated with cough, and were not exacerbated with physical activity. He described a

feeling of “not being able to get a full breath” that occurred on average 10 to 20 times per day. He denied feeling more anxious than usual, but said he had been working longer hours recently as the only individual on the base in his job capacity.

Physical exam was remarkable for normal vital signs including an oxygen saturation of 99%. He was a well appearing nonobese male. His cardiovascular and pulmonary exams were normal and no wheezing or stridor was noted (Fig. 2).

Although asthma is the most common cause of dyspnea among service members, other conditions such as vocal cord dysfunction (VCD) should be considered in the differential diagnosis. VCD is marked by paradoxical adduction of the vocal cords and often causes symptoms similar to asthma such as dyspnea, chest tightness, cough, and wheezing. Previous studies have suggested that VCD is present in 10 to 15% of military members evaluated for dyspnea. Symptoms typically occur during inspiration, but in severe cases an expiratory component might also be present. Associations include female gender, psychological conditions/anxiety, GERD, and exercise. Because symptoms are often provoked by anxiety or stress this condition is likely to be encountered in a combat zone. Historical clues that should prompt consideration of VCD include intermittent symptoms that are refractory to asthma medications, abate with distraction and during sleep, and worsen with anxiety or stress.

The diagnosis of VCD can be confirmed with direct visualization of the larynx while a patient is symptomatic. Spirometry can be useful to support a clinical diagnosis of VCD, but because of the intermittent nature of the condition should not be used to exclude the diagnosis if results are normal. Typical spirometric findings include truncation of the inspiratory loop and reduction of inspiratory flow measures. In particular, the ratio of midexpiratory to inspiratory flows (FEF50/FIF50) has been shown to be helpful in diagnosing extrathoracic airway obstruction. Normally this ratio is approximately 0.9, and a ratio >2.0 is suggestive of extrathoracic airway obstruction. Although this patient's sex and age were atypical for VCD, the history of GERD and stress at work placed VCD higher on the differential diagnosis.

Spirometry was helpful in confirming intermittent extrathoracic airway obstruction and in explaining to the patient what was likely causing his dyspnea.

Treatment for VCD often involves speech therapy focusing on relaxed breathing techniques. Simply making the correct diagnosis and explaining to the patient the nature of the condition is often reassuring and prevents unnecessary trials of medications. If an exacerbating condition exists (i.e., GERD or psychiatric impairment), it is reasonable to treat these, although no controlled studies have demonstrated an improvement in VCD symptoms after treating such conditions.

Other potential masqueraders of asthma include exercise-induced paradoxical arytenoid motion (EPAM) and hyperventilation syndrome. EPAM is similar to VCD with regards to risk factors and treatment, but involves paradoxical motion of the arytenoid cartilage rather than the vocal cords. Hyperventilation syndrome occurs when minute ventilation exceeds metabolic demands, which can result in respiratory alkalosis. In addition to dyspnea, symptoms may include chest tightness, lightheadedness, and paresthesias. Spirometry in EPAM would be similar to that seen in VCD, and for hyperventilation syndrome would likely be normal, but still helpful in excluding other diagnoses. An arterial blood gas showing decreased PCO2 with an increased pH would support the diagnosis of hyperventilation syndrome.

Discussion

These cases illustrate the utility of using portable spirometry in the deployed setting. With recent studies suggesting an increased risk of pulmonary disease among deployed soldiers, it is critical for providers to have the means to properly evaluate and manage respiratory disease at every level of care. Adding portable spirometry to the limited diagnostic armamentarium available to providers in theater would be a step toward a solution as well as a means to better quantify the problem of respiratory disease among deployed military personnel.

The U.S. military works closely with multinational forces, some of whom have limited access to medical care and do not have the accession standards of the U.S. military. In addition, deployed providers also care for interpreters, contracted civilians, and local nationals, and must be prepared to treat and manage a whole host of diseases, to include airway and pulmonary problems. Conducting and reading spirometry is relatively simple and should be considered as an additional skill recommended for deploying providers, similar to the necessary skill of performing and reading an electrocardiogram in the deployed environment. A study on the technical adequacy and accuracy of interpretation in primary care providers who had received a 2-day training on spirometric technique and reading demonstrated acceptable levels of technical quality and concordant interpretation (76% of all completed tests) with specialty experts. In this clinical study, the portable spirometer device, similar to what was used in our cases reported, was chosen for its modem capacity, but also device stability that precluded a requirement for calibration while maintaining accuracy.

Many physicians utilize spirometry in routine practice and are comfortable using it, but military medical providers have varying ranges of expertise and experience. Providing additional training for physicians, nurses, and physician assistants who are not comfortable interpreting spirometry may be necessary before implementing widespread use. Training was provided to the battalion medics, nurse, physician assistants, and other physicians on how to use the spirometer. This training utilized the American Thoracic Society criteria and focused on proper technique as well as recognizing an adequate trial based on start and end of test criteria and reproducibility of attempts. In addition, the device itself provides instant feedback on the adequacy of the trials.

Other challenges to implementing the routine use of portable spirometry in theater include the cost of spirometers and disposable mouthpieces. The spirometer used in this study retails for approximately $1,500 and mouthpieces cost $1.50 apiece. Although this seems relatively inexpensive for a piece of sophisticated medical equipment, the cost would be significant if it were implemented across the current theaters of operation. Maintaining the spirometer in an austere environment could also prove a challenge. Despite being exposed to temperature extremes and the rigors of a typical deployment, the spirometer in this study did not malfunction in theater and was still functioning correctly and within tolerance limits when evaluated by the manufacturer postdeployment.

The pulmonary literature supports the conclusion that spirometry affects patient management in the primary care setting. As many as 15% of primary care providers would change the clinical management plan based on the results of spirometry done in the clinic. Detection of unsuspected airway obstruction, or of obstruction that is more severe than clinically suspected, demonstrates how management could be improved with spirometry. Normal spirometry results are also helpful to exclude diagnoses and support the evaluation for nonpulmonary causes of respiratory complaints, prompting earlier evaluation and involvement of a higher echelon of care.

The military medical system is designed to provide the highest level of care possible to service members wherever they serve. Although much of the diagnostic skill of medical providers relies on obtaining a thorough history and physical examination, evaluating symptoms such as cough or dyspnea can prove challenging without additional diagnostic information. Advances such as digital radiography and accessibility to subspecialist care through an electronic consult service have made it possible for military providers to deliver such care while deployed. Portable spirometry provides another mechanism by which uncompromising care can be offered even in the most austere environment.

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Emergency Physician Evaluation of a Novel Surgical Cricothyroidotomy Tool in Simulated Combat and Clinical Environments

Military Medicine
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Abstract

We sought to investigate the performance of a novel cricothyroidotomy CRIC device compared to the traditional surgical in both simulated combat environments and the emergency department (ED) setting. Twenty U.S. Army staff and resident emergency medicine physicians were randomized to device and simulated setting order and performed cricothyroidotomies in the standard manner and with the CRIC device via the TraumaMan surgical simulator in three simulated settings: the ED, a day combat environment, and a night combat environment. Differences in procedural completion for the two methods in different settings were compared by two-tailed paired t-tests. The occurrence of major and minor procedural complications and questions presented as 5-point Likert scales to describe participants' preferences of cricothyroidotomy methods were compared by $\chi 2$ analysis. Time to incision, time to procedural completion, and rate of major and minor complications were not significantly different between the standard surgical method and the CRIC device ($p > 0.05$). In the simulated ED setting, 60% of participants preferred the standard surgical method (95% confidence interval: 38.5–81.5), whereas in the simulated combat settings, 50% of participants preferred each device (95% confidence interval: 28.1–71.9). In our population, we observed similar operator performance characteristics and physician preferences between the 2 methods in all simulated cricothyroidotomy settings.

Introduction

Loss of airway is the third most common cause of preventable death on the modern battlefield, and in the recent Operation Iraqi Freedom conflict, airway compromise which may be potentially survivable is reported to be a cause of death with an estimated frequency of 1.8% to 8%. Cricothyroidotomy is a lifesaving and necessary procedure in situations of airway compromise when the inability to both intubate and ventilate a patient exists. This rare but critical procedure also occurs with an estimated emergency department (ED) frequency of 0.5% of all intubations. Standard surgical cricothyroidotomy is routinely learned by emergency physicians, surgeons, and forward combat medical providers such as

medical technicians of all levels of training. On the battlefield, surgical cricothyroidotomy may be the preferred procedure of emergent airway management given the unique constraints and considerations often present in combat.

The promotion of the role of cricothyroidotomy on the battlefield and the development and investigation of ergonomically simplified airway equipment has been proposed as a potential means of improving prehospital combat care. The use of medical and combat simulation to evaluate low frequency, high stakes events such as surgical cricothyroidotomy has been previously described. The TraumaMan (Simulab; Seattle, Washington) mannequin-based human patient simulator is routinely used for procedural training in the American College of Surgeons Advanced Trauma Life Support course to enable skill training of surgical cricothyroidotomy. Such simulators are used extensively for vital cricothyroidotomy procedural training, assessment, and research. Medical and combat environments such as the ED and the battlefield can also be approximated through simulation. In our investigation, we sought to investigate the performance of a recently developed novel surgical cricothyroidotomy device (CRIC) with the assistance of emergency medicine (EM) physicians who are familiar with this procedure in a study utilizing human patient simulators in a simulated combat environment. The CRIC (Pyng, Richmond, BC, Canada) is a multitool containing the essential procedural devices (scalpel, spreaders, tracheal hook, available light source) in a single housing and is meant to be operated with one hand with minimal movements away from and within the surgical field (Fig. 1)

Methods

A total of 20 U.S. Army staff and resident EM physicians familiar with the procedure of surgical cricothyroidotomy were assigned to one of four groups using double randomization. Each of the four test groups contained two second-year EM residents, two third-year EM residents, and one board certified EM staff physician. Participants were healthy male or female second- or third-year EM residents or staff EM physicians between the ages of 18 and 50. Participants with known difficulties seeing in low-light conditions, eye or vision correction surgery within the past month, or other condition causing inability to perform the cricothyroidotomy procedure were excluded from the study. To complete the double randomization, each group was then randomly assigned as to the order they would complete the simulated scenarios, which include the ED, a daytime combat scenario, and a nighttime combat scenario.

After assignment to a group, participants completed a questionnaire to elicit overall demographic information and prior experience with cricothyroidotomy. They then completed a standardized 10-minute orientation session that began with a refresher of the standard surgical cricothyroidotomy procedure including anatomical landmarks and procedural tools. Participants were then given a structured orientation to the operation of the CRIC device according to the CRIC trainer's manual provided on the PYNG web site. At the conclusion of the orientation session, participants were allowed to practice one cricothyroidotomy with the CRIC tool in the simulated ED environment to allow for familiarization with the device.

Each participant then completed a cricothyroidotomy in each scenario using both the CRIC and the traditional method (Fig. 2). In the simulated ED setting, one TraumaMan was placed on a standard height table. Participants were provided an 11-blade scalpel, curved forceps, and a 6.0 Shiley tracheostomy tube when performing the traditional method. When using the CRIC, participants were provided the CRIC and a 6.0 Shiley tracheostomy tube. Time began once the participant reached an arm length away from the mannequin's neck and ended when the participant

stated “procedure complete.” A study investigator measured and recorded time for all participants to maintain consistency in scoring. At the completion of the cricothyroidotomy, a study investigator who was blinded to the cricothyroidotomy method performed assessed for the presence of both major and minor complications. The major complication defined before the investigation being failure to place the tracheostomy tube within the lumen of the trachea in a caudal direction. Minor complications defined a priori included multiple incisions, more than one attempt at tracheostomy tube placement as determined by investigator observation, damage to the posterior tracheal wall, and placement of the tracheostomy tube within the lumen of the trachea via an entrance other than the site of the cricothyroid membrane. At the conclusion of the simulated ED environment, the participants then completed a method preference questionnaire which included preference statements appearing on 5-point Likert scales.

In the combat environment, participants completed cricothyroidotomies using the traditional method and the CRIC in both day and night scenarios. The simulated combat environment was located in an enclosed space equipped to deliver auditory and visual cues that approximate a probable combat environment.

Procedures under day lighting conditions took place with surrounding ambient lights in full illumination and night lighting conditions were undertaken by turning down all constant ambient lighting while some strobe lighting was available to simulate nearby explosions. In both scenarios, burnt flesh-scented smoke filled the room and loud explosions and gunfire played through the speaker system. In the traditional method, participants used a headlamp with red-light filter, 11-blade scalpel, curved forceps, and a 6.0 Shiley tracheostomy tube when performing the traditional method. When using the CRIC, participants had the CRIC and a 6.0 Shiley tracheostomy tube. Time began when the participant assumed kneeling or similar position after approaching the patient and ended when the participant declared “procedure complete.” A study investigator measured and recorded time for all participants to maintain consistency in scoring. At the completion of the cricothyroidotomy, a study investigator who was blinded as to the cricothyroidotomy method performed a check for both major and minor complications as described above.

At the conclusion of the session, the participant then completed a method preference questionnaire which included preference statements appearing on 5-point Likert scales. In both combat and ED scenarios, the simulated neck tissue was exchanged after a total of four incisions per the manufacturer's recommendations.

Statistical Analysis

The primary study outcome was time to successful tube placement. Secondary outcomes included the time to incision, rate of major and minor procedural complications, and metrics of operator preference. A two-way analysis of variance was performed to evaluate significance for time to incision and time to tube placement across all groups in all scenarios. The rate of major and minor complications was calculated in percentages and was tested for significance via $\chi 2$ analysis. Operator preference was evaluated via questions presented on 5-point Likert scales.

Results

Background demographic information was collected from each participant to determine their amount of experience with cricothyroidotomy (Table I). Mean time to incision across all performed cricothyroidotomies ranged from 6.6 to 7.7 seconds (Table II).). A paired t-test of time to incision

showed no significant difference between the traditional method and the CRIC in any scenario (Table III). Mean time to tube placement across all performed cricothyroidotomies ranged from 43.2 to 55.6 seconds (Table IV). A paired t-test of time to tube placement also showed no significant difference between the traditional method and the CRIC in any scenario (Table V). The rate of major and minor complications were not significantly different between the traditional and CRIC methods when comparing all groups and all scenarios (Table VI). A single major complication was recorded during the study and occurred during the simulated ED setting with a participant using the traditional method. Specific types of minor complications were not recorded.

Operator preference after completing the ED setting was 60% for the traditional method vs. 40% for the CRIC tool (CI ± 21.5%). In response to the statement, “The standard traditional procedure of surgical cricothyroidotomy was more efficient than use of the CRIC tool,” 15% of participants strongly agreed, 10% agreed, 30% were neutral, 40% disagreed, and 5% strongly disagreed. In response to the statement, “The standard traditional procedure of surgical cricothyroidotomy was more likely to be successful than the use of the CRIC tool,” 10% of participants strongly agreed, 45% agreed, 25% were neutral, 15% disagreed, and 5% strongly disagreed. In response to the last statement, “The standard traditional procedure of surgical cricothyroidotomy was less likely to be associated with complications than was the use of the CRIC tool,” 10% of participants strongly agreed, 15% agreed, 35% were neutral, 40% disagreed, and 0% strongly disagreed.

Operator preference after completing the combat scenarios was split with 50% of participants preferring the traditional method and 50% preferring the CRIC tool (CI ± 21.9%). In response to the statement, “The standard traditional procedure of surgical cricothyroidotomy was more efficient than use of the CRIC tool,” 15% of participants strongly agreed, 25% agreed, 20% were neutral, 40% disagreed, and 0% strongly disagreed. In response to the statement, “The standard traditional procedure of surgical cricothyroidotomy was more likely to be successful than the use of the CRIC tool,” 15% of participants strongly agreed, 35% agreed, 40% were neutral, 10% disagreed, and 0% strongly disagreed. In response to the last statement, “The standard traditional procedure of surgical cricothyroidotomy was less likely to be associated with complications than was the use of the CRIC tool,” 15% of participants strongly agreed, 20% agreed, 40% were neutral, 25% disagreed, and 0% strongly disagreed.

Discussion

The findings of this pilot study suggest noninferiority of the CRIC tool. In our population, we observed similar performance between the two techniques/devices in all simulated settings. There was no significant difference in our primary outcome variable of time to tube placement between the traditional method and the CRIC device. There also was no significant difference in our secondary outcome variables of time to incision and minor complication rates between the traditional method and the CRIC device.

In most regards, participants did not seem to prefer one device over another in simulated ED or combat settings. On solicited feedback, however, multiple participants reported that they found the CRIC tool scalpel too short and that they were unable to easily get through the simulated subcutaneous tissue. This was a problem that multiple study investigators reported seeing on the study day as well. This result may be attributed either to the predefined length of the scalpel on the CRIC tool or the simulated neck tissue on the TraumaMan. Future research using a cadaver model with both obese and normal weight patients may further clarify this.

Some advantages and disadvantages of all-in-one tools in the combat environment may exist. A significant potential advantage of such as tool in under fire or in high stress scenarios, such as a surgical cricothyroidotomy, is that a single all-in-one device may eliminate the need to rummage through a medical kit to find and gather all the required tools. This advantage however may be offset by the ability of that same tool to serve multiple other purposes in the austere environment of combat. For example, a scalpel and curved forceps can be used to perform not only a surgical cricothyroidotomy but also innumerable other procedures, whereas the utility of the CRIC tool may be limited to its original purpose. Furthermore, the weight of the tools (1 oz for an 11-blade scalpel and curved forceps vs. 1.4oz for the CRIC tool) in a space and weight-constrained environment must be considered in light of any device's potential multiplicity of uses within one's medical kit.

Notable limitations to this study exist. First, all EM physician participants had previous experience with the standard surgical cricothyroidotomy procedure, potentially biasing results in favor of that method. Additional investigations may examine the relative subjective and objective performance of these methods in the hands of more novice providers. Second, since the a priori power analysis was performed within the limits of sparse existing data that may not be directly applicable to our simulation-based investigation, this study may have been underpowered to detect significant differences. Finally, it is uncertain the degree to which these results might translate to actual patients or real environments in the ED or on the modern battlefield. A notable limitation of TraumaMan is the lack of bleeding that accompanies this procedure on live tissue and how this would affect the results. As simulation can only approximate reality, future studies utilizing animal models, perfused cadaver models, or other high-fidelity human models for cricothyroidotomy may add additional insight into this device's performance characteristics.

Acknowledgements

Our utmost gratitude goes to MAJ Carl Skinner and Raywin Huang, PhD, for their assistance with the statistical analysis. We also would like to thank CPT Laura Cookman and CPT Gerald Hopkins for their help with data collection. Five CRIC Tools were provided by PYNG Medical, Richmond, BC, Canada.

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Vehicle-Mounted High-Power Microwave Systems and Health Risk Communication in a Deployed Environment

Military Medicine
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January 2013

Abstract

Vehicle-mounted high-power microwave systems have been developed to counter the improvised explosive device threat in southwest Asia. Many service members only vaguely comprehend the nature of these devices and the nonionizing radio frequency (RF) radiation they emit.

Misconceptions about the health effects of RF radiation have the potential to produce unnecessary anxiety. We report an incident in which concern for exposure to radiation from a high-power microwave device thought to be malfunctioning led to an extensive field investigation, multiple evaluations by clinicians in theater, and subsequent referrals to an Occupational Health clinic upon return from deployment. When acute exposure to RF does occur, the effects are thermally mediated and immediately perceptible—limiting the possibility of injury. Unlike ionizing radiation, RF radiation is not known to cause cancer and the adverse health effects are not cumulative. Medical officers counseling service members concerned about potential RF radiation exposure should apply established principles of risk communication, attend to real and perceived risks, and enlist the assistance of technical experts to properly characterize an exposure when appropriate.

Introduction

Improvised explosive devices (IEDs) have been used against coalition forces to deadly effect in Iraq and Afghanistan. Among the many innovations fielded to counter this threat are vehicle-mounted high-power microwave (HPM) systems. HPM devices such as the “Jackal” and “Calilgo” use directional radio frequency (RF) antennas to assist in the neutralization of IEDs via detection or premature detonation.

Although the use of HPM devices by coalition forces in theater is common, some service members lack a basic understanding of the mechanism of operation of the devices and have concerns about potential health effects related to exposure to the nonionizing radiation they emit. Misconceptions about the health effects of RF radiation have the potential to produce unwarranted fear among those whose duty requires them to work in proximity to the systems. Providers caring for these soldiers should understand the nature of HPM devices and be prepared to effectively communicate regarding the risks, real and perceived, associated with exposure.

We report an incident in which concern for exposure to a “malfunctioning” HPM device led to a field investigation, multiple visits to health care providers in theater, and subsequent referrals to a military Occupational Health clinic for evaluation upon redeployment. Following this vignette, we present a concise characterization of HPM devices followed by a brief summary of what is known about the health effects of exposure to RF radiation. In conclusion, we summarize established principles of effective risk communication likely to be useful to providers charged with explaining the health risk associated with HPM devices to operators and commanders.

Incident Summary

In the fall of 2011, four out of six soldiers from two separate teams experienced symptoms of nausea and headache during routine night convoy operations in southwest Asia. The first team reported their symptoms immediately after completing their mission and expressed concerns that their symptoms had been caused by a malfunctioning counter-IED system on their vehicle. Members of the second team arrived later and were told what had happened to the first team. Two out of the six soldiers also endorsed having had nosebleeds, which each considered to be an unusual event. Both teams were sent to the Combat Support Hospital for evaluation. None of the soldiers experienced any unusual sensation of thermal energy while in their vehicles. None of the soldiers complained of a recurrence of their symptoms after the mission.

The soldiers' perception that their symptoms had been caused by a malfunctioning HPM device was due in part to a perceived temporal relationship. Both teams reported that their symptoms began 30 minutes after the devices had been placed in “transmit,” and subsided when the devices were placed on standby during breaks in the mission; their symptoms returned when the devices were reactivated.

A subsequent investigation in accordance with Army Regulation 15-6 determined that the devices were functioning as designed and concluded that the symptoms exhibited by the soldiers could not be linked with exposure to the HPM system in any manner “consistent with current scientific literature.” The hot, arid climate, carbon monoxide exposure, and combat stress were contemplated as alternative explanations to the reported symptoms. Even so, the soldiers told investigating officers that they “did not feel confident” in the HPM device and expressed concerns about the long-term effects of RF radiation exposure. Investigators ultimately recommended that the soldiers involved obtain documentation of the event for inclusion in their Veterans Administration medical file “in order to receive follow-up care.” On redeployment, five out of the six were referred to Occupational Medicine after indicating on their Post-Deployment Health Assessment that they “worried” about their health after exposure to “Radar/Microwaves.”

Known Health Effects of Radio-Frequency Radiation

RF waves lack the energy quanta necessary to break covalent bonds and cause the genetic damage associated with higher frequency ionizing radiation such as X-rays and γ-rays. When injuries from acute exposure to microwave radiation do occur, they are thermally mediated and are the result of the denaturing of proteins, not ionization. The effect is readily apparent in microwave cooking in which nonionizing radiation passed through food forces the oscillation of polar molecules—so called dielectric heating.

Thermally mediated burns from acute exposure to microwave radiation are well described and are associated with symptoms typical of other burns, i.e., a warming sensation, skin erythema, and pain. Tissues with a diminished capacity to dissipate heat are particularly vulnerable to diathermic damage. The lens of the eye, in particular, lacks the blood supply required to mitigate heat stress, and animal models have demonstrated the formation of cataracts following exposure to high power levels of RF for extended periods. In practice, however, a human is unlikely to willingly tolerate the prolonged discomfort associated with the intensity of RF radiation required to damage the lens.

The existence of nonthermally mediated health effects from low-level RF exposure such as cell phone use has been the subject of a great deal of recent media interest. Although the difficulty of proving “noneffect” should be acknowledged, exposure to RF radiation has not been shown to cause cancer. In fact, decades of research has failed to show a consistent link between RF exposure and any nonthermally mediated long-term health effects, even in the most theoretically vulnerable populations.

HPM Devices and DOD Safety Standards

HPM devices are installed on tactical vehicles to defeat IEDs. Although the technical specifications of the systems are classified, we can state that they transmit a subset of RF radiation. The antennas of the devices are directional, emitting RF away from the protected vehicle over a wide azimuth and narrow elevation beam away from the cab.

Although there are no specific U.S. standards regulating exposure to RF and microwave radiation,4 the DoD has issued DODI Instruction 6055.11 to protect personnel from the thermally mediated effects of RF during peacetime “and to the maximum extent possible during wartime.” There is explicit acknowledgement in the instructions that “during war or combat operations, requirements in this Instruction may not be feasible.”5 In essence, the DoD instruction adopts the national consensus standard of the Institute of Electrical and Electronics Engineers C95.1-2005 on human exposure to RF radiation.6

It is official DoD policy to limit RF exposure to levels that are within maximum permissible exposure (MPE) levels and to investigate and document RF overexposure incidents. A maximum permissible exposure is a time-averaged exposure value established at a level such that no adverse health effects can be expected to occur even with repeated or long-term exposure. In testing the currently fielded vehicle-mounted HPM devices, RF radiation levels inside the cab areas of test vehicles were found to be an order of magnitude lower than required by DoD instructions. RF radiation levels directly in front of the HPM device antennas can exceed MPEs, however. As a safety control measure, technical manual instructions recommend a “stand-off” distance forward of the vehicle bumper to minimize the potential for thermal injury of personnel in front of a radiating antenna. For the Jackal, the control distance is 14 ft (4.3 m); the distance for other HPM systems are specified in the systems technical manuals and typically incorporate a 10-fold safety factor. Of note, control distances apply when a vehicle is stationary; typically, the vast majority of RF transmission would occur when the vehicle is in motion.

Suspicion of RF Radiation Overexposure

The term “overexposure” should be reserved for exposures that have exceeded the agreed-upon technical standard; therefore, a clinical history consistent with exposure necessitates investigation by technical personnel trained in RF dosimetry before an incident can be properly characterized as an overexposure. Such an analysis takes into consideration the time duration of potential exposure and part of the body exposed. The sensation of warmth associated with proximity to an HPM device is not de facto evidence of overexposure.

When evaluating a patient suspected of having sustained a thermal RF injury, the Institute of Electrical and Electronics Engineers Committee on Man and Radiation recommends particular attention to symptoms concurrent with beam exposure. An otherwise neurologically unimpaired patient who denies pain or thermal sensation during suspected exposure is unlikely to have sustained an RF injury. When RF injury is a clinical concern, the examining provider should note the presence of any areas of erythema or evidence of surface burn, particularly in proximity to metallic items. A qualified physician should then perform a meticulous ophthalmologic history and exam, documenting visual acuity and the presence or absence of lenticular opacities. In cases of potentially serious exposure, when superficial injury is likely and deep tissue damage is suspected, further workup should include diagnostic modalities appropriate for the organ system involved, such as an ECG or appropriate serum enzymes.7 Appropriate interpretation of these tests requires that clinicians rely on the same established principles of burn management associated with the care of non-RF-associated burns; patients with RF thermal injury should ultimately be dispositioned in a manner analogous to those with conventional thermal or electrical injury.

Risk Perception and Communication

People notoriously estimate health risk poorly. Risks tend to be perceived as acceptable when they are familiar, are associated with voluntary exposure (i.e., control), and are associated with a clear benefit. It is to be expected then that troops might be suspicious of radiation borne of a “black box” they are compelled to use and whose potential benefit (i.e., preventing death by IED) is not directly perceived. The universal confusion of radiation with radioactivity coupled with the use of the commonly used but poorly understood term “microwave” compound the challenges associated with health risk communication in this area.

Providers counseling service members who are concerned about exposure to HPM devices should first establish a relationship of trust with patients based on empathy, competence, honesty, commitment, and accountability.8 Careful attention to patient concerns about RF radiation will prevent needless angst and avoid the subsequent cascade of mistrust that has the potential to affect morale, impact unit safety and compromise mission effectiveness.

Empathy is established by acknowledging concern, e.g., “I can see how it would be a little scary to have to work around a device like that, especially when you're not even sure how it works.” Establishing competence requires that a provider explain in layman's terms what real health concerns exist, i.e., the potential for thermal injury. This will avoid the pitfall of being perceived as being prematurely dismissive of the very real, albeit rare, adverse health effects of acute RF overexposure. Honesty, commitment, and accountability are inherent in any healthy provider–patient relationship. Accordingly, openness about the limitations of your expertise in this area and an honest commitment to enlist technical experts when necessary to properly characterize hazards and address concerns will go a long way toward building the requisite therapeutic relationship.

Recommendations

Military health care providers should familiarize themselves with vehicle-mounted HPM devices and the thermally mediated health effects of exposure to RF radiation. Providers should recognize that in counseling patients they are more likely to communicate effectively if they earnestly apply established principles of risk communication, e.g., empathy, competence, and honesty.

Medical officers should work within command channels to ensure that initial and ongoing training addressing the risks of exposure to nonionizing radiation emitted by HPM devices is conducted in accordance with DoD policy.

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Traumatic Carotid Artery Dissection

Military Medicine
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January 2013

Abstract

Traumatic carotid artery dissections are uncommon and potentially devastating injuries that often have a delayed presentation. Soldiers often engage in leisure, training, and combat activities that place them at risk for sustaining an injury that causes a carotid artery dissection. To compound matters, spontaneous dissections are being more frequently recognized as well. Clinicians must be thorough in their history taking and maintain an elevated level of suspicion for this injury when presented with neurologic symptoms suggestive of head and neck pathology. This case study illustrates the difficulties encountered in arriving at a timely, correct diagnosis and offers treatment plan options. We hope that this case study will facilitate the early recognition and treatment of carotid artery dissections in the future.

Introduction

Cervical artery dissections (CAD) include both carotid artery dissections and vertebral artery dissections (VAD). The pathogenesis of these dissections is not well understood and has been associated with both major and minor trauma to the cervical region as well as atraumatic conditions such as genetic factors that alter the vascular structure, hypertension, and migraine headaches. Soldiers regularly engage in activities that place them at risk for neck trauma, while at home, in garrison, or deployed. Cohen et al analyzed data on 374 soldiers evacuated out of theaters of combat operations for neck pain. Over 35% of the evacuees identified injuries sustained while lifting, falling, driving, marching, and wearing Kevlar helmets. Only 3.5% were sustained during combat operations. Soldiers who sustain an injury to the neck or who present with unusual symptoms, present a challenging diagnostic dilemma since imaging resources are limited, particularly in an austere combat environment. Careful consideration of history, presenting signs and symptoms, and a wide range of differential diagnoses is essential to avoid missing this dangerous, though uncommon, diagnosis.

CADs can be extracranial (inferior to the passage through the skull) or intracranial. The extracranial segments of the arteries are more mobile and thus more susceptible to injury. Carotid artery dissections outnumber VADs three-fold to five-fold, with extracranial internal carotid artery dissections (ICAD) occurring most commonly. Carotid artery dissections occur most frequently between the ages of 35 and 50 years, peaking in the fifth decade, and affect men and women equally. They account for almost 2.5% of all first strokes and 20% of strokes in patients under age 45 years. Delayed diagnosis or treatment of a traumatic ICAD may lead to a stroke with a potentially devastating outcome. We describe a case of a traumatic ICAD with delayed presentation sustained during a softball game.

Case

In November, 2003, a 47-year-old male soldier was fielding the ball at second base when the runner ran directly into him, accidentally striking him in the left side of the neck with his elbow. The fielder fell to the ground but experienced no immediate signs or symptoms and continued to play. One week later he leapt up to reach something and, upon landing, experienced severe left neck pain and amaurosis fugax in his left eye. Seconds later he developed intense (10/10) pain to his left face and temple and loss of vision in both eyes. His vision returned after approximately 30 seconds, but the pain persisted. That same day, he presented to the local civilian Emergency Department with continued pain and extreme hypersensitivity and pallor only to the left side of his face. A stroke was suspected and a STAT computed tomography (CT) scan of the brain without contrast was done. The CT was read as negative for intracranial hemorrhage. His electrocardiogram was normal. He was diagnosed with a stress headache and discharged. He continued to experience significant pain, photosensitivity, and phonosensitivity over the next 3 days. He followed up with his Primary Care Manager (PCM) who also felt his symptoms were stress-related and advised the patient to use his favorite coping strategy: running. He went for a 10-mile run and noted that the unilateral left facial pallor and headache worsened and he lacked diaphoresis on the left side of his face and head. His PCM recommended a dental evaluation for a possible dental abscess that might be causing the pain. The dental exam was negative.

The following day the patient returned to his PCM with the continued complaints of the constant headache and unilateral facial skin color asymmetry and hypersensitivity. He was referred to the Ophthalmology Clinic where mydriatic eye drops were instilled into his eyes several times because the left pupil would not dilate. The examination revealed no problems with the optic nerve and he was released. Later that day, the ophthalmologist realized the patient's symptoms suggested Horner's syndrome (an interruption in the sympathetic nerve supply to the brain characterized by ptosis, miosis, and anhidrosis9).

He contacted the patient and ordered a STAT left carotid duplex color ultrasound (US). The US was read that evening by the vascular surgeon as being highly suspicious for dissection of the internal carotid artery. A magnetic resonance angiogram (MRA) of the neck confirmed the dissection and an underlying mural thrombus. The vascular surgeon questioned him about trauma and the patient suddenly remembered the injury at the softball game. He had not mentioned the incident to any other provider before this. The patient was immediately admitted to the hospital, and a heparin drip administered for the next week to prevent further thrombus formation. He was discharged home on warfarin and observed for healing of the dissection. Approximately 1 year later, he saw another vascular surgeon who confirmed through a follow-up carotid Doppler scan that the ICAD was healing, though slowly. She recommended stent placement. He contacted the original vascular surgeon regarding the stent and was advised to let the ICAD continue to heal on its own. Healing and warfarin therapy were completed 14 months after the dissection was diagnosed.

The patient continues to have a partial Horner's syndrome affecting his left eye, unilateral left facial pallor with exertion, and is extremely susceptible to heat injuries. During two subsequent deployments to Iraq, he suffered multiple heat injuries necessitating medical care. He can no longer tolerate running at a pace that causes his heart rate to exceed 140 beats per minute as that causes severe headaches.

Interestingly, in June 2011, during a routine physical examination, the patient was noted to have a partial Horner's syndrome on the right side causing right eye ptosis and miosis; anhydrosis was absent. An extensive workup to elucidate the etiology of this was performed and was negative for stroke, brain tumor, lung cancer, and new carotid artery dissection. It has been deemed idiopathic. Though the patient continues to suffer with residual heat and exercise intolerance and now a contralateral partial Horner's syndrome, he enjoys a relatively unencumbered life.

Discussion

With an annual incidence rate of 2.6 to 2.9 per 100,000, carotid artery dissections are relatively uncommon events but are increasingly recognized as a cause of stroke among middle-aged patients. They should be considered with a history of neck trauma or in the presence of a partial or complete Horner's syndrome.

If the mechanism of injury is traumatic, it usually involves a whiplash-type event, cervical spine fracture, other soft tissue injury to the neck, or maxillofacial fracture, but may also involve mechanisms of a more trivial force such as looking backward while backing up a vehicle, coughing, vomiting, sleeping in an unusual position, abrupt movements of the head and neck in rhythm with music, and others. Major trauma is a common cause of vertebral artery injury. Blunt injury represents 3 to 10% of carotid artery injuries and over 90% involve the ICA.

Spontaneous CAD are being increasingly diagnosed. Several risk factors for CAD have been proposed (Table I), but atherosclerosis does not appear to be an independent risk factor. The actual pathogenesis is likely an interaction among potential causes. A careful consideration for potential predisposing risk factors for CAD is prudent given some growing research concerning underlying arterial abnormalities (e.g., hypertension, recent infection, history of migraine headaches). Multiple concurrent CAD have been identified in 13 to 33% of cases.

In an ICAD, the arterial intimal lining separates from its medial division providing a surface for platelet aggregation and clot formation and an exit opening for a dissecting column of blood. The intimal tear location is usually about 2 cm distal to the carotid bulb (C2–C3 level). The length of the dissection is variable, but generally ends at the base of the skull where the carotid begins its passage through the skull. Based on the size of the thrombus, the carotid lumen may only be mildly narrowed or may progress to full occlusion. Recanalization of the artery in the postacute period may be through the true physiologic lumen or through the aneurysmal lumen. If medial or subadventitial layers of the arterial wall are affected, the enlarging dissection may lead to further dilatation and formation of a pseudoaneurysm.

Pseudoaneurysms differ from true aneurysms in that true aneurysms involve the intimal, medial, and adventitial layers of the arterial wall. Rupture of these extracranial aneurysms is not common, but is disastrous should it occur.

Carotid artery dissections are difficult to diagnose in the absence of a thorough history and a high index of suspicion. The average age of a patient presenting with a spontaneous CAD, is 40 to 45.8 years, and the most often frequent clinical manifestations are head or neck pain (80–96%), cerebral ischemic symptoms (67%), and ocularsympathetic paresis or Horner's syndrome (25–58%).

Clinical presentation of a CAD depends on the artery involved and the level of the lesion (i.e., extracranial or intracranial). Extracranial ICAD will demonstrate pain in the ipsilateral anterior neck and face, partial or complete Horner's syndrome, ischemic symptoms, and possibly lower cranial nerve (CN) palsies (CN IX–XII) (Table II). About one-third will have a carotid bruit. VADs will have symptoms of pain in the posterior neck and head and ischemic symptoms of the vertebrobasilar area.

Signs of Horner's syndrome include miosis, ptosis, and anhydrosis and are produced by a lesion along the three-neuron sympathetic pathway that supplies the head, eye, and neck. (Table III) The first-order neuron descends from the hypothalamus to the first synapse in the cervical spinal cord

(C8-T2). The second-order neuron runs from the sympathetic trunk through the brachial plexus and up to the superior cervical ganglion near the bifurcation of the common carotid artery. The third-order neuron ascends within the adventitia of the carotid artery through the cavernous sinus in close relationship to the sixth CN. Anhydrosis is only present in first- or second-order neuron lesions as the fibers for facial sweating travel along the external carotid artery. The oculosympathetic pathway innervates the iris dilator muscle and the muscles in the eyelids responsible for opening them. Anisorcoria is more marked in dark than in light environments. In Horner's syndrome, the affected pupil dilates significantly more slowly than the normal pupil. About 40 to 60% of patients with ICAD exhibit a painful third-order Horner's syndrome characterized by unilateral head, face, or neck pain.

A unique feature of ICAD is the latent period between the injury and the onset of clinical symptoms. Only 10% of patients display immediate symptoms, 58% present 10 or more hours after the injury, and 35 to 36% develop symptoms 24 hours or more after the injury. About 43% of diagnoses are missed until a neurological deficit manifests with an average delay of up to 53 hours from the injury to definitive diagnosis.17 Given the trivial and commonplace nature of many of the contributing factors, along with the variable time interval for presentation of symptoms, a careful questioning of the patient is often needed to elicit the information required to establish the diagnosis.

Multiple diagnostic modality options are available. These include carotid Doppler US, CT angiogram, MRA, and a catheter angiogram. A color-coded duplex Doppler US allows visualization of the dissected arterial wall to include a double lumen and hematoma. Unfortunately, it does not allow optimal imaging of the distal ICA, the site most commonly affected in blunt trauma. For example, although the ultrasonic techniques will often identify abnormal pattern of flow in more than 90 percent of patients, the site of dissection may not be identified. Though US lacks sensitivity and is operator dependent, it is less expensive and easily repeatable. Imaging via CT angiogram is 98.6% sensitive and 100% specific, but carries the risks of intravenous contrast administration and radiation exposure and requires a stable patient. An MRA shows high sensitivity and specificity for detecting ICADs, but requires a stable, cooperative patient and may not be readily available in all facilities. A catheter angiogram is the gold standard for diagnosis of vascular trauma and may allow for concurrent intervention, but is invasive and carries the risks of intravenous contrast administration and possible embolization.

Differential Diagnosis

It is important to consider that ICAD are dynamic processes and radiographic findings may change dramatically within days or even hours during the acute phase of the dissection. Differential diagnoses to be considered during an evaluation of symptoms suggestive of an ICAD include cluster headache, migraine, acute stroke, and herpes zoster ophthalmicus. A cluster headache may present with unilateral facial pain and ipsilateral Horner's syndrome, but generally resolves after about 30 minutes while symptoms of an ICAD would persist. Horner's syndrome would be extremely rare with a classical migraine, and most patients are able to recognize their typical migraine pain and associated symptoms.

Note, however, that migraines and dissections are not mutually exclusive and there may be a possible association between them. An acute stroke must be ruled out in any person presenting with a sudden or atypical headache and contralateral deficit. A patient developing herpes zoster ophthalmicus may present with severe unilateral pain and changes in vision before developing the typical dermatomal zoster rash.

Treatment

Most ICAD will heal spontaneously, and therefore more conservative approaches are usually indicated in the absence of persistent ischemia. Conservative treatment with anticoagulation to prevent further thrombus formation and to promote internal thrombotic fibrinolysis and subsequent healing is most favored. Anticoagulation is continued with periodic monitoring of the dissection via Doppler ultrasonography until healing is achieved, generally for several months. For patients in whom anticoagulation is contraindicated because of bleeding risks, antiplatelet therapy is appropriate.

Surgical resection of the aneurysm with arterial reconstruction and carotid ligations or a cervical to intracranial carotid artery bypass is reserved for patients with occlusive dissections. Though generally good postoperative outcomes have been reported, surgical intervention is indicated only for patients who continue to experience ischemic symptoms despite therapeutic anticoagulation and for those who have progressing aneurysms. Though most ICADs spontaneously heal, approximately 40% of traumatic dissections and most pseudoaneurysms do not. This places the patient at risk for embolization or flow-related complications. Stents may be used in the cases of pseudoaneurysm or dissections with a greater than 50% reduction in blood flow. However, consideration must be given to demonstrations of the efficacy of long-term stenting as well as considerations for complexity of stent-related complications of treatment. The recurrence rate for CAD is low and rarely does the dissection recur in the same artery.

Conclusion

We described a case of a traumatic ICAD with delayed presentation. This patient demonstrated several common symptoms of an ICAD: ipsilateral neck pain and headache, ipsilateral partial Horner's syndrome (miosis), ischemic symptoms (i.e., amaurosis fugax, facial hypersensitivity, and pallor), and ipsilateral anhydrosis. The symptom presentation was delayed by 1 week and the diagnosis was delayed by 6 days because of lack of prompt recognition of the trauma and of the partial Horner's syndrome. Extracranial as well as intracranial causes for unusual neurologic symptoms must be considered. Conservative treatment with anticoagulation and monitoring showed eventual resolution of our patient's dissection without necessitating invasive intervention.

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PTSD

Writing Therapy for Posttraumatic Stress: A Meta-Analysis

Psychotherapy and Psychosomatics
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January 2013

Background: Face-to-face psychological treatments have difficulty meeting today's growing mental health needs. For the highly prevalent posttraumatic stress (PTS) conditions, accumulating evidence suggests that writing therapy may constitute an efficient treatment modality, especially when administered through the Internet. We therefore conducted a meta-analysis to investigate the efficacy of writing therapies for PTS and comorbid depressive symptoms.

Methods: The literature was searched using several structured and unstructured strategies, including key word searches of the PubMed, Web of Science, PsycINFO, and PILOTS databases. Six studies met eligibility criteria and were included in the analyses. These studies included a total of 633 participants, of which 304 were assigned to writing therapy.

Results: Across 5 direct comparisons of writing therapy to waiting-list control, writing therapy resulted in significant and substantial short-term reductions in PTS and comorbid depressive symptoms. There was no difference in efficacy between writing therapy and trauma-focused cognitive behavioral therapy, but we caution that this finding was based on only 2 direct comparisons.

Conclusions: Writing therapy is an evidence-based treatment for PTS, and constitutes a useful treatment alternative for patients who do not respond to other evidence-based treatments. Internet adaptations of writing therapy for PTS may be especially useful for reaching trauma survivors in need of evidence-based mental health care who live in remote areas or who prefer to retain their anonymity.

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Service Utilization Following Participation in Cognitive Processing Therapy or Prolonged Exposure Therapy for Post-Traumatic Stress Disorder

Military Medicine
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January 2013

ABSTRACT

This study evaluated the impact of a course of prolonged exposure or cognitive processing therapy on mental health and medical service utilization and health care service costs provided by the Department of Veterans Affairs (VA). Data on VA health service utilization and health care costs were obtained from national VA databases for 70 veterans who completed prolonged exposure or cognitive processing therapy at a Midwestern VA medical center. Utilization of services and cost data were examined for the year before and after treatment. Results demonstrated a significant decrease in the use of individual and group psychotherapy. Direct costs associated with mental health care decreased by 39.4%. Primary care and emergency department services remained unchanged.

INTRODUCTION

The wars in Iraq and Afghanistan have led to an increased need for mental health services. This growing demand among Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) veterans has resulted in heightened awareness of the effects of mental illness on the lives of veterans and commitment by the Department of Veterans Affairs (VA) to provide the most effective, evidence-based treatments for mental health diagnoses for all veterans, across service eras. Of particular focus has been the mental health diagnosis of post-traumatic stress disorder (PTSD), which has been found to affect up to 25% of these newly returning veterans seeking VA health care. In response, the VA and Department of Defense (DoD) have recommended the treatments of prolonged exposure (PE) and cognitive processing therapy (CPT) for PTSD at the highest level. Following this recommendation, the VA established the policy that all veterans diagnosed with PTSD have access to either PE or CPT and implemented a nationwide dissemination initiative to ensure access to PE or CPT at every facility. Although a high degree of emphasis has been placed on the efficacy of CPT and PE to treat the symptoms of PTSD and comorbid depression, the impact of these treatments on subsequent medical and mental health service utilization has not yet been explored.

The individual and societal costs of PTSD are enormous. It is estimated that PTSD results in an estimated $3 billion of lost productivity per year, lowers the likelihood of veterans working for pay, and negatively impacts veterans' wages. Further, across the age span, a diagnosis of PTSD has been associated with significantly greater inpatient and outpatient mental health services. Previous research has found that Vietnam-era veterans diagnosed with PTSD utilize health care services at a greater rate than those without PTSD. Similar results have been found for returning OEF/OIF veterans, in that positive PTSD screens were significantly associated with the use of mental health services, with 56% of these veterans engaging in mental health within 6 months from returning from deployment. When level of depression was factored into the analyses, PTSD continued to independently predict increased mental health utilization rates in both Vietnam and OEF/OIF populations. Further, younger veterans with PTSD were found to utilize physical health visits at 124% higher rate than those without PTSD, and those rates of utilization continue to increase. Although diagnoses of PTSD and depression have been associated with greater service use, it is not clear if reducing these symptoms would result in a decreased use of services.

PE and CPT have demonstrated impressive results for the treatment of PTSD. PE is a treatment for PTSD that includes psychoeducation, imaginal retelling of the traumatic event, and in vivo exposure exercises. These experiences create new learning and habituation to the traumatic memory and avoid safe situations. In nonveteran populations, PE has been shown to be effective in decreasing anxiety, depression, and PTSD symptoms. In veteran samples, PE has shown promising results in a small sample (N = 10) of OIF/OEF, Vietnam, and Military Sexual Trauma survivors. This study demonstrated a clinically significant reduction in PTSD symptoms in 80% of patients and in depression symptoms in 40% of patients. In a randomized controlled trial among female active duty personnel and veterans, PE was shown to be more effective than present-centered therapy in the reduction of PTSD symptoms. Results indicated 41% of veterans in PE, versus 27.8% in present-centered therapy, lost their PTSD diagnosis at the termination of treatment.

CPT is a treatment for PTSD which involves writing of the traumatic event and challenging of unhelpful beliefs, or “stuck points,” that resulted from the trauma and are serving to create and promote symptoms. CPT has been found to be superior to wait-list conditions among childhood sexual abuse survivors and female rape victims in reducing symptoms of PTSD. In a primarily Vietnam veteran population, CPT was found to be effective

in reducing PTSD symptoms in 50% of patients, with 40% losing their PTSD diagnosis. In a comparison study between Vietnam and OEF/OIF veterans, both groups reported fewer PTSD symptoms, with 40% of Vietnam veterans and 59% of OIF/OEF veterans losing their PTSD diagnosis at post-treatment.

PE and CPT have been recommended by the VA and DoD as first-line treatments for PTSD. Further, because of recent dissemination efforts, both CPT and PE are offered as front-line treatments for PTSD nationwide. Although it is known that PE and CPT reduce symptoms of PTSD and comorbid depression, the impact of such treatments on health care utilization and corresponding costs are unknown. This type of information holds implications for administrators within the VA and DoD when making decisions regarding treatment programming. Therefore, the purpose of the present study was to evaluate the impact of PE and CPT on mental health and medical service utilization and cost of health care services provided by the VA. It was expected that veterans who successfully completed PE or CPT would utilize less mental and physical health care services in the year following treatment as compared to the year before treatment.

METHODS

Participants and Procedures

Participants were 70 outpatients at a Midwestern VA medical center being treated for significant levels of trauma-related symptoms. The average age was 48.1 years (SD = 14.3). Approximately 75% (53) of the sample was male and 86% (50 of 58) of those disclosing ethnic identity were Caucasian. Most patients (91.4%) had a chart diagnosis of PTSD; 66% had a comorbid diagnosis of depression, 21% had a comorbid substance use diagnosis, and 10% had been diagnosed with an Axis II personality disorder. Formal inclusion and exclusion criteria were not utilized; however, veterans with active psychosis, unmedicated bipolar disorder, imminent suicidal or homicidal ideation or self-harm, and severe uncontrolled substance dependence are typically not enrolled in PE or CPT. Reliable data regarding veterans who initiated but did not complete PE or CPT were not available.

Veterans who had successfully completed either PE or CPT were identified through existing administrative databases. Data were gathered from computerized medical records for a period of 1 year before the start of treatment and 1 year after the conclusion of treatment. Encounters during treatment were not included. Data included encounter location and treatment procedures. Encounters were coded by stop code, which indicate whether the encounter took place in primary care, emergency department, or mental health (includes all mental health stop codes). Mental health encounters were further subdivided into group or individual encounters. Cost data was pulled by the Decision Support Services (a division of VA's business operation support) for these patients for the same period of time as the encounter and procedure data.

Pre- and post-treatment comparisons were made on cost data for all primary stop codes in mental health, the emergency department, and primary care. For continuously distributed data (e.g., PTSD and depressive symptoms, cost data), matched-pairs *t*-tests were conducted to look at change before and after treatment. Within group, pre-to-post effect sizes were calculated using Cohen's *d*. Mental and physical health care utilization data were highly positively skewed (skew > 1.5) and Wilcoxon signed-rank tests were conducted to examine pre–post differences.

Treatment

Veterans were referred for PE or CPT as a part of their routine mental health clinical care. If a veteran was diagnosed with PTSD or significant trauma-related symptoms by their referring therapist, they were offered treatment in either PE or CPT. If they agreed, they were referred to a clinician trained in either model of therapy. Referral to PE versus CPT was determined by veteran's preference (e.g., interest and willingness to engage in group component of CPT) and availability of providers. All veterans had a structured clinical intake assessing for psychiatric disorders before initiating treatment, administered by their PE or CPT therapist. The PTSD Checklist Military Version and the Beck Depression Inventory-II were administered at baseline and final session by the veteran's PE or CPT therapist. Treatment was conducted by psychologists, social workers, and psychology or social work interns who had completed a comprehensive training workshop and participated in ongoing clinical consultation during the provision of treatment. Training and consultation for PE was provided by clinicians who were certified by the VA as national consultants for PE. Training and consultation for CPT was provided by clinicians who had completed all VA CPT certification requirements. Veterans receiving CPT (N = 39) completed a standard 12-week protocol of group and individual sessions, while those receiving PE (N = 31) completed an average of 13 individual sessions (SD = 4.3). Completion for PE was defined by completing a minimum of 7 sessions and the therapist's clinical judgment that the patient ended therapy because of reaching treatment goals.

RESULTS

Preliminary analyses revealed no significant difference in outcome between veterans receiving PE or CPT, therefore outcomes were combined. Veterans demonstrated significant decreases in PTSD symptom severity from pre- (M = 58.5, SD = 11.8) to post-treatment (M = 42.1, SD = 13.8), $t(61) = 8.5$, $p < 0.001$, Cohen's $d = 1.08$. Depression symptoms declined significantly from baseline (M = 28, SD = 10.3) to post-treatment (M = 15.7, SD = 9.8), $t(61) = 7.77$, $p < 0.001$, Cohen's $d = 0.99$. These declines were equivalent for both male and female patients.

We found a decrease in the use of mental health services from 23.4 (SD = 29.3) visits in the year before treatment to an average of 16.0 (SD = 19.8) visits in the year after treatment ($Z = 2.79$, $p = 0.005$). Because of the large number of encounters that accompany use of partial day hospital programs (PPH), we removed this type of encounters from the analysis as a small number of individuals (i.e., 4) could distort the number of encounters observed overall. We re-examined pre–post differences in utilization and significant pre–post differences remained with 20.3 encounters before treatment and 16.0 after treatment ($Z = 2.36$, $p = 0.018$). When further broken down by individual versus group visits, the decrease in overall visits was significant for group visits (from 3.7 to 3.3, $Z = 2.24$, $p = 0.025$) and also for individual visits (from 16.5 to 12.9, $Z = 2.28$, $p = 0.023$). We also found that the use of mental health urgent care (e.g., mental health walk-in assessment) decreased significantly from 0.4 visits before treatment to practically none (0.01) following treatment, $Z = 3.28$, $p = 0.001$.

We also examined the use of primary care and the emergency department pre- and post-therapy. We found that the decline in primary care was slight (3.2 to 2.9) and not significant, $Z = 1.23$, $p = 0.22$. Emergency department usage remained virtually the same (0.63 to 0.70 visits), $Z = 0.47$, $p = 0.64$.

We found that direct costs associated with mental health care were significantly reduced in the 1-year period following PE or CPT when compared to the same period before treatment [$t(69) = 3.84$, $p < 0.001$]. This reduction, from $3215.70 (SD = 2710.50) to $1860.00 (SD = 2105.20) per patient, yields an effect size of $d = 0.46$. Similar reductions in total costs, $5173.20 (SD = 4418.20) to $3133.10 (SD = 3566.30), were also found

[$t(69) = 3.57$, $p = 0.001$]. We did not find significant differences in direct costs before and after treatment in either primary care [$t(69) = 0.61$, $p = 0.54$] or emergency department associated costs [$t(69) = 0.13$, $p = 0.9$].

DISCUSSION

PE and CPT resulted in a reduction of PTSD and depression symptomatology consistent with outcome data from the ongoing dissemination initiative within the VA. The present study found that veterans who had successfully completed PE or CPT reduced their mental health service utilization by 32% the year following treatment when compared to the year before the initiation of PE or CPT. This statistically significant reduction in service consumption resulted in a 39.4% reduction in direct costs from an average of $5173.20 in the year before treatment to $3133.10 in the year following treatment per veteran. The estimated cost of providing PE is $2267.68 and for CPT is $2082.42. These findings are consistent with prominent service-utilization frameworks and lends support to the notion that illness severity characteristics play a large role in service consumption. These preliminary findings are the first to demonstrate that within veteran samples, the successful completion of PE and CPT for PTSD significantly reduces mental health service utilization and outweighs the investment cost of providing these services.

Although there was a reduction in the use of primary care noted in the present analyses, the finding was nonsignificant and emergency department usage remained unchanged. The lack of significance may be attributable to several factors. First, the present sample is small and, because of the clinic policies that direct who received PE and CPT, excluded high-risk patients who traditionally utilize medical services at high rates (e.g., exclusion of veterans at significant risk for self-harm, exclusion of veterans with primary substance dependence disorders). Further, although PTSD has been shown to predict increased medical care, the finding is not universal across all studies.

These preliminary findings hold significant implications for clinicians and administrators within VA settings. Authors have noted that VA clinicians encounter significant barriers to learning and implementing PE and CPT, such as caseload expectations, emphasis on unique patient contacts as one metric for caseload size, and administrative scheduling difficulties. These findings lend preliminary support that implementation of PE or CPT would serve to decrease these demands on clinicians, as patients receiving these therapies may no longer require as many mental health services. The VA's prioritization of PE and CPT for the treatment of PTSD may suggest an avenue for providers to begin to manage large caseloads, which are increasing because of ongoing military conflicts.

The strengths of the present study are the “real world” nature of the clinical sample, the use of computerized medical records, and a yearlong pre-/post-comparison addresses, all of which address methodological criticisms of past service utilization research. However, several limitations are worth noting. First, the sample size is relatively small and was collected at only one clinical site. Second, because of the clinical nature of the sample, many factors were not controlled (e.g., medication usage) and the identification of an adequate control condition was not possible. Finally, because of the standard exclusion of high-risk clinical cases, the present design may have excluded groups that normally may seek higher rates of mental health and medical services. Future research in this area would be enhanced through the use of multicenter datasets, the inclusion of an adequate control condition, and the inclusion of individual use predictors such as personality variables, role and type of support system, and the presence of comorbid conditions. Finally, assessing clinicians' views of practice patterns post-treatment would be useful in understanding what

role clinician expectations may play in facilitating discharge versus maintaining long-term treatment models. However, these data suggest that the delivery of time-intensive PTSD treatments, such as PE and CPT, may result in a long-term reduction in caseloads for VA clinicians.

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Influence of predispositions on post-traumatic stress disorder: does it vary by trauma severity?

Psychological Medicine
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Abstract

Background: Only a minority of trauma victims (<10%) develops post-traumatic stress disorder (PTSD), suggesting that victims vary in predispositions to the PTSD response to traumas. It is assumed that the influence of predispositions is inversely related to trauma severity: when trauma is extreme predispositions are assumed to play a secondary role. This assumption has not been tested. We estimate the influence of key predispositions on PTSD induced by an extreme trauma – associated with a high percentage of PTSD – (sexual assault), relative to events of lower magnitude (accidents, disaster, and unexpected death of someone close).

Method: The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) is representative of the adult population of the USA. A total of 34 653 respondents completed the second wave in which lifetime PTSD was assessed. We conducted three series of multinomial logistic regressions, comparing the influence of six predispositions on the PTSD effect of sexual assault with each comparison event. Three pre-existing disorders and three parental history variables were examined.

Results: Predispositions predicted elevated PTSD risk among victims of sexual assault as they did among victims of comparison events. We detected no evidence that the influence of predispositions on PTSD risk was significantly lower when the event was sexual assault, relative to accidents, disasters and unexpected death of someone close.

Conclusions: Important predispositions increase the risk of PTSD following sexual assault as much as they do following accidents, disaster, and unexpected death of someone close. Research on other predispositions and alternative classifications of event severity would be illuminating.

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Group Therapy Among OEF/OIF Veterans: Treatment Barriers and Preferences

Military Medicine

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ABSTRACT

Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) combat Veterans are at risk for developing post-traumatic stress disorder (PTSD). Many are seeking treatment from the Veterans Health Administration; yet, it is an ongoing challenge to engage some Veterans in sustained mental health services, especially group therapy for PTSD. This pilot study assessed OEF/OIF Veterans' prior use of mental health treatment and perceived barriers to and interest in group therapy for PTSD using a survey distributed in one outpatient OEF/OIF PTSD specialty clinic in the Midwest. The 110 OEF/OIF Veterans reported experience with a range of mental health treatment services and most frequently identified perceptions of the group process to be barriers to engaging in group therapy. Specifically, OEF/OIF Veterans endorsed concerns about taking part in a group, expressing emotions, being misunderstood, and disliking the group composition. A clear preference for individual over group therapy for PTSD treatment was reported with 57% reporting disinterest in group therapy. Data suggest that Veterans are apprehensive about taking part in group therapy for PTSD. Awareness of barriers and treatment preferences can inform clinical practice and aid in developing patient-centered Veterans Health Administration services.

INTRODUCTION

The Veterans Health Administration (VHA) is the single largest provider of mental health care for U.S. Veterans from Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF). With current estimates of post-traumatic stress disorder (PTSD) among Veterans ranging from 5% to 20%, there has been a corresponding increase in the demand for PTSD treatment. The Department of Defense and VHA recently updated the PTSD Clinical Practice Guidelines, which recommend that Veterans be offered evidence-based practice (EBPs) and have timely access to treatment. Group therapy as a treatment modality is of interest in the VHA system as it enables more efficient service delivery of some recommended EBPs for PTSD. Recent research has demonstrated that certain EBPs, such as Cognitive Processing Therapy, are effective when offered in a group format.

Despite the need for treatment, engaging military personnel or Veterans in sustained mental health services can be challenging. Research has explored a variety of perceived barriers to mental health care. Recently, Kim et al conducted a factor analysis and identified the following barriers to care among soldiers: social stigma, negative attitudes about treatment, and organizational barriers. However, there is a paucity of research on how to engage OEF/OIF Veterans in group therapy. Therefore, the aim of this pilot study was to assess OEF/OIF Veterans' use of previous mental health treatment and their perceived barriers to and interest in group therapy for PTSD. To the authors' knowledge, this is one of the first studies to examine barriers to group mental health treatment from the perspective of OEF/OIF Veterans. Although there are various forms of group therapy, this study did not seek to assess perceptions about any specific group type or intervention, but rather global perceptions of group therapy within this relatively new VHA patient population of OEF/OIF Veterans.

METHODS

Participants

A total of 110 OEF/OIF Veterans were recruited while waiting for appointments in a combat-PTSD outpatient specialty clinic within an urban VHA facility in the Midwest. Veterans were approached by a study representative with a flyer describing the study and were invited to participate on a voluntary basis. Eligible individuals for this study were Veterans deployed for combat operations since September 2001, an established clinic patient (one previous appointment in the past year) presenting with PTSD symptoms, aged 18 years or older, and able to complete an anonymous written survey. This study did not track the number of potential participants or those who declined to participate in an effort to maintain anonymity. No incentives were provided for participation. The study was approved by the Institutional Review Board at the local VHA facility.

Measures and Data Analysis

The survey assessed the following.

Demographics

Demographics included age, gender, race/ethnicity, employment, marital status, branch of service, number of deployments, and disability rating.

Mental Health Treatment Utilization

Mental health treatment utilization was assessed with 3 questions: lifetime mental health treatment adapted from Kim et al regarding the receipt of help for a stress, emotional, alcohol, or family problem from a treatment provider. To assess additional lifetime treatment options, another question asked if they had ever met with a counselor or psychiatrist, attended individual or group therapy, attended a self-help group, or been mandated to attend psychological treatment. Finally, participants were asked to rate their “overall experiences” in individual and group sessions as positive, neutral, negative, or not applicable.

Perceived Barriers to Group Therapy

Perceived barriers to group therapy were assessed with a total of 37 self-report items. Fifteen items were adapted from Hoge et al, three items from Mackenzie et al, and four items from Kim et al. Fifteen additional items were developed through an extensive review of the literature and in consultation with experienced PTSD clinicians. Participants were asked to, “Rate each of the following factors related to receiving mental health services in a GROUP setting by checking the appropriate box.” All items were rated on a 5-point Likert scale (1 = strongly disagree to 5 = strongly agree).

Treatment Preferences

Treatment preferences were assessed with 2 items. A dichotomous item (yes or no) measured interest in group therapy, “I would be interested in participating in GROUP therapy for PTSD in this clinic.” The second item required participants to rank preferences for PTSD treatment (1 = most desirable to 3 = least desirable) when presented with the options of “Individual therapy,” “Group therapy,” and “Medication only.”

Data were analyzed using SPSS Version 17. Descriptive statistics and measures of central tendency for the barriers were calculated and are presented.

RESULTS

The majority of OEF/OIF Veterans in this sample were Caucasian, non-Hispanic males under 40-years old who had served more than one deployment in the Army. Given this VHA specialty clinic and patient profile, the sample was overwhelmingly male (90%). Less than half of the sample reported currently attending school or working. The majority (75%) reported having a VHA service-connected disability for a physical or mental health condition. Most (91%) traveled more than 10 miles to their VHA appointments; 23% traveled more than 50 miles. The greatest percentage (36%) returned from their last deployment more than 5 years ago. None of the Veterans in the sample reported a deployment in the past 6 months.

The OEF/OIF Veterans in this study reported a range of past mental health treatment with 92% reported having met with a psychiatrist, 86% reported engaging in individual therapy, and 51% reported participation in group therapy. Seventy-nine percent and 32% of the sample reported favorable experiences in individual and group therapy, respectively.

Although the entire sample reported some experience with mental health treatment services, specific barriers to engaging in group therapy were identified for a complete list of barriers). The following items related to barriers were most frequently endorsed by this sample of OEF/OIF Veterans: “I am uncomfortable in crowds/groups” (75%) and “I am not comfortable showing emotions in front of others” (65%). The items least endorsed as barriers to group therapy were: “My family/friends would blame me for the problem if I attend group therapy” (3.6%) and “I would think less of a veteran if I knew he/she was receiving mental health counseling” (0.9%).

Fifty-seven percent of the sample reported that they were not interested in participating in group therapy. When asked to rank their preferences for PTSD treatment, 83% identified individual therapy as most desirable; less than 2% ranked individual therapy as least desirable. In contrast, 13% identified group therapy as most desirable, whereas 57% of the sample ranked group therapy as least desirable. About 15% endorsed medication only as most desirable; 44% ranked medication only as least desirable. Participants were not prohibited from ranking more than one treatment option as “1”; hence, the sum of the rankings is greater than 100%.

DISCUSSION

This study, which is among the first to examine barriers to group mental health treatment in the VHA, aimed to identify OEF/OIF Veterans' perceived barriers to and interest in group therapy for PTSD. Study results indicate perceived barriers among the OEF/OIF Veteran population that are novel to extant research. Previous research has explored possible perceived barriers to mental health care among soldiers and Veterans and

identified the influence of social stigma, negative attitudes about treatment, and organizational barriers. Current findings from this sample of Veterans highlight different concerns, and interestingly, the most frequently endorsed barriers were items derived from clinical observations and not currently addressed in the existing literature. These barriers tap into concerns about taking part in a group, expressing emotions, being misunderstood, and disliking the group composition. This suggests that Veterans are apprehensive about taking part in group therapy and may consequently dismiss it as a treatment option despite the potential benefits.

Of the top items endorsed, only one was an organizational barrier ("It is difficult to get time off work/school for group therapy"). Only 40% of Veterans endorsed this item; all other organizational barriers were endorsed by less than 25% of the sample. Perceived stigma as a barrier was also not supported; when barriers were ranked by frequency of endorsement, no stigma-related barriers were in the top 14 items. Similarly, results from this study do not suggest that negative perceptions about treatment are a significant barrier to group. In fact, many endorsed positive perceptions of past mental health treatment.

In their rankings of treatment options, OEF/OIF Veterans endorsed a clear preference for individual therapy over group therapy for PTSD treatment; over half (57%) of the sample was disinterested in participating in group therapy. Although there may be a natural tendency to be anxious about engaging in group therapy, a Veteran struggling with PTSD may be especially uncomfortable because of the disorder's hallmark avoidance and arousal symptoms. It is possible that addressing misperceptions might increase Veterans' willingness to participate in group.

Several limitations are noted. First, the population was a convenience sample from one VHA specialty clinic in the Midwest representing a predominantly male, treatment-seeking sample; therefore, generalizability to other populations is limited (i.e., female Veterans and Veterans not yet engaged in mental health care). The number of participants and the homogeneity of the sample also limit the generalizability of the data beyond the sample. Yet, emerging data such as these can directly inform clinical practice and aid in developing patient-centered services because they reflect the preferences of this very specific VHA treatment-seeking population.

A second limitation is that the survey presented to participants was developed for this study and has not been subject to rigorous psychometric testing. Although a reliable and validated measure would have been preferred, a review of the scientific literature did not yield an instrument that fully assessed mental health treatment utilization, perceived barriers to group therapy, and treatment preferences. As much as possible, items were drawn from previously used measures and adapted and augmented as existing items did not capture the clinical observations of the study authors when attempting to engage Veterans in group therapy.

Ongoing research is needed to better understand the barriers to mental health care, specifically treatment delivered in group settings. The findings from this pilot study can inform future measurement development regarding OEF/OIF Veterans' perceptions of mental health treatment and barriers to group therapy for PTSD. Future research might also assess the role of pregroup therapy clinical interventions that can assist Veterans in making fully informed treatment decisions.

Group therapy, as a treatment modality offered for PTSD, is clearly efficient for service delivery in VHA and offers unique clinical benefits for Veterans. Study results highlight perceived barriers about group therapy that have not been identified in previous research. Information regarding

treatment preferences is critically important in the design and implementation of mental health services for treatment-seeking OEF/OIF Veterans. Awareness of these barriers and treatment preferences is valuable as it can inform clinical practice and potentially increase Veterans' access to the best available treatments for PTSD.

BACK TO TOP

Substance Abuse

Unmet Need for Treatment of Substance Use Disorders and Serious Psychological Distress Among Veterans: A Nationwide Analysis Using the NSDUH

Military Medicine
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ABSTRACT

Many veterans returning from Afghanistan and Iraq experience serious mental health (MH) concerns including substance use disorders (SUD), post-traumatic stress disorder, traumatic brain injury, depression, or serious psychological distress (SPD). This article uses data from the 2004 to 2010 National Survey on Drug Use and Health to examine the prevalence of unmet MH needs among veterans aged 21 to 34 in the general population. The prevalence of untreated SUD among veterans (16%) was twice as high as untreated SPD (8%), a nonspecific diagnosis of serious MH concerns. Surprisingly, similar rates of untreated SUD and SPD were found among a nonveteran comparison sample matched on gender and age. These findings suggest that reducing unmet need for MH treatment for veterans in the general population may require improving outreach to all Americans and creating greater acceptance for MH treatment. The need for further analyses of reasons for not obtaining treatment is discussed.

INTRODUCTION

Veterans reintegrating into civilian life after serving in Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) have been facing mental health (MH) concerns, especially post-traumatic stress disorder (PTSD), traumatic brain injury (TBI), depression, and substance use disorders (SUD). Prior research has evaluated the prevalence of MH concerns and opportunities for treatment at various points in the military/veteran career including postdeployment, among those being treated at Veterans Affairs (VA) facilities, and in the general population. This article analyzes the prevalence and covariates of unmet need for MH treatment among young veterans in the general population using data collected by the National Survey on Drug Use and Health (NSDUH).

There are various reasons veterans may not be in treatment at the VA. They may be receiving treatment elsewhere. Alternatively, some research indicates that onset or attenuation of symptoms can be delayed, especially for PTSD. On a related matter, people often delay for years after onset before obtaining MH treatment. Thus, some veterans with unmet need at any time will eventually receive treatment. There are also various reasons veterans avoid MH treatment. Some may not be screened for MH problems or not encouraged to seek treatment for problems such as hazardous drinking behaviors. Many wish to treat their problems on their own. Many veterans and military personnel attach a stigma to MH treatment, especially SUDs, which they or their peers perceive as inconsistent with the mental toughness prized in the military. Other research identifies negative attitude toward MH care as a major factor. The prevalence of unmet MH treatment need in the general population is reduced to the extent that people receive successful treatment and their concerns are addressed.

More than half of the OEF/OIF veterans coming in contact with the VA for any reason had MH concerns. Among those seeking treatment, the covariates differ substantially across disorders. Studies indicate PTSD was higher among veterans who were male, African American, younger, and married or divorced. In contrast, depression was higher among those who were female, White non-Hispanic, older, divorced/separated/widowed, enlisted, in the Army, and Reserve/National Guard. SUDs were more common among veterans who were male, younger, not married, enlisted, and in the Army; Hispanic veterans were less likely to have a drug use disorder (DUD) but not an alcohol use disorder (AUD).

In 2007–2008, the RAND Corporation conducted a survey of 1,965 OEF/OIF veterans to estimate the prevalence of MH concerns among veterans in the general population, who were not necessarily in contact with the VA. PTSD was higher among veterans who were female, Hispanic, enlisted, and in the Army, which differs substantially from the covariates in the VA study described above. The covariates of major depressive episode (MDE) were similar to those for PTSD: female, Hispanic, and enlisted. TBI did not vary significantly with any veteran characteristics.

The Substance Abuse and Mental Health Services Administration (SAMHSA) has used the NSDUH to produce a series of articles examining MH concerns and unmet treatment need among veterans in the general population. They found Serious Psychological Distress (SPD)—a nonspecific diagnosis of serious MH concerns—was higher among veterans who were female, younger, and whose families earned less than $20,000 per year. MDE was higher among those who were female and younger. 60% of veterans with an MDE received past-year treatment. SUDs were more common among veterans who were younger and whose families earned less than $20,000 per year. In 2003, 85% of veterans dependent on alcohol or drugs had not received treatment, which was slightly better than the 91% in a comparable nonveteran population.

The SAMHSA reports are short and limited. Wagner et al provided a more extensive analysis of SUDs among veterans interviewed by the NSDUH 2000–2003. They found the prevalence of SUDs among veterans was 7.0%, which was not statistically different from the 6.8% among comparable nonveterans. Few veterans received SUD treatment in the past year (0.8%), but this percentage was higher than among comparable nonveterans (0.5%). This article replicates prior NSDUH analyses of veterans using recent data and presents findings regarding SUD, SPD, and unmet need for treatment as well as their covariates. The conclusion examines the implications of the findings with regard to the provision of outreach, screening, and treatment programs.

METHODS

Participants

The NSDUH is the primary source of statistical information on the use of illicit drugs and alcohol in the civilian, noninstitutionalized population of the United States. The survey employs a multilevel stratified hierarchical sampling procedure. Participants are interviewed face-to-face in their place of residence. Audio computer-assisted self-interviewing is used to assure confidentiality for sensitive questions. Participants receive $30 for completing the survey. This analysis used the NSDUH public-release data for 2004 through 2010 obtained from the Interuniversity Consortium for Political and Social Research. From 2004 to 2010, the response rate varied between 74% and 77%. The complete sample includes 118,625 participants aged 21 to 34 of whom 3,826 (3%) are veterans. All analyses presented used sample weights, stratification information, and complex samples procedures to obtain unbiased estimates and accurate statistical tests that control for design effects.

Unfortunately, the NSDUH does not distinguish OEF/OIF veterans from those who served elsewhere. The NSDUH asks a single question about veteran status, “Have you ever been in the United States armed forces?” It was assumed that many of the youngest veterans would have served more recently and served in Iraq and/or Afghanistan. Accordingly, the analysis was restricted to younger veterans aged 21 to 34 at the time of the interview. A comparable nonveterans group was constructed by standardizing the weights of the nonveteran subsample to match the age and gender distribution of the veteran subsample, a conventional demographic procedure used by SAMHSA in their analyses of veterans.

Measures

The primary dependent variables were SUD and SPD in the past year. The NSDUH defines SUD as abuse or dependence on alcohol or illicit drugs based on Diagnostic and Statistical Manual of Mental Disorders criteria. To measure SPD, the NSDUH uses the K6 screener, which was designed to identify serious impairment from any MH concern other than SUD with six short questions (e.g., “How often did you feel nervous?”) rated on a scale from none to all of the time.

Analyses

The article presents population estimates of SUD and SPD. Unmet need for SUD or SPD treatment was estimated as those participants with the condition who did not receive treatment in the past year. The analysis also examined self-reported need for treatment provided in response to the question, “During the past 12 months, was there any time when you needed MH treatment or counseling for yourself but didn't get it?” Separate estimates of unmet need for treatment were calculated for the veterans and the standardized nonveterans population as well as the unstandardized population of all NSDUH participants aged 21 to 34.

Logistic regression was used to estimate how the prevalence of past-year SPD and SUD varied across participant characteristics including veteran status, gender, race/ethnicity, age, education, employment, family income, marital status, urbanicity, and interview year. Unfortunately, the NSDUH public use datasets do not include a measure of region, which precluded its analysis. The NSDUH urbanicity measure is also quite limited indicating only whether a participant lives in a core-based statistical area (CBSA) or a more rural location. The NSDUH measure of race/ethnicity distinguishes White non-Hispanic, African American non-Hispanic, and Hispanic participants. The remaining less common categories were combined. Logistic regression was also used to estimate the likelihood that a person with SPD received MH treatment and similarly that a person

with SUD received alcohol or drug treatment. Each regression model included an interaction term for each variable with veteran status (e.g., veteran × gender) to identify whether the covariates for veterans differed from those of the general population. Because of the large sample size, many parameter estimates were statistically significant. Accordingly, the analysis placed greater emphasis on parameter estimates that were not only statistically significant but also substantial such as an odds ratio greater than 1.5.

RESULTS

The nonveteran demographic entries for gender, age, and race/ethnicity were not standardized. The subsequent measures of social integration were standardized to control for differences in gender and age between veterans and nonveterans. The total column is not standardized by gender and race. It thus gives much greater weight to females than the prior columns. Consequently, characteristics that are more common among females such as poverty were higher among the total population than among either the veteran or the standardized nonveteran subpopulations. Veterans were much more likely to be male, were slightly older (perhaps because younger persons are more likely to be still in the service), and were more likely to be White or African American as opposed to Hispanic or other.

Veterans were more likely to have completed high school (generally a requirement to enter the military) and more likely to have gone to college, though less likely to have graduated. Veterans and nonveterans had relatively similar employment profiles. Veterans were less likely to be living in poverty. Veterans were more likely to be married, an important protective factor; however, they were also more likely to be separated, divorced, or widowed, which is often associated with MH concerns as either a cause or a consequence. More than 90% of the sample lived in a CBSA, although veterans were slightly more likely to live in a more rural area outside of any CBSA.

Veterans were not more likely than nonveterans to use illegal drugs or be dependent on them. Most veterans (75%) reported having consumed alcohol in the past month, slightly more than nonveterans (68%). However, veterans were not more likely than nonveterans to binge drink (defined as 5 or more drinks in a single session), drink heavily (defined as binge drinking on 5 or more of the past 30 days), or have an AUD. Veterans in the general population were slightly more likely to have SPD than their nonveteran counterparts (14% vs. 12%) and even more likely than nonveterans to have had an MDE (10% vs. 7%). There was substantial overlap between SUD and SPD; 5% of veterans had both conditions representing 29% of those with SUD and 38% of those with SPD.

The variation with veteran status was not statistically significant in either model, although several of the interaction terms were, especially for SPD. Unlike in the previous tables, the first column for each model presents the factors for all NSDUH participants (nonveteran and veteran) and the second column presents the interaction terms identifying how veterans differ from nonveterans. The factor most associated with variation in both SPD and SUD based on the Wald statistic was gender, although with the opposite effects between the models. Men were twice as likely as women to have SUD. In contrast, women were 70% more likely to have SPD. The second most significant factor was marital status. Being married was strongly associated with lower SUD and SPD. This is consistent with the idea that marriage serves as a protective factor against MH concerns. However, there is a possibility of reverse causation—that MH concerns can contribute to the dissolution of a relationship. Consistent with this alternative explanation, being separated, widowed, or divorced was associated with higher rates of SPD (but not SUD). SUD and SPD

were higher among Whites, higher among the unemployed, and declined modestly with educational level. SUD (but not SPD) declined with age and was slightly higher within a CBSA than more rural location.

SPD (but not SUD) was higher among the poor and near poor (those earning above the poverty level but below twice this level). The interaction terms indicate that poor and near poor veterans were even more likely to have experienced SPD than comparable nonveterans. Having more than 1 covariate that differs from the reference population in a logistic regression results in a multiplicative compound effect on the odds. The rate of SPD was 20% higher than among those of higher income and the rate among poor veterans was 40% higher than among poor persons in general. Thus, poor veterans were 70% more likely (1.2 × 1.4 ≈ 1.7) to have SPD than the reference population of otherwise comparable wealthier nonveterans. Near poor veterans were nearly twice as likely (1.1 × 1.7 ≈ 1.9). Veterans aged 21 were more likely to have SPD, though rates were similar among those aged 22 to 34. Among veterans, SUD was lower in 2004–2008, only 60% to 70% as in 2010 and 40% higher in 2009. We do not have any meaningful explanation for this observation at this time.

The figure shows that whereas 18% of veterans met the criteria for SUD, only 2% received treatment and an estimated 16% of all veterans in the general population did not receive treatment. In strong contrast, relatively few (1%) veterans reported that they had an unmet need for SUD treatment. Surprisingly, the extent of SUD and the percentages of met and unmet treatment needs among nonveterans were very similar to those among veterans.

SPD was slightly less common than SUD in the general population and much more likely to have been treated. About half as many veterans (8%) and nonveterans had untreated SPD as SUD. The rate of treatment for SPD among veterans (43%) was much higher than among nonveterans (34%). Veterans (5%) were also more likely to self-report an unmet need for SPD treatment than nonveterans (3%).

There were many similarities between the models and several very noticeable differences. The strongest association with SPD treatment was gender. Women were nearly twice as likely to receive treatment for SPD as men but comparably likely to receive treatment for SUD. Whites were about twice as likely to receive treatment for both SUD and SPD as African Americans and Hispanics. This difference was even more pronounced among minority veterans, with the one exception of Hispanic veterans who were almost as likely to receive treatment for SPD (but not SUD) as their nonveteran counterparts.

Treatment for both SUD and SPD increased with age. Persons who were employed were less likely to have received treatment for both SUD and SPD. This relationship however could be quite complex. Those employed full time may have had less opportunity to seek treatment or alternatively been concerned that the stigma of treatment could affect how they are perceived at work. Additionally, persons with serious MH concerns may have been compelled to leave their jobs, at least temporarily, as they attended to their treatment.

More educated persons were less likely to have received treatment for SUD but more likely for SPD. However, the parameter estimates (as near multiplicative inverses) indicate that the decrease in SUD treatment with education does not pertain to veterans. Notably, poor veterans were only 30% as likely to have received treatment for SPD but not SUD. Married persons were less likely to have received treatment for SUD; those who were separated, widowed, or divorced were more likely. Interview year was not associated with variation in the receipt of treatment.

DISCUSSION

The NSDUH data indicate that a substantial portion of young veterans in the general population have SUD (18%) or SPD (14%). Most of the SUDs involved use of alcohol and not illegal drugs or unauthorized use of prescription drugs. These rates underestimate the total number of veterans who are struggling with MH concerns because they do not include veterans living in institutions including VA hospitals, substance abuse treatment programs, and homeless shelters. Surprisingly, the rate of SUD among comparable nonveterans in the general population was about the same and the rate of SPD only a few percentage points lower than among veterans. The covariates among veterans were also similar to those among nonveterans with only a few exceptions. Most notably, veterans living in low-income families (up to 200% of the poverty level) were more likely to have SPD but not SUD. The rates of SUD and SPD among veterans in the general population were no higher than among comparable nonveterans. This finding is consistent with the possibility that the Department of Defense and VA MH screening and referral programs may be quite effective overall. An alternative interpretation is that the rates of MH concerns in the general population is substantial and needs to be addressed.

This analysis suggests treatment programs are reaching very few persons with SUDs in the general population. Only 10% of veterans who screened positive for SUD had received treatment in the past year. As a result, an estimated 16% of veterans in the general population were dealing with an untreated SUD. Again, the rate was similar for comparable nonveterans. Of note, African American and Hispanic veterans who screened positive for SUD or SPD were much less likely to have received treatment in the past year. Accordingly, research needs to focus on the specific reasons African American and Hispanic veterans are not seeking treatment.

Interestingly, only 1% of all veterans reported an unmet need for alcohol or drug treatment compared to the 16% of unmet need for treatment estimated. There are several possible explanations for this disparity. One possibility is instrumentation; the NSDUH screener might identify many less serious SUD cases. Another and more likely possibility is denial—a reluctance to admit a need for treatment.

Treatment rates for SPD were higher than for SUD and higher for veterans than nonveterans. Less than half of veterans (43%) who met criteria for SPD reported receiving treatment in the past year. However, the rate for comparable nonveterans was even lower (34%). The self-report rate of unmet treatment need among veterans was fairly close to the screener-based estimate. The gap was wider for nonveterans. Overall, these findings indicate that outreach programs aimed at veterans in the general community are fairly effective. A substantial proportion of veterans with MH concerns other than SUD are receiving treatment. This could be the result of programs available to returning veterans and existing outreach programs. Other veterans are aware that they need MH treatment but are not obtaining it. Further research needs to examine the reasons why veterans who are aware of their MH problems are not getting treatment. Veterans who screened positive for SPD who were either African American, Hispanic, or living in an impoverished family (below the poverty line) were significantly less likely to have received treatment. Further research into their reasons for not getting treatment is needed to identify likely historical, cultural, and financial barriers to treatment for these subpopulations.

The findings presented established that veterans in the general population have similar levels of SUD and SPD as comparable nonveterans, which is not necessarily good since most MH concerns in the general population go untreated in any year. More importantly, veterans are more likely to

be aware of their need for SPD treatment and more likely to receive it. These findings suggest an alternative approach to serving MH concerns among veterans. Perhaps, there are barriers and cultural norms that discourage both veterans and nonveterans from seeking treatment, especially for SUDs which mostly involves the use of alcohol. Perhaps, the larger need is to increase MH outreach and services to the general population at large, including veterans and nonveterans alike. In this manner, the goal would be to increase treatment seeking as part of the broader American culture. This could be coupled with financial assistance and greatly reduce the stigma or perceptions of vulnerability associated with getting treatment. This effort might prove more effective than any veteran-specific program and bring the remaining veteran population in need of treatment into contact with providers and social service organizations. It would have the further benefit of getting nonveterans with treatment needs into treatment.

Limitations and Future Directions

A comparison of veterans' and nonveterans' reasons for not entering treatment would provide further insight into whether this type of strategy might prove successful. Indeed, it would be useful to understand why those who do not think they have a problem would not enter treatment too. Hoge et al[7] obtained this information from a sample of military personnel by asking participants to, "Rate each of the possible concerns that might affect your decision to receive MH counseling or services if you ever had a problem." The responses for those who screened positive for MH concerns were different from those who did not. In contrast, the NSDUH only asks about reasons for not going to treatment of those who reported having had a need for treatment in the past year but did not get it. It would be highly useful if the NSDUH revised their questions and skip patterns to match those of Hoge et al to identify the larger attitude about MH treatment prevailing in society, not just among those in need of treatment.

All in all, the NSDUH proved to be an extremely valuable resource for this study. Indeed, the results of this analysis for unmet treatment need have identified important directions for further research into reasons for not getting treatment, especially for SPD. The public-release NSDUH data include the information regarding reasons and barriers to treatment that could support this additional effort. A major limitation of the NSDUH is the lack of information about military service. For the purposes of our analysis and based on the larger veterans' MH literature, we would ideally like to see additional military service questions added to the NSDUH including the following: When did you return from your last tour of duty? Where were you deployed? Did you experience combat? Were you enlisted or an officer? In which branch did you serve? And, in which component did you serve (Active Duty, Reserves, or National Guard)? This additional information would further the usefulness of the NSDUH for analyzing health concerns and tracking trends among veterans in the general population, who are not necessarily in contact with the VA.

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Understanding Opioids: Part 1

Medscape Neurology
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Editor's Note:

In the late 1990s, a perfect storm hit the medical community. The pharmaceutical industry started promoting new opioid formulations for chronic pain conditions, which, when used properly, could be very effective. At the same time, and based on previous success in the surgical, cancer, and palliative care settings, a school of thought formed among pain specialists that opioid analgesics could be used effectively to treat chronic pain -- what many clinicians recall as a genuine attempt at more compassionate pain management. But an unforeseen consequence of increased opioid prescribing and availability was the epidemic of opioid abuse and addiction that ensued. According to the Centers for Disease Control and Prevention, "The unprecedented rise in overdose deaths in the US parallels a 300% increase since 1999 in the sale of these strong painkillers. These drugs were involved in 14,800 overdose deaths in 2008, more than cocaine and heroin combined."

In May 2012, at the 31st Annual Scientific Meeting of the American Pain Society, Dr. Beth D. Darnall, PhD, now Clinical Associate Professor at Stanford University, moderated a panel discussion on translating opioid research into clinical practice. As Part 1 in Medscape's 2-part "Understanding Opioids" series, Medscape recently invited Dr. Darnall to moderate a virtual email discussion among the same panel of experts, further addressing the nuances of opioid prescribing. On the panel are Jane C. Ballantyne, MD, Professor of Education and Research in the Department of Anesthesiology and Pain Medicine at University of Washington Medicine; Michael E. Schatman, PhD, CPE, Executive Director of the Foundation for Ethics in Pain Care; and Charles E. Argoff, MD, Professor of Neurology at Albany Medical College and Director of the Comprehensive Pain Program at Albany Medical Center. What follows is their discussion.

Opioid Prescribing: Introduction

Dr. Darnall: Long-term opioid use has increased substantially in the United States over the past decade. Of note, opioid prescribing practices in Europe are generally quite conservative compared with practices in the United States. What are the factors that explain this difference, given that there is no greater prevalence of chronic pain in Europe compared with the United States?

Dr. Schatman: First and foremost, there is a greater emphasis on adherence to evidence-based medicine in Europe and other Western nations than in the United States, due in great part to American physicians' insistence upon the right to practice autonomously. It has been noted that despite the lack of a viable evidence basis for long-term use for noncancer pain, the increased prescription of opioids has been fueled by the publication of extremely weak evidence of chronic opioid therapy's efficacy and safety. Manchikanti and colleagues interpreted the results of a Danish study that supported the lack of efficacy of chronic opioid therapy as providing "prima facie evidence that when opioids are prescribed liberally, even if a small number of patients benefit, the overall population does not.". In the United States, access to opioids has become considered a "human right," although few would argue that chronic opioid therapy provides a "societal good." In European medicine, on the other hand, there is more emphasis on societal good vs individual choice than in the United States.

Dr. Ballantyne: I do agree with Dr. Schatman's first point, that the US opioid phenomenon is in part due to US physicians' insistence on practicing autonomously. In fact, as someone who came to the United States from Europe, I have thought long and hard about these differences. There are, of course, many cultural differences that underpin prescribing differences. What I have observed is that US prescribers used to worry much more

about the addictiveness of opioids than European prescribers, to the extent that they tended to undertreat pain in the acute setting and at the end of life. I really noticed this undertreatment of pain when I came to the United States from the United Kingdom in 1986. But a powerful factor in changing the prescribing of US physicians was the marketing of "designer"' opioids aimed at the much larger market of chronic pain. Part of the message was that when treating pain, addiction is rare. Gradually, US physicians were persuaded that opioids were not as addictive as they had thought, that patients have a right to receive this treatment, and that to deny this treatment is unethical. I would like to add 2 other factors to Dr. Schatman's comments that have been important: patient autonomy, which is much greater in the United States where there is a free market in healthcare; and aggressive marketing by the pharmaceutical industry, the United States being one of the few countries in the world in which the pharmaceutical industry can market directly to patients.

Dr. Argoff: It has been well documented that long-term opioid use has increased substantially in the United States over the past decade, but why? Both Drs. Schatman and Ballantyne thoughtfully outline several factors that may underlie this practice; however, I must strongly disagree with their assertion that physicians (and potentially other prescribers) prescribe autonomously, and thus I feel that they are missing a key truth about how medicine is currently practiced in the United States. In the state of Washington, where both Drs. Schatman and Ballantyne work, prescribers may be free to prescribe those treatments they feel would be the best treatment approaches for the management of chronic pain for a given patient, but can they be practically instituted if they are not "covered" by the payer? Of course not, in many instances.

In the state of Washington, the state in which multidisciplinary pain management was developed, are all of the multidisciplinary approaches that we know to be available for the management of various conditions associated with chronic pain available to each patient? I think not. The extent to which treatments are actually available for an individual patient from a "what will be paid for?" viewpoint is significantly influential, to the potential severe detriment of the patient. This extends specifically to pharmacotherapy and even more specifically to one subtype of pharmacotherapy, opioid therapy. How can we have a meaningful discussion about opioid therapy in the United States without an honest recognition of the healthcare system factors that underlie it?

If a payer's opioid prescribing policy mandates that methadone, with its relatively short analgesic half-life, be used first line as a "long-acting" opioid regardless of whether or not the prescriber has adequate knowledge regarding the complexities of this drug -- and we now know the true staggering numbers of just how many opioid overdose-related deaths have been related to methadone -- does anyone not see how US healthcare system issues have to be more effectively managed now? To the best of my knowledge, methadone is not actively marketed in a widespread manner in the United States by any pharmaceutical company. Although it's interesting to compare opioid prescribing practices in Europe vs the United States, we need to get to the root causes of why opioids are prescribed in the manner they have been here and address these assertively so that meaningful changes can occur. If chronic pain is truly managed "better" in Europe (multiple distinct countries and healthcare systems), then let us learn from the European experience. But this is not merely a matter of how opioids are prescribed or marketed in the United States compared with Europe.

Dr. Schatman: I agree that the payer issue is a critical one, which I addressed in my article last year in Pain Medicine. One of the factors that makes pain management superior in much of Europe is that the government-run healthcare systems cover interdisciplinary approaches; as the number of programs per capita has decreased dramatically in the United States, we are seeing a rapid increase in the availability of such

programs in countries like the United Kingdom and Canada. (See my chapter in the most recent edition of Bonica's Management of Pain). I agree that the lack of availability of access to interdisciplinary programs in the United States has contributed to the overprescription of opioids. Washington State is a particularly problematic place in which to have chronic pain, between the insurance industry's refusal to cover interdisciplinary approaches in conjunction with the WA Opioid Law's approach of "narcoterrorism."

Risks to Consider

Dr. Darnall: The popular press is quite focused on the opioid epidemic from the abuse and diversion perspective. In terms of caring for the patient with chronic pain, there are many other risks that are relevant to all patients who take opioids, yet these garner little attention. In your opinion, what are the most important risks for prescribers to consider?

Dr. Ballantyne: Mostly the risks of opioids to patients receiving opioid pain treatment arise when high doses are used (>100 mg/day morphine or morphine equivalence). This is because: (a) a number of toxicities arise during high dose therapy; and (b) individuals who dose-escalate tend to have less control over use than those who do not. Dying of respiratory depression during sleep must surely be the most serious adverse outcome of opioid therapy, and a number of studies now demonstrate that such deaths are strongly associated with high dose and erratic usage, especially in patients with a tendency to develop control issues, such as those with comorbid depression, anxiety, posttraumatic stress disorder, and substance use disorder. Obesity and sleep apnea further increase risk for death from nocturnal respiratory depression. Other serious risks of continuous high-dose opioid therapy include a tendency to falls and fractures and cognitive dysfunction, both of which occur particularly in the elderly. For younger patients, the endocrine dysfunction that is known to be associated with continuous opioid therapy represents a serious adverse effect with consequent infertility and lack of libido and drive, which likely compromise function and quality of life for younger individuals. High-dose usage could also indicate developing addiction -- a much feared and devastating adverse outcome of chronic opioid therapy, the risk for which has been difficult to quantify, but which tends to arise as outlined above in patients who have difficulty controlling usage.

Dr. Schatman: I believe that Dr. Ballantyne has addressed most of the salient issues of risk associated with chronic opioid therapy. I would like to go into greater detail, however, regarding the risk for opioid-induced endocrinopathy and other related problems. Recently, investigators have noted iatrogeneses that are more deleterious to certain groups. For example, emergent research has highlighted the threats to women of amenorrhea, infertility, and reduced sex hormone levels in postmenopausal women (potentially resulting in increased pain intensity, impaired stress, and immune responses). Among pregnant woman, increased infant risks including conoventricular, atrioventricular, and atrial septal defects; hypoplastic left heart syndrome; tetralogy of Fallot; pulmonary valve stenosis; spina bifida; and gastroschisis have been empirically identified.

Males on chronic opioid therapy certainly run their own unique risks, including erectile dysfunction, decreased libido, infertility, fatigue, decreased muscle strength, and mood disorders. Older adults need to be aware of their own unique threats associated with chronic opioid use, including increased pneumonia risk due to immunosuppressive issues, elevated rates of composite fractures (eg, wrists, hips) when compared with nonsteroidal anti-inflammatory drugs, laxative use (for the treatment of constipation) doubling the risk for falls among older patients, and the finding that 5% of all adults over the age of 65 years on chronic opioids were hospitalized for adverse events. Even cancer patients may have

specific risks associated with chronic opioid therapy, with 3 recent studies suggesting that opioid therapy may actually facilitate tumor progression. Dr. Ballantyne was certainly astute in her summary of the wide range of risks associated with chronic opioid therapy. However, perhaps the greatest risk with this type of treatment is associated with our failure to inform potential patients of the iatrogeneses specific to their demographic and disease groups, as such failure deprives them of their right to true autonomy.

Dr. Argoff: Thank you to Drs. Ballantyne and Schatman for their excellent and valid points. We cannot ever underestimate the risks of any treatment, invasive or noninvasive, opioid or nonopioid, that we prescribe for our patients. I think that it is fair to state that healthcare providers are trained to consider the risks of individual treatments prior to offering a treatment to an individual and that in general, if multiple equally effective treatments are available for a given medical condition, those with the most favorable risk profile should be considered ahead of a more risky approach. Here is where it gets more complicated: (1) There are virtually no long-term data of any true value from a practical clinical decision-making viewpoint for most chronic pain treatments; (2) we currently have no infrastructure or database to routinely collect such data; (3) there is a "loophole" in the pharmaceutical development process in the United States whereby an analgesic may be approved only having been successfully compared to a placebo unlike in other non-US systems where instead of placebo, the proposed treatment would need to be compared favorably to an established medication -- this "loophole" allows for new analgesics to become available and marketed without any true sense of their practical clinical value; and (4) we have virtually no meaningful data regarding how to optimize the use of available pain management strategies, of any type, in a "real-world" environment.

This last point may be particularly important for the majority of healthcare practitioners and prescribers because such data could be used to assist in clinical decision-making while its absence hinders this process. The extrapolation of data obtained from an exquisitely completed clinical trial for US Food and Drug Administration (FDA) registration purposes to "real-world" clinical practice is fraught with too many issues, most notably, perhaps, that in comparing vastly different populations, the extrapolation itself is not valid! So, if we agree that we must be as safe as possible when prescribing opioid analgesics and we agree that for a subset of patients for whom these are prescribed, safe and clinically meaningful outcomes will be reached on a long-term basis (3 months or more), what else can we do now? I am a member of the Patient Safety Workgroup created by the FDA. This workgroup is focused on means to improve the safe and effective prescribing of opioids. So few data have been published regarding "real-world" experiences with long-term opioid prescribing; however, fortunately there are some that can guide us. Saper and colleagues published their long-term observations of the use of daily scheduled opioids for intractable head pain in 2004. They included in their analysis only those individuals who remained on opioids for at least 3 years. They concluded: "For a select group of intractable headache patients, daily scheduled opioids can offer significant benefit. However, 74% of those treated either failed to show significant improvement or were discontinued from the program for clinical reasons." In a separate effort, the Opioid Utilization Study (OPUS) in chronic noncancer pain has just been completed, and the results are being analyzed. OPUS was designed as a prospective observational registry conducted in the United States set up to describe "real-world" practices as well as to assess clinical, quality-of-life, and economic outcomes in patients with chronic noncancer-related pain receiving opioid treatment for over 1 year. It is hoped that prescriber knowledge of these and other studies that may be performed in the future, in combination with the studies already cited by Drs. Ballantyne and Schatman, will result in more benefit and less harm for patients prescribed opioids on a long-term basis.

Dr. Darnall: Thank you, Dr. Argoff. Saper and colleagues reported that 26% of those on opioids benefited while 74% did not. It should be noted this was a headache sample, and opioids are generally discouraged for this condition. Regardless, based on our discussion so far it seems like everyone is in agreement: (1) Opioids are overprescribed in the United States; (2) opioids may help a small subset of patients; (3) opioids have major risks; (4) formidable barriers to nonopioid pain care exist in the United States; and (5) there is much we can learn from the European model of pain care. Part of the issue is providing patient and physician education about the risks and limitations of opioids, but the other side of the equation is political and involves access to pain care and reimbursement. To wrap up our discussion, my last question is: What do you feel is the most important to address right now in order to best affect patient care?

Dr. Schatman: In an article on which I'm currently working that will appear in the International Association for the Study of Pain publication, Pain: Clinical Updates, I examine international perspectives on interdisciplinary pain management programs. Myriad studies, as well as multiple systematic reviews, have supported the clinical efficacy as well as the cost-effectiveness of interdisciplinary pain treatment. However, since 1999, the number of such programs in the United States has decreased from over 1000 to under 150. In Europe and developed nations in Asia, however, the past decade has witnessed an increase in the number of interdisciplinary pain management programs, resulting in increased access for pain sufferers in those nations. It is not a coincidence that the decrease in the availability of interdisciplinary pain management in the United States has paralleled our dramatic increase in opioid prescription and the tragedies that have accompanied this mode of pain practice.

While it is easy to blame physicians for being irresponsible in their prescription of opioid analgesics, the demise of interdisciplinary treatment begs the question of what else the physician can offer the patient with chronic pain. The United States' consumption of exponentially more opioid analgesics than are consumed in the rest of the developed world likely relates, to a certain extent, to the fact that other developed nations' governments have set policies encouraging the development and funding of progressively more interdisciplinary treatment facilities.

Compared with other nations in my analysis, the United States is unique in its primarily privatized payer system for medical services. Commercial insurance carriers are fully aware of the cost-effectiveness of interdisciplinary care -- particularly in the long run. These carriers are undoubtedly aware of the iatrogenic complications associated with chronic opioid therapy and the "hidden" cost of treating patients with opioids on a long-term basis. However, as the insurance industry also recognizes that enrollees change their insurance coverage with surprising frequency (often due to employer decisions to change group coverage as a form of cost containment), carriers believe that it makes good sense actuarially to ignore the evidence basis as well as the well-being of their enrollees. By refusing to pay for interdisciplinary pain management programs while covering chronic opioid therapy, the American insurance industry is, at a minimum, passively encouraging the proliferation of non-evidence-based and potentially deleterious and dangerous chronic opioid therapy. It is not surprising that the only payer/provider of healthcare in the United States that is actually making an effort to increase the availability of interdisciplinary pain care is the military -- through the Department of Defense (DoD) and Veterans Affairs (VA). The DoD and the VA are rapidly becoming leaders in the United States with regard to efforts to develop and implement chronic pain management strategies other than use of prescription opioids. Certainly, when considering pain care, the government is the only entity that seems to recognize the moral imperative of reducing suffering on a large scale. This reality clearly provides support for the development of a single-payer healthcare system in the United States.

Dr. Ballantyne: Dr Schatman addresses the issue of lack of alternatives to opioids driving overprescribing of opioids. Any attempt to cut back on opioid prescribing tends to be countered with: If we don't give opioids, what else can we give? Dr. Schatman makes the comparison with other developed nations where opioid prescribing has not increased exponentially, unlike in the United States, and where interdisciplinary pain programs have actually increased in number whereas in the United States they have decreased almost to the point of extinction. Would opioid prescribing be reduced, then, if we had more interdisciplinary pain programs in the United States? The reasons for increases in opioid prescribing in the United States are many and complex, but one likely factor in an era when there is an expectation that medicine can fix pain is that the prescribers may not know what else to do, and even if they do, they may not have the time or the resources to avoid the prescription pad reflex. The reason interdisciplinary programs work best is that they allow patients and their providers to explore pain's deepest roots, which are not addressed by drugs, injections, or operations. What we hope comes out of the process is empowerment, self-efficacy, and a healthier lifestyle. Interdisciplinary pain management may be expensive, but only when taking the short view. The long view suggests that self-management, or the road to it, is both effective and cost-effective.

Dr. Argoff: The single most important issue in my view is the lack of open access for all patients who experience chronic pain to the most effective evidence-based pain management strategies. There are likely multiple reasons for this lack of open access. These include but are not restricted to: a frank lack of sufficient training for all healthcare providers in pain management, a frankly narrow use of the term "interdisciplinary" or "multidisciplinary" when describing certain approaches to treatment, a dysfunctional healthcare system that includes allowing payers to literally promote and even mandate off-label use of pharmacologic therapies ahead of FDA-approved approaches for specific chronic pain conditions in addition to limiting coverage for a variety of nonpharmacologic proven pain management treatments such as cognitive behavioral approaches, and a frankly immoral pain management system that results in patients being told all too often by a pain practitioner that the only available treatments involve invasive strategies. Patients hear all too often, "We only do injections or procedures here. No medications or other treatment will be offered." The bottom line? Even given the current emphasis on "evidence-based medicine," there are no consistent clinical trial data, head-to-head or otherwise, nor any published guidelines that are available to predict with sufficient certainty what will be the "right" treatment for an individual patient -- the person who is in your office now -- with chronic pain; thus, access to all proven therapies is imperative.

With respect to education, a recently published report describing pain education in medical schools in North America concluded that there are notable gaps between recommended pain curricula and documented educational content and that "pain education was limited and fragmentary." In a separate report, Yanni and colleagues in their assessment of chronic noncancer pain education in graduate medical education concluded that pain management education should begin in medical school and continue through graduate medical education, regardless of specialty! They noted that early and sustained training interventions in residency and fellowship are needed to better foster patient-centered pain care. Therefore, access to better undergraduate as well as postgraduate pain management training must occur in a widespread manner to allow for better treatment of our patients with chronic pain.

The term interdisciplinary is defined in the Merriam-Webster dictionary as: "involving two or more academic, scientific, or artistic disciplines." The term multidisciplinary is defined in the Oxford Dictionary as "combining or involving several academic disciplines or professional specializations in an approach to a topic or problem." The multiple published studies of interdisciplinary and multidisciplinary pain management care are disconnected from reality because they manage to leave out any mention of commonly used medical or invasive pain management strategies as

part of such care, instead concentrating nearly solely on the role of rehabilitative and cognitive behavioral approaches. Yes, these are 2 disciplines and thus by definition represent interdisciplinary care, but are there not numerous patients with chronic pain who have benefitted from a coordinated patient-centered approach to their care that integrated medical, invasive, cognitive behavioral, and rehabilitative strategies? Open access to all strategies in a truly widely interdisciplinary -- not bare minimum -- manner would likely result in reduced overreliance by specific practitioners on one type of treatment over another. We must be thoughtful about providing the most appropriate individualized care for each person with chronic pain. This approach may result, for one person, in optimal treatment being an invasive procedure; for another, optimal treatment might be chronic medical therapies (eg, opioid and nonopioid); and for a third, optimal treatment might be an extensive interdisciplinary approach. What is most important is that access for these be widely available so that we can provide broad evidence-based treatment options seamlessly for our patients.

Dr. Schatman has highlighted important issues regarding the manner in which third-party reimbursement policies may contribute to many of the pain management assessment and treatment challenges currently facing healthcare providers as well as their patients. The heterogeneity of our patients with chronic pain is mirrored by the heterogeneous results of nearly all chronic pain clinical trials. This heterogeneity must be respected for the sake of our patients' safety and comfort. Our health system does not currently provide full and practical access for our patients for all proven pain management strategies -- "fixing" this is what we must do right now.

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Examining the Association Between Binge Drinking and Propensity to Join the Military

Military Medicine
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ABSTRACT

It is unclear to what degree previous and/or current alcohol consumption predicts enlistment into the military. The current investigation explored the extent to which binge drinking was related to propensity to join the military among a national sample of high school seniors (n = 14,577) responding to the 2008 Monitoring the Future survey. Independent sample t-tests and logistic regression analyses were employed to explore the research question. Results indicated that twelfth grade students who intended to join the military after graduating from high school binge drank a significantly greater number of days ($p < 0.001$, Cohen's $d = -0.22$) than those not intending to enlist. Even after controlling for various sociodemographic and lifetime drinking characteristics, binge drinkers had a higher propensity to join the military (odds ratio = 1.079, Wald = 5.53, $df = 1$, $p < 0.05$) than those who did not binge. Moreover, as binge drinking increased, so did one's propensity to join the military. Our findings lend

credence to the notion that high school binge drinkers may be self-selecting into military service. These findings underscore the importance of adequately assessing the frequency of high-risk alcohol consumption and their associated correlates among potential military recruits before accession.

INTRODUCTION

Alcohol use and misuse have been present in the U.S. military's culture, rituals, and practices throughout its long and storied history. Although the military's zero-tolerance policy toward drug use has effectively lowered illicit drug use over the past 30 years, excessive alcohol use in the military continues to be a problem. The use of alcohol to “cope with stress, boredom, loneliness” has been pervasive within military culture as a result of norms associated with heavy drinking and easy access to beer and liquor. In the last decade, binge drinking (i.e., consuming five or more drinks on the same occasion at least once a week in the past 30 days) has increased significantly among military personnel. In fact, compared to a number of other factors derived from the Health Risk Appraisal (e.g., driven a motorcycle, driven after drinking, work stress, and life satisfaction), consuming five or more drinks contributed to the most excess deaths (i.e., difference between observed and expected deaths) among males serving in the U.S. Army who died from unintentional injuries while on active duty. The recently released Army 2020: Generating Health & Discipline in the Force Ahead of the Strategic Reset (also known as the Gold Book) documents an extremely high prevalence of high-risk behaviors (e.g., criminal activities, suicide attempts) among active soldiers, one of the more salient being drug and alcohol offenses.

Similar to the alcohol-related consequences documented in the civilian realm, excessive drinking among military personnel can (1) increase the likelihood of injuries and health problems, (2) contribute to decreased productivity and lack of deployment readiness, and (3) deteriorate personal and social relationships potentially leading to domestic violence. Approximately, 23% of all military-affiliated heavy drinkers suffer one or more serious life consequences (e.g., time away from work, arrest for driving under the influence, engaging in physical altercations, suffering from work-related accident, low job performance rating) as a result of their alcohol use.

Although excessive alcohol use is clearly prevalent among military personnel, it is unclear if the military experience and/or environment is causing personnel to drink in greater quantities or if these behaviors are already established before military enlistment and/or service. Among the few studies examining drinking behaviors of personnel before enlistment, both Naval and Air Force recruits had consumed alcohol within the year before enlistment (between 75% and 78%) despite the vast majority being under the minimum legal drinking age. Moreover, many engaged in binge drinking and experienced both first- and second-hand alcohol-related consequences.

Self-Selecting into High-Risk Drinking Environments

Recent research suggests persons self-select into risky drinking environments that support their personal drinking behaviors. Self-selection refers to the influence of individual characteristics in guiding an individual toward certain experiences, organizations, or environments, whereas socialization refers to the influence of experiences, norms, organizations, or environments on individual behavior. Thus, the question remains whether the military environment truly fosters a culture supportive of heavy drinking through socialization of enlistees or whether heavy drinkers

themselves self-select into the military environment and continue previous alcohol consumption patterns in their new military environment. Furthermore, it is unclear to what degree previous and/or current alcohol consumption behaviors influence desire to enlist into the military.

Personality studies have found that individuals actively choose environments similar to their own disposition even if that means selecting into a high-risk environment. With regard to high-risk drinking, research has shown that "selection effects are substantially and consistently stronger than the social influence effects (p 196)." Young adults who engage in high-risk drinking seek out participation in groups who drink more heavily, and occupations and environments where binge drinking is customary. For instance, research indicates that college students who join Greek organizations known for the customary practice of high-risk drinking exhibit preinduction characteristics of heavy substance use and "partying" well before joining. At the same time, research has also found evidence of socialization effects on heavy drinking among emerging adults. A recent study noted that patterns of heavy drinking among college students increased after they became associated with heavy-drinking groups and then decreased after becoming disassociated with such groups.

Current Investigation

Considering the aforementioned culture of alcohol use present among military personnel in combination with the penchant for heavy drinkers to purposefully enter into situations in which alcohol use/misuse is the norm, it is reasonable to ask: Are heavy drinkers self-selecting into the military? Consequently, the purpose of this investigation was to explore the extent to which binge drinking was related to the propensity to join the military after graduating high school among a national sample of high school seniors responding to the 2008 Monitoring the Future (MTF) survey. Based upon previous examinations examining propensity to join the military, MTF was deemed an appropriate data source.

METHODS

Participants

For the purpose of this study, responses from twelfth grade students (*n* = 14,577) participating in MTF were analyzed (because of interest in examining intent for future plans after high school). The overall student response rate for 2008 was approximately 79%. The majority of respondents were Caucasian (57%) females (52%) with no intent to join the military (90%). The vast majority of the students reported having consumed alcohol in their lifetime (73%), and 26% reported binge drinking within the past 2 weeks.

Procedures

The University of Michigan's Institute for Social Research has conducted the MTF project since 1975. Funded by a series of research grants from the National Institute of Drug Abuse, MTF methods are vetted not only by funding agents but also on an annual basis by the University of Michigan's Institutional Review Board. The twelfth grade surveys are confidential and completely voluntary. Although the project includes a nationally representative multistage area probability sample of eighth-, tenth-, and twelfth-grade students in 130 public and private secondary schools throughout the United States, the current investigation limited analysis to only those respondents in twelfth grade. Stage 1 involves selecting geographic areas to be included in the sample, and then stage 2 proceeds by selecting high schools from these geographical areas.

Stage 3 involves select students attending the high schools identified in stage 2. Confidential questionnaires are administered (typically durlng class time) to students by local field representatives, who follow standard procedures. Respondents who are high school seniors are asked to provide their name and mailing address following survey administration to provide opportunities for longitudinal follow-up surveys. For more information regarding the MTF design, sampling methods, and missing data imputation codes, readers can consult www.monitoringthefuture.org.

Measures

Content areas within the MTF survey address demographic variables, lifestyle beliefs, satisfaction with academic performance, interpersonal attitudes, and beliefs related to use of alcohol and drugs. One-third of each instrument contains “core” variables that assess demographic variables and measures of drug and alcohol use. In this particular study, we were interested in items which assessed alcohol-related behavior (independent variables) and intent to join the military (dependent variable).

Lifetime Alcohol Use

Lifetime alcohol use was measured using the item: “On how many occasions (if any) have you had alcoholic beverages to drink—more than just a few sips—in your lifetime?” Response scale options included: 0 occasions (0), 1 to 2 occasions (1), 3 to 5 occasions (2), 6 to 9 occasions (3), 10 to 19 occasions (4), 20 to 39 occasions (5), and 40 or more (6).

Binge Drinking

Binge drinking was measured using the item: “Think back over the LAST TWO WEEKS. How many times have you had five or more drinks in a row? (A “drink” is a bottle of beer, a glass of wine, a wine cooler, a shot glass of liquor, a mixed drink, etc.).” Response categories included: none (0), once (1), twice (2), three to five times (3), six to nine times (4), and ten or more times (5). Higher scores indicated a greater frequency of binge drinking across the 2 weeks before the survey.

Propensity to Join the Military

Propensity to join the military was evaluated utilizing the following item: “How likely is it that you will serve in the Armed Forces after high school?” The response scale consisted of the following categories: Definitely Won't, Probably Won't, Probably Will, and Definitely Will. Responses were dummy coded as “0” for both “definitely won't” and “probably won't,” indicating no intent to join and as “1” for both “probably will” and “definitely will,” indicating an expressed intent to join. Previous examinations into propensity to enlist and actual enlistment behaviors reveal propensity to be highly predictive of enlistment within the next 6 years following high school.

Data Analysis

Using Statistical Package for Social Sciences (PASW, Version 20; SPSS, Chicago, Illinois), independent sample *t*-tests were first conducted to compare mean alcohol consumption (lifetime and binge) rates among those who did and did not intend to join the military. To account for this

investigation's large sample size, effect sizes (Cohen's *d*) are reported for all significant mean differences. To determine the impact of high-risk drinking behaviors on intent to join the military, we ran a logistic regression model testing whether propensity to join the military was associated with one's binge drinking. Several demographic variables (e.g., race, parents' education level) and academic (i.e., self-rated intelligence) covariates were selected as control variables based on previous investigations examining propensity to enlist in the U.S. military. Specifically, the regression model controlled for the covariates sex, race (White, Hispanic, and Black), political beliefs (conservative, moderate, and liberal), their mother's and father's education level, self-reported level of intelligence, and lifetime drinking status. For the logistic regression, lifetime drinking was dummy coded as "0" for those who had never consumed alcohol in their life and as "1" for those who had consumed alcohol more than once in their life. In all of the aforementioned analyses, 2-tailed *p*-values of ≤0.05 were deemed statistically significant.

RESULTS

An independent samples *t*-test compared alcohol consumption rates for those intending to join the military versus those who did not intend to join the military. Respondents intending to join the military reported significantly greater levels of alcohol consumption (M = 3.18, SD = 2.33) from those not intending to join the military (M = 2.84, SD = 2.30) with regard to lifetime drinking (t (12,578) = −4.89, $p < 0.001$). Those with a propensity to join the military also binge drank (M = 0.68, SD = 1.23) more days within the past 2 weeks than those not intending to join (M = 0.53, SD = 1.05; t (1378.08) = −4.07, $p < 0.001$). However, the magnitude of the differences in group means for lifetime (mean difference = −0.340, 95% confidence interval [CI]: −0.476 to −0.204) and binge drinking (mean difference = −0.151, 95% CI: −0.223 to −0.078) was relatively small (d = −0.09, −0.22, respectively).

Before the logistic regression analysis examining the impact of one's binge drinking behaviors on propensity to join the military, correlations across independent variables were assessed to determine if multicollinearity would influence the models. None of the variables were highly correlated (e.g., Pearson correlations were all less than 0.70). To further ensure our models would not be influenced, collinearity diagnostics between the alcohol consumption variables indicated collinearity was not present. Both the variance inflation factors (≤1.485) and tolerance statistics (≤0.673) met their respective suggested cutoffs of less than 10^{24} and greater than 0.2.

Overall, the full model was statistically significant (χ^2 [df = 11] = 433.53, $p < 0.0001$), indicating the model was able to distinguish between those who did and did not intend to join the military after high school. That said, the model only accounted for a small amount of the variance (Nagelkerke R^2 = 9.8%). Binge drinking (odds ratio [OR] = 1.079, Wald = 5.53, df = 1, $p < 0.05$) exhibited a strong association with propensity to join the military above and beyond our numerous controls. Specifically, the more respondents binge drank (B = 0.08), the more likely it was that they would report a propensity to join the military. It is also noteworthy that those who had drunk alcohol in their lifetime (OR = 1.27, Wald = 6.52, df = 1, $p < 0.011$) were more likely to indicate intent to join the military. Males (B = 1.31) were significantly more likely to join the military than their female counterparts (OR = 3.69, Wald = 244.55, df = 1, $p < 0.001$), as well as those indicating a conservative political affiliation (OR = 1.42, Wald = 11.85, df = 1, $p < 0.001$). Students identifying themselves as being liberals were far less likely (B = −0.38) to indicate an intent to join the military (OR = 0.57, Wald = 29.06, df = 1, $p < 0.001$). Both father's (B = −0.12) and mother's (B = −0.09) education level were also negatively associated with propensity to join the military.

DISCUSSION

Overall, the general rates of binge drinking documented among the current sample (26%) are identical to those of previous investigations specifically examining substance use among military recruits. Recent results associated with the Recruit Assessment Program closely resemble our findings as well, documenting 32.6% Marine Corps recruits to be high-risk, potentially problematic drinkers. As is the case previously, alcohol use remains a prevalent behavior before accession into the military. Respondents in our sample who had engaged in binge drinking were significantly more likely than their peers to demonstrate a propensity to join the military postgraduation, even when controlling for lifetime drinking status, sex, race, political affiliation, mother and father's education level, and self-reported level of intelligence. Moreover, as binge drinking increased, so did one's propensity to join the military. Therefore, our findings lend credence to the notion of self-selection; in other words, it appears binge drinkers may be self-selecting into the military. It is important to note, however, that the documented effect size was small.

These findings underscore the importance of enforcing civilian programs and policies, such as the minimum legal drinking age. It is noteworthy to highlight that the current investigation reports on the alcohol use of U.S. high school students in twelfth grade, an underage group for which consuming alcohol is illegal. Investigations of Marine Corps recruits document approximately 59.8% of those aged 18 to 21 as current, underage, illegal drinkers. Age of first alcohol use among military recruits has been identified as a strong correlate of clinical (AUDIT-C) cutoff scores for problematic drinking. Investigations of the civilian population mirror these findings, documenting age of first alcohol use as a significant predictor of adult alcohol diagnoses, disorders, and unintentional injury.

In addition to civilian policies and programs, these findings highlight the necessity of the military to thoroughly assess alcohol-related behaviors and associated correlates before accession. Compared to their light-drinking peers, heavy drinkers responding to the Department of Defense Worldwide Survey exhibited a greater relative risk for exhibiting several work-related productivity losses (i.e., self-reported lateness, leaving early, low performance, and on-the-job injury). Hunter et al contend that high-risk drinking falls into a broader risk behavior category for military personnel. Specifically, among a sample (*n* = 32,144) of Air Force recruits entering basic training, the frequency of consuming eight or more drinks per occasion, frequency of fighting while drinking, and typical frequency of drinking were linked to positive rebellious and risk-taking attitudes and increased likelihood of engaging in risky behaviors such as decreased seat belt use.

Considering the costs associated with physically training and mentally preparing an enlistee, it would be prudent for the military to account for one's alcohol-related behaviors (e.g., age of initiation, binge drinking) and associated correlates (e.g., other deviant behaviors, adverse childhood experiences) before accession. Although the military currently maintains enlistment standards relating to alcohol use, with small variations between service branches, only a history of severe alcohol dependence is disqualifying. As the aforementioned literature makes clear, however, there are considerable factors that impact alcohol abuse, which may also require inspection. As the Army's Gold Book enunciates, the health-related factors and behaviors of military personnel “are interrelated and will require interdisciplinary solutions.”

Limitations

It is important that readers consider the aforementioned findings within the context of several limitations. Most notably, this investigation inherits the limitations associated with the original MTF study design. As outlined in the "MTF National Survey Results," this includes the "exclusion of [the] young men and women who drop out of high school before graduation – between 13% and 20% of each age cohort nationally … (p 62)."

Like all secondary data analyses, the selection of independent, dependent, and control variables is restricted to those available within the original dataset. Moreover, the operationalization of these variables is also limited to the manner in which MTF initially assessed them. Although the available data preclude inclusion, future research should assess (or at least control for) family structure and history, as well as prior traumatic experiences/exposure. High-risk Marine Corps drinkers have been identified as more likely to be smokers, grown up with an alcoholic, problem drinker or mentally ill person, and to have experienced a sexual or emotional childhood abuse. Adverse childhood experiences (e.g., physical or sexual abuse, substance abuse in the home, and parental discord or divorce) have been significantly associated with initiating alcohol use at, or before, the age of 14. Systematic literature reviews document parental and peer approval and behavioral modeling of drinking as well as previous involvement in delinquent behavior as the strongest predictors of imitating alcohol use in adolescence. It should be noted, however, that the literature base examining propensity to join the military is primarily based upon the MTF-dependent variable examined herein.

Last, the self-reported nature of the MTF data is also a limitation; however, there exist substantial "inferential evidence [to] strongly suggest that the self-report questions used in the MTF produce largely valid data."

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Tobacco Product Usage Among Deployed Male and Female Military Personnel in Kuwait

Military Medicine
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January 2013

According to the National Health Interview Survey of 2009, an estimated 20.6% of adults in the United States were smokers. Given the prevalence of tobacco usage, a better understanding of tobacco habits among deployed military personnel will help in determining the importance and prospective benefits of implementing an effective antitobacco use campaign which, in turn, would improve physical endurance and reduce the risk of hypertension, cardiovascular disease, stroke, emphysema, and cancer associated with tobacco use.

Previous studies have noted that, regarding smoking and military readiness, smoking is one of the best predictors of military training failure; smoking is associated with significant increased hospitalization and lost work days; and smoking is a strong marker for other causes of low readiness such as alcohol abuse, low physical activity, and illicit drug abuse. Also, smokers in the military are more likely to sustain injuries, especially musculoskeletal injuries.

Among deployed male and female military personnel stationed in Kuwait during Summer to Autumn of 2012, 402 military members (383 Enlisted and 19 Officers) with ages ranging from 19 to 55 years (mean age 32 years) were randomly surveyed regarding their tobacco usage habits (cigarette smoking and chewing tobacco). Those randomly surveyed were Active Army, National Guard, and Army Reserve members. The ethnicity of those surveyed were predominantly Caucasian (80%), followed in descending order by African American (9%), Hispanic (5%), Asian (4%), and Pacific Islander/Native American (2%).

Of the 402 military members surveyed, 41% (164/402) used tobacco products during the Kuwait deployment. Among the tobacco product users, 87% (142/164) were male and 13% (22/164) were female. The mean age of the tobacco users was 30 years. In contrast, of the 238 nontobacco product users, 73% (173/238) were male and 27% (65/238) were female. The mean age of the nontobacco product users was 34 years. Thus, a higher percentage of males, as opposed to females, used tobacco products.

Of the 164 military members using tobacco products, 9% (14/164) did not use tobacco products before the deployment. During the deployment, 21% (35/164) of tobacco users further increased tobacco product usage and 6% (10/164) decreased tobacco usage.

Forty-six percent (75/164) of military personnel identified craving/habit as the primary motivating factor for their tobacco usage. Thirty-two percent (53/164) of military personnel blamed anxiety/stress, 16% (26/164) blamed boredom, and 6% (10/164) identified socializing as the primary motivating factor for tobacco use. Fifty-seven percent (94/164) of all tobacco users during deployment wanted to stop tobacco use upon redeployment. Seventy-five percent (40/53) of those members associating their tobacco use with anxiety intended on stopping tobacco use upon redeployment.

Based on the above data, tobacco use prevalence for deployed military personnel was approximately two times the U.S. national average, with prevalence of tobacco product usage greater for males than females. Our survey also concluded that during the deployment, a significant number of individual tobacco users further increased the quantity of tobacco consumed. Lastly, among deployed military personnel, craving/habit (addiction) and anxiety/stress are the two main factors influencing tobacco usage, with greater than 50% of tobacco users intending on stopping tobacco use upon return to the United States. The increased use of tobacco during deployment is probably associated with the increased psychological and emotional stresses incurred during deployment.

In conclusion, this data demonstrates the magnitude of the tobacco use problem among deployed military personnel. Effective and constructive policies regarding the tobacco use issue in the military are long overdue.

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Substance Use Among Military-Connected Youth

American Journal of Preventative Medicine
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8 Jan 2013

Background: Young people in military-connected families may be exposed to deleterious stressors, related to family member deployment, that have been associated with externalizing behaviors such as substance use. Substance use predisposes youth to myriad health and social problems across the life span.

Purpose: This study examined the prevalence and correlates of lifetime and recent substance use in a normative sample of youth who were either connected or not connected to the military.

Methods: Data are from a subsample of the 2011 California Healthy Kids Survey (N_14,149). Items in the present analyses included present familial military affıliation (no one, parent, sibling); number of deployments (none, one, two or more); gender; grade; and race/ethnicity. Substance use items assessed whether the youth reported lifetime use of alcohol, tobacco, marijuana, other drugs, or prescription drugs; and recent (past 30 days) use of alcohol, tobacco, marijuana, and other drugs.

Results: Multivariate analysis conducted in 2012 revealed that an increase in the number of deployments was associated with a higher likelihood of lifetime and recent use, with the exception of lifetime smoking.

Conclusions: These results indicate that experiences associated with deployment of a family member may increase the likelihood of substance use.

Background

There is concern that the wars in Afghanistan and Iraq are associated with negative psychological and behavioral outcomes for children in military families.1–3 The increased number and longer duration of deployments for those serving exceed those during any other point in the modern history of the U.S. military.

The stressors associated with being connected to the military can predispose youth to both internalizing and externalizing behaviors, such as substance use, that have negative health and social consequences. Parental deployment, in particular, is theorized to affect adolescent well-being and behavior through the disruption of family routines, increased distress of the remaining parent, and increased familial responsibility for the adolescent.

Although there is research into the influence of parental military service, only one study has addressed sibling service, and no studies have examined the influence of sibling military service on adolescent substance use. Research in the general adolescent substance use literature has suggested that siblings potentially provide access to drugs and/or serve as role models of drug use behavior.

Thus, having a sibling in the military may expose an adolescent to the stress of having that sibling deployed, role-modeling of substance use behaviors, and a direct or inadvertent increase in access to alcohol and other substances, due to that sibling's use. The present study explores the associations of being connected to the military with adolescent substance use.

Study Hypotheses

To our knowledge, to date, there are no large-scale normative studies published of adolescent substance use that focus on a comparison between those who are connected (via either parent or sibling service) versus unconnected to the military. Given the extant literature and theories of stress and coping, it is anticipated that those youth with parents or siblings who are actively serving in the military will have a higher lifetime prevalence of and recent substance use compared to those who are not connected to the military. A higher number of familial deployments was expected also to be related to a higher likelihood of substance use.

Methods

The present study uses the California Healthy Kids Survey (CHKS), which consists of a core survey module that gathers demographic background data (e.g., grade, gender, and race/ethnicity) and inquires about students' health-related behaviors, tobacco use, alcohol use, drug use, violence behaviors, and school safety. A 39-item "military module" was developed to identify the needs and experiences of military children and was administered to 21,740 students in the 5th, 7th, 9th, and 11th grades during late February and early March 2011. The present analysis focuses on students in schools in southern California (N_14,149). These schools are in militaryconnected (average daily attendance of more than 400 military students or 10%) public school districts.

Appropriate institutional and district- and state-level permissions and reviews were completed. Review board approval was obtained from the University of Southern California Human Subjects Review Board. Parent/guardian consent was obtained for all participants where required. Data collection involved the student participants completing a voluntary, anonymous, and confidential paper-and-pencil survey during one class session.

The consent rate was 96.7%, and the completion rate of students present in class was 86.5%.

Dependent Variables

Lifetime and recent (past 30 days) levels of use of alcohol, tobacco, or marijuana were used in separate models as dichotomized outcomes. Lifetime substance use was examined given the likelihood that there may be a substantial portion of seventh-graders and some ninth-graders who, although they may have "ever" tried alcohol, tobacco, or marijuana, had not used them within the past 30 days. Additional outcomes included lifetime and recent use of "other" drugs. This included any reported use of inhalants, cocaine/crack, methamphetamine, or LSD. Lifetime use of prescription drugs also was assessed as a dichotomy. The substances of interest included painkillers, barbiturates, tranquilizers, cold medicine, and Ritalin® or Adderall®.

Independent Variables

The independent variables included grade, gender, race/ethnicity, whether the student had a family member currently serving in the military (no one, parent, or sibling) and deployment of a family member in the past 10 years. Race/ethnicity categories were Asian American/Pacifıc Islander, black, white, multiple races, and Hispanic ethnicity.

Data Analysis

The analysis was completed using SAS, version 9.2. Frequency distributions and cross-classifıcation tables (chi-square analysis) were performed to compare sociodemographic characteristics and key variables related to military connection. Multiple logistic regression (MLR) was used to predict the probability of lifetime versus never use (separately for alcohol, tobacco,

Results

Alcohol and Other Drug Use Those youth who reported having a sibling in the military had the highest prevalence of all lifetime substance use. There were several associations between substance use prevalence and military connection. Specifıcally, lifetime alcohol (chi-square_12.2, p_ 0.002); marijuana (chisquare_9.7; p_0.008); and prescription (chisquare_6.5; p_0.04) drug use showed variation according to military-connection status.

No differences were found in prevalence of recent drug use. Youth who reported either one, or two or more, familial deployments had the highest prevalence of substance use. Higher numbers of deployments were associated with higher levels of lifetime tobacco use (chisquare_8.6; p_0.01) and other drug use (chisquare_22.6 p_0.0001). There were also differences in the number of deployments and the likelihood of recent use of alcohol, tobacco, marijuana, and other drugs.

Lifetime and Recent Drug Use Models

Controlling for grade, gender, race, and familial deployments, current military connection was not a predictor in any of the lifetime or recent substance use models. A higher number of family member deployments was, however, associated with increased likelihood of use in all of the models. Among the lifetime substance use models, it contributed at least a 14% increase in likelihood of drug use (prescription drugs; OR_1.14, 95% CI_1.06, 1.24) to a maximum of a 25% increase (other drugs; OR_1.25, 95% CI_1.15, 1.35). Within the recent (past 30 days) drug use models, an increase in the number of deployments contributed at least an 18% increase in likelihood of drug use (marijuana: OR_1.18, 95% CI_1.08, 1.28) to a maximum of a 34% increase (other drugs: OR_1.34, 95% CI_1.20, 1.50).

Discussion

To our knowledge, the present study is the fırst to examine the prevalence of substance use among youth in families connected versus not connected to the military, in normative settings such as schools. Further, this study is one of the fırst to examine the impact of military connection

via both parental and sibling service. The results show that overall, military-connected youth have a higher prevalence of substance use. The prevalence of lifetime use of alcohol, tobacco, marijuana, other drugs, and prescription drugs was consistently highest among those with a sibling in the military. Recent drug use was the only category of use found to be highest among those who reported having a parent serving in the military.

The multivariate analyses revealed that after controlling for demographics, being from a military family alone was not associated with lifetime or recent substance use. However, a higher number of family member deployments was associated with all substance use categories except for lifetime smoking. These findings indicate that it may be the experiences associated with prolonged war that increase behavioral health stresses on military connected youth and their families.

The results raise the question of why having a sibling in the military was associated with higher rates of substance use than was having a parent in the military. Much of the literature focuses on parent– child relationships and the impact of parental deployment11 and/or injury on youth mental health. The immense number of adolescents potentially affected by close family member deployment has been documented but few studies have explored the experiences of the many families affected by having a close family member serve in the armed forces.

In a qualitative study of individual and family systems, findings showed that reactions to sibling deployment were similar to those resulting from having a parent deploy. Theories of uncertainty (e.g., injury or death, changes in duration of deployment/service) and ambiguous loss indicate that a loss (lack of physical presence of a loved one) combined with uncertainty or ambiguity greatly slows the ability to cope or grieve. Thus, losing the physical presence of a close loved one is likely stressful both because of the ambiguity of the loss and the stress related to changes in interpersonal dynamics and shifts in responsibilities within a familial unit.

The increased use of reservists and national guardsmen means that more families exposed to stressors associated with deployment are using non-military-affiliated public resources (e.g., schools or clinics) that are less likely to take into account the special considerations pertinent to military families. Additional school-based social–emotional supports around deployment and reintegration can be offered to youth and their family members to cope with their loved ones' absence and other deployment related stressors. Schools with a high density of students whose family members are already known to have deployed multiple times may decide to provide universal substance use education curricula and added internal referrals for parents and students.

Finally, these findings support making other community based medical care providers cognizant of the need to screen for possible substance use and abuse problems among youth who are identified to be experiencing familial deployment.

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The 21st century hazards of smoking and benefits of stopping: a prospective study of one million women in the UK

The Lancet
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12 January 2013

Summary

Background

Women born around 1940 in countries such as the UK and USA were the first generation in which many smoked substantial numbers of cigarettes throughout adult life. Hence, only in the 21st century can we observe directly the full effects of prolonged smoking, and of prolonged cessation, on mortality among women in the UK.

Methods

For this prospective study, 1•3 million UK women were recruited in 1996—2001 and resurveyed postally about 3 and 8 years later. All were followed to Jan 1, 2011, through national mortality records (mean 12 woman-years, SD 2). Participants were asked at entry whether they were current or ex-smokers, and how many cigarettes they currently smoked. Those who were ex-smokers at both entry and the 3-year resurvey and had stopped before the age of 55 years were categorised by the age they had stopped smoking. We used Cox regression models to obtain adjusted relative risks that compared categories of smokers or ex-smokers with otherwise similar never-smokers.

Findings

After excluding 0•1 million women with previous disease, 1•2 million women remained, with median birth year 1943 (IQR 1938—46) and age 55 years (IQR 52—60). Overall, 6% (66 489/1 180 652) died, at mean age 65 years (SD 6). At baseline, 20% (232 461) were current smokers, 28% (328 417) were ex-smokers, and 52% (619 774) were never-smokers. For 12-year mortality, those smoking at baseline had a mortality rate ratio of 2•76 (95% CI 2•71—2•81) compared with never-smokers, even though 44% (37 240/85 256) of the baseline smokers who responded to the 8-year resurvey had by then stopped smoking. Mortality was tripled, largely irrespective of age, in those still smoking at the 3-year resurvey (rate ratio 2•97, 2•88—3•07). Even for women smoking fewer than ten cigarettes per day at baseline, 12-year mortality was doubled (rate ratio 1•98, 1•91—2•04). Of the 30 most common causes of death, 23 were increased significantly in smokers; for lung cancer, the rate ratio was 21•4 (19•7—23•2). The excess mortality among smokers (in comparison with never-smokers) was mainly from diseases that, like lung cancer, can be caused by smoking. Among ex-smokers who had stopped permanently at ages 25—34 years or at ages 35—44 years, the respective relative risks were 1•05 (95% CI 1•00—1•11) and 1•20 (1•14—1•26) for all-cause mortality and 1•84 (1•45—2•34) and 3•34 (2•76—4•03) for lung cancer mortality. Thus, although some excess mortality remains among these long-term ex-smokers, it is only 3% and 10% of the excess mortality among continuing

smokers. If combined with 2010 UK national death rates, tripled mortality rates among smokers indicate 53% of smokers and 22% of never-smokers dying before age 80 years, and an 11-year lifespan difference.

Interpretation

Among UK women, two-thirds of all deaths of smokers in their 50s, 60s, and 70s are caused by smoking; smokers lose at least 10 years of lifespan. Although the hazards of smoking until age 40 years and then stopping are substantial, the hazards of continuing are ten times greater. Stopping before age 40 years (and preferably well before age 40 years) avoids more than 90% of the excess mortality caused by continuing smoking; stopping before age 30 years avoids more than 97% of it.

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Suicide

Hospitalization for physical illness and risk of subsequent suicide: a population study

Journal of Internal Medicine
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January 2013

Abstract

Objective

To examine suicide risk in relation to physical illness across a broad range of illnesses, including hospitalization history, specific organ or system illness and comorbidity.

Design

A nested case–control study.

Setting

Data were retrieved from five Danish national registers.

Subjects

On the basis of the entire population of Denmark, this study included 27 262 suicide cases, and 468 007 live controls matched for sex and date of birth.

Main outcome measures

Risk of suicide was assessed using conditional logistic regression.

Results

In the study population, 63.5% of suicide cases and 44.5% of comparison controls had a history of hospitalization for physical illness. A physical illness significantly increased the risk of subsequent suicide (incidence rate ratios 2.13, 95% CI 2.07–2.18) with a substantially greater effect in women than in men ($P < 0.01$). The elevated risk increased progressively with frequency and recency of hospitalization and was significant for diseases occurring in all organs or systems of the body. Comorbidity involving several organs or systems increased the risk substantially. The associated estimates were to some extent reduced but remained highly significant after adjustment for psychiatric history and socio-economic status. Taking into account both prevalence and adjusted effect size, physical illness accounted for 24.4%, 21.0% and 32.3% of population attributable risk for suicide in total, male and female populations, respectively.

Conclusions

Physical illness constitutes a significant risk factor for suicide independent of psychiatric and socio-economic factors. Clinicians treating physically ill patients should be aware of the risk, especially amongst those with multiple or recent hospitalizations, or multiple comorbidities.

Introduction

It is well known that people with physical illness are at increased risk of suicide, but the strength of the effect and the differences across a broad range of diagnoses are poorly understood. In general, studies have been conducted to examine whether suicide is associated with a single specific physical illness or generally ill condition. For instance, previous epidemiological studies have indicated an increased suicide risk associated with cancer, diabetes, epilepsy, multiple sclerosis, stroke, myocardial infarction and allergy. Rarely has any large population been systematically examined for suicide risk across a range of physical conditions simultaneously, to explore the effect of level of comorbidity and to assess the association whilst taking into account personal socio-economic status and psychiatric history. A major reason for this could be the difficulty of obtaining the necessary data. In this large population study, using data from Danish national registers, we have investigated the risk of suicide in relation to physical illness, examining the effects of frequency and recency of hospitalization, diagnosis according to the categories of the International Classification of Diseases (ICD) and number of comorbid conditions.

Material and methods

Setting

We conducted this study in Denmark (population 5.4 million), where hospital treatment is provided free of charge to all residents. Individual-level data for the entire population were retrieved from several national longitudinal registries and merged using the unique personal identifier (CPR number) given to all Danes by the Civil Registration System at birth and to new residents upon immigration.

The Cause-of-Death Register contains information on cause and date of all deaths that have occurred in Denmark since 1969. The Danish National Hospital Register contains individual-level data on diagnoses and dates of contact with all nonpsychiatric hospitals in Denmark since 1978. The Danish Psychiatric Central Register, covering all psychiatric facilities in Denmark, maintains a cumulative record of all hospital admissions and discharges since 1969. Data on outpatient contact (visits to emergency departments, hospital outpatient clinics and ambulance calls) have been included in both general and psychiatric hospital registers from 1995. Diagnoses of illness and causes of death were coded according to the ICD, 8th revision (ICD-8), until the end of 1993 and the 10th revision (ICD-10) thereafter. The ICD 9th revision has never been used in Denmark.

The IDA Database (Danish acronym for 'the Integrated Database for Labour Market Research') records annual information on labour market conditions (employment status, type of occupation, job function, employer) and sociodemographic status for all Danish residents. Individual socio-economic data for a given calendar year are complete only for individuals living in Denmark on 31 December of that year.

Study design and participants

We utilized a nested case–control design to select study participants from the national population of Denmark. The Cause-of-Death Register allowed us to identify all suicides (*n* = 27 380; ICD-8 codes E950–959 and ICD-10 X60–84) that occurred during the period 1981–2006. In line with previous studies of suicide in Denmark, we included as study cases only individuals for whom the cause of death was a definite suicide. We excluded individuals (*n* = 118) who were not residing in Denmark on 31 December in the preceding year because of the incompleteness of their socio-economic data in the IDA database. Using incidence density sampling, we randomly selected up to 20 live controls per suicide case, matched by sex and date of birth, from a 25% representative sample of the national population in the Civil Registration System. The rationale for sampling 20 controls per case was to enable the examination of uncommon exposures with reasonable statistical precision. In total, 27 262 suicide cases, representing 99.6% of all national suicides during the study period, and 468 007 live population controls were included in the study.

Study variables and covariates

We assessed personal history of physical illness through patient records in the Danish National Hospital Register. For each study subject, we retrieved the records of inpatient treatment for physical illness prior to the date of suicide or the matching date for controls and classified the diagnosis of illness by areas of organ or system of the body according to categories of the ICD-10 (chapter headings). We excluded the following conditions from our definition of a physical illness: mental and behavioural disorders (Chapter V), pregnancy and childbirth (Chapter XV), certain conditions of the prenatal period (Chapter XVI) and external causes (chapters XIX and XX, covering all accidental or intentional poisonings and injuries). Details regarding diagnostic codes in ICD-10 and conversion from ICD-8 to ICD-10 codes are provided in the Appendix. We also

constructed a few variables of interest including the total number of hospitalizations, time elapsed from the most recent hospitalization and number of comorbid physical illnesses.

At the same time, we obtained personal data on psychiatric history, including both inpatient and outpatient care, from the Danish Psychiatric Central Register. We also extracted individual data on socio-economic status, that is, marital status, annual gross income, place of residence and citizenship, from the IDA database. These data were included for adjustment purposes in the analyses.

Statistical analysis

We constructed contingency tables for the main study variables and computed the associated risk of suicide using conditional logistic regression with the PhReg procedure available in SAS version 9 with each case forming a separate stratum. Because the controls were sampled from individuals at risk of suicide (i.e. incidence density sampling), the estimated odds ratios (ORs) from the analyses were unbiased estimates of incidence rate ratios (IRRs). We estimated IRRs from crude analyses and from adjusted models controlling for effects of psychiatric history and socio-economic factors. For estimates associated with a specific organ or system illness, we used a generic reference group, that is, individuals without hospitalization for any of the physical illnesses included in the study, and adjusted the estimates for the effect of any illness other than the specified one.

The Wald test was used to determine the significance of estimates relative to the reference group and to examine the overall effect difference across the range of organ or system illnesses. Interactions between sex and overall physical illness and between sex and specific organ or system illness were additionally examined through the likelihood ratio test. Test for trend associated with the number of comorbid illnesses was performed by treating number of physical illnesses as a continuous variable. Population attributable risk (PAR) associated with physical illness was calculated based on the adjusted IRRs estimated from the conditional logistic regression analyses and the prevalence in suicide cases of the physical illnesses considered in the study. All *P* values were two sided.

Ethical approval

We obtained approval to conduct the study from the Danish Data Protection Agency.

Results

The study included a total of 27 262 suicide cases and 468 007 live population controls, comprising 18 099 male and 9163 female suicide cases and 307 729 male and 160 278 female control subjects. In the study population, 63.5% of suicide cases and 44.5% of comparison controls had a history of hospitalization because of physical illness. For both suicide cases and controls, physical illness was generally more common in women (70.8% of cases; 50.0% of controls) than men (59.7% of cases; 41.6% of controls). A psychiatric history was more common in individuals with physical illness compared with those without: 47.2% of physically ill suicide cases, 40.8% of physically healthy suicide cases, 7.7% of physically ill controls and 3.6% of healthy controls.

Frequency and recency of hospitalization for serious physical illness

Multiple hospitalizations for physical illness as well as a recent hospitalization were more common amongst suicide cases, relative to the control group. Of suicide cases with physical illness, 50.2% had been hospitalized three or more times, and 39.8% had been hospitalized within the year prior to suicide; the corresponding values for the comparison controls were 35.3% and 19.4%, respectively.

Using conditional logistic regression to analyse the data, we found that a history of physical illness significantly increased the risk of suicide (crude IRR 2.13, 95% CI 2.07–2.18) and that the effect was greater amongst women than men (crude IRR 1.97, 95% CI 1.91–2.03 for men; crude IRR 2.50, 95% CI 2.38–2.62 for women; test of sex differences: $\chi^2 = 64.64$, $P < 0.001$). We also noted a progressively increased suicide risk associated with both the frequency of previous hospitalizations and the recency of the last hospitalization – the greater the number of hospitalizations or the more recent the last hospitalization, the higher the risk of suicide. The observed pattern persisted in the analyses stratified by sex although the associated IRRs were generally higher in women than that in men (data not shown). When the data were adjusted for history of psychiatric illness, the associated IRRs were reduced to some extent, especially in the presence of multiple hospitalizations for physical illness. Still, the increase in associated risks remained highly elevated. Further adjustment for socio-economic status had minimal effect on the risk estimates (adjusted IRR 1.62, 95% CI 1.58–1.67 for total cases; adjusted IRR 1.54, 95% CI 1.49–1.60 for men; adjusted IRR 1.84, 95% CI 1.74–1.94 for women; test of sex differences: $\chi^2 = 51.04$, $P < 0.001$).

Diagnosis by ICD main categories and number of physical illnesses

When diagnoses of physical illness were grouped according to ICD-10 categories a significantly higher prevalence of physical illness was observed in suicide cases than in controls across all organs or systems of the body. Digestive, circulatory and genitourinary system diseases were amongst the most common illnesses in both suicide cases and comparison controls. It is interesting that a substantial proportion of suicide cases (19.1%) had been hospitalized at least once because of symptoms, signs and abnormal clinical and laboratory findings not included in other categories.

With the group of individuals with no hospitalization for any physical illness included in the study as a reference, there was a significantly increased risk of suicide associated with specific diseases in all organs or systems of the body. The IRRs associated with the different specific organ or system illnesses varied significantly in magnitude ($P < 0.001$ in both crude and adjusted analyses), from 2.07 to 3.83 in the crude analysis and from 1.56 to 2.04 in the analysis adjusted for psychiatric history and socio-economic status. The highest IRRs were associated with nervous system diseases and the group of unspecified symptoms, signs and abnormal clinical and laboratory findings; the remaining groups of diseases had a comparable effect on suicide risk.

Although analyses stratified by sex showed somewhat similar patterns, the effects of some organ or system illnesses differed significantly between men and women. Combining the results from adjusted IRRs and the test for sex interaction showed that infectious and parasitic diseases (Chapter I), nervous system diseases (Chapter VI), respiratory system diseases (Chapter X), digestive system diseases (Chapter XI), skin diseases (Chapter XII), musculoskeletal system diseases (Chapter XIII), congenital malformations (Chapter XVII) and unspecified symptoms, signs and

abnormal clinical and laboratory findings (Chapter XVII) increased suicide risk significantly more in women than in men, whereas neoplasms (Chapter II) had a significantly greater effect on suicide in men. The increased suicide risk for the other diagnostic categories was comparable for both sexes.

Comorbid illnesses involving multiple organs or systems were more common in suicide cases than in controls. Overall, 35.5% of suicide cases, but only 18.4% of controls, had been hospitalized for diseases occurring in more than one organ or system. The associated suicide risk increased progressively with the number of comorbid organ or system diseases, and the test of trend was highly significant (analogous IRR 1.44, 95% CI 1.42–1.45; $P < 0.0001$). The highly elevated risks associated with multiple comorbidities were largely reduced when the data were adjusted for psychiatric and socio-economic status. Still, the progressive increase in suicide risk associated with multiple comorbidities remained prominent for both sexes together (analogous IRR for trend test 1.23, 95% CI 1.21–1.24; $P < 0.0001$) as well as for men and women separately (data not shown).

Population attributable risk

To assess the proportion of suicides in the population that is attributable to exposure to the physical illnesses considered in this study, we computed the PAR – a measurement that takes into account both the prevalence of physical illness in the population and the magnitude of its effect on suicide risk. We estimated a PAR of 24.4% for the total population, 21.0% for men and 32.3% for women, including a contribution because of a recent hospitalization for physical illness within 30 days of 7.7%, 7.2% and 8.6%, respectively. Illness categories with a high PAR included the group of unspecified symptoms, signs and abnormal clinical and laboratory findings, as well as digestive, circulatory and genitourinary system diseases.

Discussion

The findings of this large study in the entire population of Denmark show that hospitalization for a physical illness significantly increases the risk of subsequent suicide, with a substantially greater effect in women than men. The elevated risk increased progressively with the frequency and recency of hospitalization and was significant for all diagnostic groups of disease in any organ or system defined by ICD-10 categories. Comorbidity involving several organs or systems greatly increased suicide risk. At the same time, the observed effect of physical illness was somewhat reduced after adjustment for history of psychiatric illness, which was especially apparent for the estimated risks associated with multiple hospitalizations and multiple comorbidities. Nevertheless, the elevated risks remained highly significant after adjusting for psychiatric history and socio-economic status. Moreover, hospitalization for physical illness accounted for 24.4% of the PAR for suicide in the general population, with a higher attributable fraction for female (32.3%) than for male (21.0%) suicide.

These robust findings support a strong link between physical illness and risk of subsequent suicide in the general population. There have been a number of reports of an increased suicide risk associated with several severe diseases, including amongst others cancer and diabetes. The findings of this study extend the existing evidence by demonstrating that a disease of any organ or physical system significantly increases the risk of subsequent suicide, regardless of sex and after controlling for individual psychiatric history and socio-economic status.

A serious physical illness is often accompanied by pain, disability, limited social activity and worry about prognosis and financial loss and can lead to many problems with respect to physical, psychological and social well-being. Although we were not able to assess the severity of specific diagnoses, the observed progressive increase in suicide risk associated with frequency of hospitalization and multiple comorbidities indicates that the severity of physical illness plays an important role in the risk of subsequent suicide. The observed effects of these factors were apparently reduced after adjustment for psychiatric history. Still, being physically severely ill, as evidenced by either multiple hospitalizations or the involvement of several organs or systems, confers a strong risk of subsequent suicide. Patients may choose to end their life to obtain release from a long-term debilitating condition or to avoid experiencing the progression of an illness.

Our finding that variation in effect size across illnesses in various organs or systems is relatively small differs somewhat from the findings of previous studies of suicide in relation to single-disease entities. One methodological explanation could be that diagnoses in this study were broadly grouped on the basis of ICD-10 categories, covering a diversity of illnesses that occur in both severe and less severe forms or have a strong or weak relation to suicide. For instance, the group of nervous system diseases includes both diagnostic entities such as multiple sclerosis with a high risk of suicide and other diagnoses such as Parkinson's disease with a low suicide risk. Another possible explanation is that the variation in risk reported from the previous studies of single-disease groups may be subject to differential selection and information biases. A key strength of this register-based population study was the ability to estimate relative risk across a broad range of different physical illness types within the same study cohort compared with a generic reference category (i.e. individuals without any of the physical illnesses included in the study). This excluded the possibility of differential types and levels of bias, making comparison of risk between diagnostic groups more straightforward.

We observed that a psychiatric history was significantly more common in suicide cases with physical illness compared with those without (47.2% vs. 40.8%) and also that the elevated suicide risk associated with physical illness weakened to some extent after adjustment for history of contact with psychiatric services. These findings are consistent with previous reports of high comorbidity of psychiatric illness, especially depression, in people with physical diseases, and suggest that psychiatric illness is an important confounding or mediating factor in the link between physical illness and suicide risk.

To our knowledge, this study is the first to demonstrate a strong impact of the ICD-10 category of unspecified symptoms, signs and abnormal clinical and laboratory findings, in terms of both increased IRR and contributed PAR of suicide. This is noteworthy and consistent with reports indicating that the presence of unexplained somatic symptoms is associated with psychiatric disorders such as major depression and anxiety and that complaints of illness or feeling unwell may provide clues to patients' desire for emotional support. Although our estimates were controlled for the effects of psychiatric history and socio-economic status as well as of specified diagnoses from other ICD chapters, it is still possible that complaints of unspecified symptoms and signs may be linked to undiagnosed psychological symptoms, stress or somatization.

Our observation of a generally stronger effect of physical illness on suicide risk in women than in men suggests that women probably react more strongly to poor health than their male counterparts. This notion is also supported by previous evidence that psychiatric history has a significantly stronger impact on suicide in women than in men. At the same time, some physical illnesses and their influences on suicide may be more sex specific. For instance, we found that illnesses in most organs or systems have a stronger effect on increasing suicide risk in women than in men,

but neoplasms increased the risk significantly more in men. Further investigation of detailed diagnoses stratified by sex is needed for better understanding of this issue.

Relative to the intensive research and preventive efforts focusing on suicide in patients with psychiatric illness, subsequent suicide related to physical illness has received little attention. This study is the first to report that around a quarter of all suicides in the general population is attributable to exposure to physical illnesses that require hospital admission for treatment, including a 7.6% contribution because of a recent hospitalization for physical illness within 30 days. These PAR estimates could be subject to revision if more factors that may underlay the link between physical illness and subsequent suicide are taken into consideration. It does, however, indicate that suicide in patients with physical illness is clearly an important public health problem and warrants more investment of social resources and prevention efforts.

Limitations and strengths

A limitation of this study is that we considered only serious physical illnesses resulting in hospitalization. This may provide a slightly skewed picture as the influence of milder physical illnesses was not ascertained and because some severe medical conditions are treated in outpatient care. Similarly, we used psychiatric service contact as a proxy for psychiatric status. This underestimates the full extent of psychiatric disorders and reflects more serious disorders. Moreover, we were only able to obtain individual data on serious physical illness starting in 1978 when the Danish National Hospital Register was established. Thus, our data cover a relatively long period, but do not represent the lifetime of older subjects. Additionally, we detected a strong modification effect of psychiatric history on the link between physical illness and suicide risk, but did not address specifically the temporal relationship between physical illness and comorbid psychiatric disorders in this study. Furthermore, we grouped the diagnosis of illness based on areas of organ or system using the ICD-10 categories (chapter headings), which captures a mixed effect of illnesses occurring in one organ or body system but is not able to separate individual effects of specific clinical diagnoses on risk of suicide.

A major strength of this study is the coverage of the entire population of Denmark and the availability of precise data collected systematically without any research purpose. This ensures the full representation of a national population and minimizes possible biases that are often induced by recall of information and selected access to healthcare. The results should also be highly applicable to the general public, especially in countries or regions with comparable social settings.

To our knowledge, this study is the first to document suicide risk in relation to physical illness, encompassing hospitalization history, diagnosis and comorbidity and to assess the effect in the context of personal psychiatric and socio-economic status. It is also the first to evaluate the proportion of suicides in the population that is attributable to exposure to the physical illnesses included in the study. These findings will be informative for making strategies to reduce suicide in the general population.

Clinical implications

The results from this population study indicate the need to integrate suicide prevention within hospital treatment as well as within general medical practice. Patients hospitalized for physical illness not only form a well-defined population group at high risk of suicide, but also maintain frequent contact with their general practitioner after hospital discharge. This provides opportunities for both risk assessment and prevention. According to

our estimates, almost a quarter of all suicides in the general population could be avoided if prevention efforts were sufficiently implemented in services and settings dealing with people who are hospitalized because of physical illness. Although it is impossible to prevent all suicides in physically ill people, a considerable number of lives could be saved. Clinicians treating people with physical illness should be aware of the risk of suicide, especially amongst patients with multiple or recent hospitalizations or with comorbid physical illnesses.

At the same time, our findings underscore the necessity of further investigation. Whilst physical illness is common, only a small proportion of physically ill patients commit suicide. Therefore, we need to explore more thoroughly the link between various specific diagnoses of physical illness and subsequent suicide and to better understand the characteristics, medical conditions and outlook amongst individuals who are physically ill but do not commit suicide.

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Gabapentin Overdose in a Military Beneficiary

Military Medicine
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January 2013

ABSTRACT

We report the case of a 59-year-old military beneficiary that presented to the emergency department after ingesting approximately 90 g of gabapentin immediate-release capsules during a deliberate self-harm attempt. Her serum gabapentin level was 72.8 mcg/mL approximately 3 hours after ingestion. Her renal function panel, complete blood count, and liver function panel were normal. Her urine drug screen, aspirin, ethanol, and acetaminophen level were negative. Her electrocardiogram was normal, including a normal QTc interval. Her only symptoms were nausea and mild sedation. She was admitted for observation with no sequelae noted. She was transferred to a psychiatric facility at that time for further evaluation and treatment. We report a case of gabapentin overdose that presented to the emergency department. Given the large volume ingestion with minimal morbidity, it appears that gabapentin has a wide therapeutic margin and may be safe in overdose.

INTRODUCTION

A 59-year-old, 84-kg female military beneficiary was presented to our emergency department (ED) after an argument with her spouse and a subsequent suicide attempt at home. By her own admission, she ingested up to 300 capsules of immediate-release gabapentin at 300 mg each (90 g; about 1,070 mg/kg), along with 4 hydrocodone/acetaminophen 5/325 mg tablets approximately 1 hour before arrival. She had filled a prescription earlier that day for 1,080 capsules of gabapentin 300 mg. Remaining pill counts using her prescription bottles that emergency medical services (EMS) brought to the ED, in addition to the EMS report of no scattered pills at home and the recently filled prescription from that morning, verified the approximate reported amount ingested. We also verified the fill dates and pill counts in our electronic dispensing system. Her husband

corroborated her story. On presentation, the patient reported only mild sedation and nausea without vomiting. She denied ingesting any other substances.

Her past medical history was remarkable for depression, hypertension, diabetes mellitus, and hyperlipidemia for which she took venlafaxine, telmisartan, glipizide, metformin, simvastatin, and gemfibrozil. She had an extensive history of depression and anxiety but no prior suicide attempts. Her primary care provider started her on gabapentin for her chronic back pain several months before this presentation, in addition to acetaminophen/hydrocodone as needed. Surgical history included eye surgery, rotator cuff repair, tubal ligation, appendectomy, partial hysterectomy, and cone biopsy. She denied history of abusing alcohol, tobacco, or illicit drugs. She lived with her homebound husband who notified EMS after the ingestion. He was unavailable for additional history at the time of presentation but was later available to verify her history to the inpatient team.

An electrocardiogram (ECG) was performed and was normal, including the QTc interval. A renal function panel, complete blood count, and liver function panel were also normal. A urine toxicology screen by immunoassay assessed for the presence of amphetamines, barbiturates, benzodiazepines, benzoylecgonine (cocaine), opiates, phencyclidine, propoxyphene, and tetrahydrocannabinol (marijuana) and was negative. Serum aspirin, ethanol, and acetaminophen levels were not detectable. A serum gabapentin level was drawn approximately 6 hours from reported ingestion time and sent to Qwest Diagnostics and not available for immediate results. The gabapentin level was later reported as 72.8 mcg/mL (therapeutic range 2–20 mcg/mL). Given the negative urine toxicology screen and lack of clinical toxidrome suggesting that another medication was ingested, no other levels were indicated. Furthermore, the patient remained asymptomatic, so a follow-up gabapentin level was not obtained. Additionally, all recent prescription bottles (as verified against our electronic dispensing system) were available to verify appropriate remaining pill counts.

The psychiatry service evaluated the patient in the ED. Given the rarity of such a massive overdose without significant literature to guide our management, she was admitted to a telemetry-monitored bed on the internal medicine service. The following day, she was transferred to an inpatient psychiatric service at another facility.

To the best of our knowledge, this is the largest reported isolated acute gabapentin ingestion and the highest gabapentin serum level in an acute overdose patient who survived.

DISCUSSION

Gabapentin (brand name Neurontin) is a neurotransmitter structurally similar to gamma-aminobutyric acid (GABA) but does not bind to $GABA_A$ or $GABA_B$ receptors or have any effect on GABA synthesis, uptake, or degradation. Its mechanism of action is thought to be modulation of excitatory neurotransmitters via inhibition of presynaptic voltage-gated calcium channels. Gabapentin was initially approved for use in 1994 for treating partial seizure and in 2002 for postherpetic neuralgia. In 2004, the Food and Drug Administration (FDA) approved generic manufacturing of the drug. In the 2 years before transitioning to generic status, it was in the top 10 selling drugs with sales as high as $2.7 billion annually. Despite having only 2 FDA-approved indications, it was promoted for at least 11 off-label uses, including seizures, restless leg syndrome, bipolar disorder,

migraines, and alcohol withdrawal seizures before patent loss. A study in 2001 noted that gabapentin had the highest proportion of off-label use among office-based physicians. Gabapentin is widely used in the military. Nearly 1.3 million prescriptions for gabapentin were dispensed from our Fort Sam Houston pharmacies between January 1, 2011 and December 31, 2011 (LTC Debra Cosby, MSC USA, Officer-in-Charge, Pharmacy Services, SAMMC, personal communication).

Gabapentin is commonly used to treat both acute and chronic pain. In addition, gabapentin is widely used among U.S. service members for the treatment of post-traumatic stress disorder (PTSD) and chronic pain. PTSD affects over 30% of burned service members from the Iraq and Afghanistan campaigns. One study suggests that 4 to 17% of U.S. Iraq War veterans will experience PTSD. With the number of wounded warriors growing as the Afghanistan campaign continues, it is reasonable to presume that the number of patients we will see at military treatment facilities using gabapentin or analogues, such as pregabalin, will continue to rise as well. Suicide and suicide attempts continue to rise despite increasing awareness and attempts to address this within the military community. With a rise in prescription dispensing of gabapentin and analogues, along with this continuing increase in suicidal behavior, it would behoove military physicians to be aware of this medication's overdose profile.

Suicide rates among military members have been rising since 2004 despite intervention attempts. For unclear reasons, gabapentin is associated with an increased risk of suicide attempt. Our case highlights use of gabapentin in a suicide attempt, but it is not certain if this were due to chronic pain, depression, or another explanation. Additionally, gabapentin has been used as a drug of abuse on the streets and inside prisons.

A 2006 case report demonstrated a prolonged QTc and widened QRS complex on ECG in a patient that presented after ingestion of both gabapentin and nefazodone (a serotonin reuptake inhibitor). It is unclear which drug may have caused the ECG changes. The authors noted that the prolongation resolved after infusion of sodium bicarbonate.

Several case reports have noted alterations in gabapentin metabolism and symptomatic overdoses secondary to its use in patients with renal failure. Dogukan et al reported a 60-year-old female with chronic renal failure that became comatose (Glasgow Coma Score of 10) after a single dose of gabapentin for sciatica. Her symptoms resolved with hemodialysis. Verma et al presented a 30-year-old, dialysis-dependent female that developed a resting tremor and encephalopathy after several weeks of taking gabapentin 600 mg 3 times daily. Her gabapentin level at that time was 85 mcg/mL. After reducing her gabapentin dosing to 600 mg after each dialysis session (Monday, Wednesday, and Friday), her serum level at 3 months was 12 mcg/mL. This case highlights the risks associated with chronically elevated gabapentin levels. The effects of chronically elevated levels in nondialysis-dependent patients with chronic renal impairment have also been demonstrated.

Gabapentin's bioavailability is inversely proportional to the dose ingested because of facilitated transport during absorption by the L-amino acid transporter. Gabapentin's transport system becomes saturated at higher doses, limiting absorption. This may explain why our patient's serum level after a large acute ingestion was not as high as in chronic overdose with therapeutic dosing. Oral bioavailability after a 300 mg dose is 60%, but decreases to 35% when doses are increased to 3,600 to 4,800 mg/day. Gabapentin does not undergo metabolism and is excreted unchanged by the kidneys. There is no plasma protein binding that occurs. In a typical adult receiving 900 to 1,800 mg/day, expected plasma concentrations range from 2.7 to 4.1 mcg/mL following a single dose, but multiple days of this dosing result in concentrations from 4.0 to 8.5 mcg/mL. Peak serum levels of immediate-release capsules occur at 2 to 4 hours, and the elimination half-life is 5 to 7 hours with normal renal function.[1] Gabapentin

exhibits saturable absorption and follows nonlinear kinetics. The reduced bioavailability after large ingestions, in addition to the linear kinetics, likely contributed to the unpredictable serum level in our patient.

Fischer reported a case of a 16-year-old girl who consumed approximately 50 g of gabapentin and manifested hypersomnolence, dizziness, and small volume liquid stools. The 8.5-hour level was 62 mcg/mL, and she recovered without sequelae. A 2003 case series by Klein-Schwartz presented acute ingestions, mostly in children and adolescents, ranging from 50 mg to 35 g. They noted minimal symptoms of toxicity and no long-term sequelae. Our case is similar to this case series.

Middleton described a suicide by gabapentin overdose in a 62-year-old woman. An autopsy was performed 22 hours after her discovery and overnight refrigeration. She had a postmortem serum gabapentin level of 88 mcg/mL, clonazepam level of 7.7 ng/mL (reference range 10–60 ng/mL), and clonazepam metabolite level of 56 ng/mL (reference range 20–140 ng/mL). The cause of death was certified as gabapentin toxicity. Given the paucity of literature reporting death by gabapentin overdose, comparing drug kinetics in healthy volunteers to postmortem evaluations is challenging. Additionally, there is limited information on drug–drug interactions of gabapentin and clonazepam. This case differs from our patient because our patient survived after a large gabapentin ingestion and a negligible amount of acetaminophen with hydrocodone (verified by remaining pill counts).

Spiller et al reported a case with a gabapentin serum level of 104 mcg/mL in a symptomatic patient with a polydrug overdose including quetiapine. The reported ingestion was much smaller than ours at 54 g. The difference may be due to the times at which the level was drawn and/or unknown drug–drug interactions that may have occurred with the other ingestions. In their case, the ingestion time was unknown, and they did not specify whether the medication was sustained- or immediate-release. We contrast that with our case that featured an isolated drug ingestion rather than a polydrug ingestion.

Our case report has limitations including an unwitnessed ingestion and receiving report from the suicidal patient herself. However, EMS brought in 2 partially filled bottles that were dispensed earlier the same day from which we could compare the volume stated by the patient with remaining pill counts. The patient tried to commit suicide according to herself and her husband. In addition, her serum gabapentin level was high—consistent with the drug's pharmacokinetics for peak serum level, suggesting that she had ingested a large amount of gabapentin.

CONCLUSIONS

Our case highlights the large therapeutic margin for gabapentin relative to other drugs with a very narrow therapeutic window, i.e., opioids. To our knowledge, our case is both the largest reported single-agent gabapentin ingestion by patient admission and the highest documented gabapentin serum level in an acute overdose with minimal acute sequelae and no adverse events as of 3 months from the ingestion period.

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Increase in Suicide by Hanging/Suffocation in the U.S., 2000 –2010

American Journal for Preventive Medicine
Susan P. Baker, MPH, Guoqing Hu, PhD, Holly C. Wilcox, PhD, Timothy D. Baker, MD, MPH
February 2013

Background:

Recently, suicide exceeded motor vehicle crashes as the leading cause of injury death in the U.S. However, details of this change in suicide methods and the relationship to individual demographics, such as age and societal influences, have not been reported.

Purpose:

To determine the characteristics of the changes in suicide rates between 2000 and 2010.

Methods:

Data came from CDC's Web-Based Injury Statistics Query and Reporting System (WISQARS™). Line charts were plotted to reveal changes in suicide rates by fırearm, poisoning, and hanging/suffocation (ICD-10 codes: X72–X74, X60 –X69, and X70). The measure of change used is the percentage change in suicide rate between 2000 and 2010.

Results:

The overall suicide rate increased from 10.4 to 12.1 per 100,000 population between 2000 and 2010, a 16% increase. The majority of the increase was attributable to suicide by hanging/ suffocation (52%) and by poisoning (19%). Subgroup analysis showed: (1) suicide by hanging/ suffocation increased by 104% among those aged 45–59 years and rose steadily in all age groups except those aged Ž70 years; (2) the largest increase in suicide by poisoning (85%) occurred among those aged 60 – 69 years; and (3) suicide by fırearm decreased by 24% among those aged 15–24 years but increased by 22% among those aged 45–59 years. The case fatality rates for suicide by hanging/ suffocation during 2000 –2010 ranged from 69% to 84%, close to those for suicide by fırearm. Analyses were conducted in 2012.

Conclusions:

Substantial increases in suicide by hanging/suffocation and poisoning merit attention from policymakers and call for innovations and changes in suicide prevention approaches.

Introduction

Suicide was recently reported1 to exceed motor vehicle crashes as the leading cause of injury death among Americans. The increasing prevalence of suicide mortality poses a challenge to injury prevention efforts. Unreported are the changes in the epidemiologic characteristics of

suicide, an understanding of which is critical to prevention. The current paper highlights changes in the methods of suicide in the U.S. between 2000 and 2010, particularly in relation to age and methods.

Methods

Data were extracted from the CDC's Web-based Injury Statistics Query and Reporting System (WISQARS™).2 The ICD-10 de-scribes deaths coded as X70 as "intentional self-harm by hanging, strangulation, and suffocation." In the current paper, the cause of these deaths is referred to as "hanging/suffocation," given that suffocation means depriving access to air or oxygen, and a common means of accomplishing this in order to kill oneself is by suspension or hanging. The ICD-10 codes for suicide by fırearm, poisoning, and hanging/suffocation are X72–X74, X60 –X69, and X70, respectively.

The case fatality rate was determined from WISQARS data for mortality and morbidity and was calculated as:

$_3$age-adjusted mortality$_3$/$_3$age-adjusted mortality $_3$

age-adjusted morbidity$_3$ $_3$ 100%.

Morbidity data used in WISQARS Nonfatal Injury Reports were obtained from an expansion of the National Electronic Injury Surveil-lance System (NEISS) that is based on data from approximately 500,000injury-relatedemergencydepartmentcasesyearly. Linecharts were plotted to reveal changes over the period studied in suicide rates per 100,000 population by method for each age group. In addition, the percentage change in rate was used to quantify changes in suicide rates between 2000 and 2010, calculated as:

rate in 2010 $_3$ rate in 2000 $_3$ / $_3$ rate in 2000 $_3$ $_3$ 100%.

A $_3$2 test was used to examine the signifıcance of rate differences. Analyses were conducted in 2012.

Results

In 2010, the 38,364 suicides in the U.S. reflected an overall rate increase of 16% since 2000, from 10.4 to 12.1 per 100,000 population (Table 1). Taken together, suicide by firearm, poisoning constituted 93% of suicide by all methods. Between 2000 and 2010, most of the increase in suicide was due to an increase in hanging/suffocation. The proportion of all suicide by hanging/suffocation increased from 19% to 26% and that by poisoning increased from 16% to 17%. Suicide by firearm remained the predominant type, although the proportion decreased from 56% to 50%.

Detailed examination by population group and method revealed that between 2000 and 2010, suicide rates increased faster for women than for men (percentage change in rates: 26% vs 11%). The rates for whites, Asians, and Native Americans rose by 20%, 12%, and 10%, respectively, and rates among blacks decreased by 6%. The suicide rate increased most among those aged 45-59 years (by 39%); in contrast, it dropped by 8% among the population aged ≥70 years. Suicide by hanging/suffocation increased by 52% for all ages combined, and by poisoning increased by

19%. There was little net change in the rate of suicide by firearm, which decreased slightly between 2000 and 2006 and then increased gradually between 2006 and 2010 (Figure 1).

Changes in method of suicide varied across age groups. Suicide by firearm, which is the most common type, decreased by 24% in the group aged 15-24 years, and increased by 22% in the group aged 45-59 years. For those aged 25-44 years, firearm suicide began to increase substantially in 2006 following a slight decrease during 2000-2006. Between 2000 and 2010, suicide by hanging/suffocation rose by 104% (i.e. more than doubled) for those aged 45-59 years and increased steadily in all other age groups except those aged ≥70 years (Table 1), for whom there was a small decline.

The largest increase in suicide by poisoning (85%) was in the group aged 60-69 years. Rates of suicide by poisoning changed little during these years for some age groups; however, in the groups aged 45-59 years and 60-69 years, rates increased steadily (Figure 1). The case fatality rates for each of three most common suicide methods remained relatively stable. The case fatality rates for suicide by hanging/suffocation were close to those by firearm, ranging from 69% to 84%. In 2010, the case fatality rates were 81% for suicide by firearm, 75% for hanging/suffocation, and 2% for poisoning.

Discussion

The current findings reveal that hanging/suffocation played a major role in the increase in suicide rates between 2000 and 2010. Similar increases through 2005 were reported among whites by Hu et al. in 2008, but few efforts have been made to respond to these changes. Recognition of the changes in suicide methods is important because of the need for preventive measures directed toward this growing problem.

The increase in suicide was evident beginning in 2001, prior to the economic downturn. After 2005, the increase accelerated and may well have been influenced by the effects of the recession. With several notable exceptions, little attention has been given to the methods used in suicide and suicide attempts, although the availability of specific means of self-destruction has been shown to influence both preferred methods and case/fatality rates.

Reductions in availability of firearms, pesticides, and coal gas have been associated with reduced suicide rates. Important reductions have occurred in the lethality of some means, such as motor vehicle exhaust. The choice of means and methods is often influenced by cultural, religious, and social factors. In addition to changes in the availability of means (as in the case of some drugs and medications), changes in the social acceptability of means and methods may also reduce suicide rates. Reporting by the media, as well as other individual and community perceptions, may play a role in shaping social acceptability norms.

Hanging/suffocation is almost as lethal as firearm use as a means of suicide. The lack of an increase in case fatality rates indicates that the increase in mortality rates from suicide by hanging/suffocation is related to an increase in suicide attempts by this method. The dramatic increase in suicide by hanging in the U.S. is of special concern because of the widespread availability of rope and other accessories used in hanging. Prevention strategies that are effective within inpatient settings should be given greater attention for their potential to reduce suicide in other

settings as well. Such strategies include installing break-away closet bars, lowering the height of anchor points, and increasing the awareness of risk indicators.

In the absence of evidence of a trend in assigning suicidal intent to poisoning deaths, it seems reasonable to interpret the increase in suicide by poisoning as being due to the increase in intentional overdoses. Fortunately, the recent attention to the problem of increased fatal overdoses and availability of prescription opioids may result in some reduction in the widespread availability of painkillers, with concomitant decreases in suicide by poisoning.

Conclusion

The recent increases in suicide by hanging/suffocation and poisoning call for innovations and changes in suicide prevention approaches. The revised National Suicide Prevention Strategy released on September 10, 2012 (World Suicide Prevention Day) outlines national priorities for suicide prevention in the next decade. One goal is to promote efforts to reduce access to lethal means of self-harm; however, no proposal has been made to date on how, specifically, to reduce hanging deaths. High-quality research should be supported to develop interventions to curb the rise in suicide by hanging.

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TBI

More Cognitive Deficits, Depression in Former NFL Players

Journal of the American Medical Association: Neurology
Fran Lowry
8 Jan 2013

Cognitive deficits and depression appear to be more common in aging former National Football League (NFL) players compared with healthy controls, a new study finds.

Moreover, the researchers, led by John Hart Jr, MD, from the University of Texas, Dallas, write that these deficits are correlated with white-matter abnormalities and changes in regional cerebral blood flow seen on imaging.

However, the good news is that many former NFL players who took part in the study, even those with extensive concussion histories, are healthy and cognitively normal, Dr. Hart told *Medscape Medical News*.

"In 60% of our participants, most of whom had sustained prior concussions, we found no cognitive problems, no mood problems and no structural brain abnormalities," Dr. Hart said.

This should be reassuring news to the former athletes, he added.

"Many former NFL players think that because they played football or had concussions, they are certain to face severe neurological consequences, but that is not always the case," he said. "What's promising is that we were able to locate and document imaging markers that may account for why some patients develop problems and we may be able to determine who might be at risk for cognitive impairment later in life."

Their findings were published online January 7 in *JAMA Neurology*, formerly the *Archives of Neurology*.

A Pattern of Impairments?

Dr. Hart said he was prompted to do the current study after he started seeing athletes and former NFL players for neurologic evaluation.

"I noticed a pattern of impairments and wanted to formally study the causes and effects, both cognitively and structurally within the brain," he said.

Dr. Hart and his team compared former NFL players with cognitive impairment and depression, cognitively normal retired players who were not depressed, and a group of healthy controls. The players, with and without a history of concussion, were recruited from the North Texas region.

A total of 34 retired NFL players (mean age, 61.8 years) underwent neurologic and neuropsychological assessment. A subset of 26 players also underwent detailed neuroimaging, including fluid-attenuated inversion recovery (FLAIR), hemosiderin scanning, diffusion tensor imaging, and arterial spin labeling.

The results showed that 14 (41%) NFL players had cognitive deficits, including 4 (12%) with fixed cognitive deficits, 8 (24%) with mild cognitive impairment (MCI), and 2 (6%) with dementia.

"In our sample, the number of individuals with dementia was not different than expected in the general population at this age," Dr. Hart noted. "Previous studies have noted a higher incidence of dementia in retired players as they aged. The lower incidence in the present study could be the result of a small, motivated volunteer sample or the higher mean IQ of the participants."

The number of participants with MCI, on the other hand, was slightly higher than that expected in the general population.

Eight (24%) retired players had clinical depression. "This rate was slightly higher than that expected for this age group, which is approximately 15%. This finding underscores the need for screening for depression and cognitive dysfunction in retired athletes," Dr. Hart said.

Among participants who underwent neuroimaging studies, cognitively impaired individuals showed the greatest deficits on tests of naming, word finding, and visual and verbal episodic memory compared with healthy controls ($P < .001$).

The researchers also identified a correlation between cognitive impairment and cerebral white-matter abnormalities.

Among the ex-NFL players with cognitive deficits, depression, or both, FLAIR imaging showed significantly more disrupted integrity in the brain's white matter compared with healthy controls ($P > .05$).

There were also associated brain blood flow changes in those who developed cognitive impairments, providing clues to the active brain changes resulting in deficits, Dr. Hart said.

Fractional anisotropy on diffusion tensor imaging was significantly lower in the ex-NFL players with cognitive impairment, depression, or both, compared with healthy controls ($P < .05$).

What this study does tell us is that it is important to monitor player safety at all levels. Dr. John Hart

Arterial spin labeling studies showed regions in the left inferior parietal lobe, posterior superior temporal gyrus, bilateral midcingulate gyri, and right middle frontal gyrus that demonstrated significant increases in regional blood flow in impaired players compared with healthy controls ($P < .001$).

Dr. Hart and colleagues conclude that their comprehensive and multimodal investigation suggests that retired NFL players may be more likely to develop cognitive impairments or depression as they age than the general population.

Nevertheless, Dr. Hart emphasizes: "Just because a concussion is experienced, this does not mean that cognitive, mood and structural brain differences will develop."

"What this study does tell us is that it is important to monitor player safety at all levels," he concludes. "Return-to-play rules need to be outlined and enacted if a head injury is suspected. Physicians should also add a depression screener to their evaluation of any head injury patient."

A Novel Target

In an accompanying editorial, Ramon Diaz-Arrastia, MD, PhD, and Daniel Perl, MD, from Uniformed Services University of the Health Sciences, Bethesda, Maryland, write that the major finding of the study is that cognitive impairment in ex-NFL players was associated with disrupted white matter.

They add that the main value of this study is that it "potentially identifies a novel target for measuring disease progression and developing therapies."

White-matter disruption, the editorialists note, is not widely recognized as a feature of chronic traumatic encephalopathy, a condition increasingly being recognized as the result of repeated blows to the head.

The findings from this study and others suggest that the use of diffusion tensor imaging may be useful for monitoring the cumulative burden of concussions in athletes and other individuals who have sustained multiple mild traumatic brain injuries.

"It also suggests that axonoprotective or axonoregenerative therapies may be useful for preventing or ameliorating the chronic consequences of TBI [traumatic brain injury]," the editorialists conclude.

The study was supported by the Brain Health Institute for Athletes at the Center for Brain-Health, The University of Texas at Dallas, and from the National Institute on Aging. Dr. Hart, Dr. Diaz-Arrastia, and Dr. Perl have disclosed no relevant financial relationships.

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Dehydroepiandrosterone and Dehydroepiandrosterone Sulfate: Anabolic, Neuroprotective, and Neuroexcitatory Properties in Military Men

Military Medicine
Marcus K. Taylor, PhD
January 2013

ABSTRACT

Evidence links dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) to crucial military health issues, including operational stress, resilience, and traumatic brain injury. This study evaluated the anabolic, neuroprotective, and neuroexcitatory properties of DHEA(S) in healthy military men. A salivary sample was obtained from 42 men and assayed for DHEA(S), testosterone, nerve growth factor (NGF; which supports nerve cell proliferation), and salivary alpha amylase (sAA; a proxy of sympathetic nervous system function). Separate regression analyses were conducted with DHEA and DHEAS as independent variables, and testosterone, NGF, and sAA as dependent variables, respectively. The models explained 23.4% of variance in testosterone ($p < 0.01$), 17.2% of variance in NGF ($p < 0.01$), and 7.4% of variance in sAA ($p = 0.09$). Standardized beta coefficients revealed that DHEA independently influenced testosterone ($\beta = 0.40$, $p < 0.01$), whereas DHEAS independently influenced NGF ($\beta = 0.48$, $p < 0.01$) and sAA ($\beta = 0.36$, $p < 0.05$). DHEA demonstrated anabolic properties, whereas DHEAS demonstrated neuroprotective and neuroexcitatory properties in military men. This area of study has broad implications for stress inoculation, traumatic brain injury rehabilitation, and regenerative medicine in military personnel.

INTRODUCTION

Dehydroepiandrosterone (DHEA) and its sulfate ester dehydroepiandrosterone sulfate (DHEAS) (collectively referred to as DHEA[S]) are cosecreted with cortisol from the adrenal cortex, whereas DHEA is further produced by neurons and glia within the brain. Their precise mechanisms of action are not fully understood. Preclinical evidence suggests that these steroids precurse the sex steroids testosterone and estrogen; confer neuroprotection as a result of antiglucocorticoid/antitoxin action and interaction with neurotrophins; and also stimulate the sympathetic nervous system via both gamma-aminobutyric acid (GABA) inhibition and glutamate activation. Little available data, however, quantify

these properties in humans. A better understanding of these relationships may have broad implications for stress inoculation, traumatic brain injury (TBI) rehabilitation, and regenerative medicine in military personnel. This cross-sectional study examined anabolic, neuroprotective, and neuroexcitatory properties of DHEA(S) in healthy, free-living military men.

DHEA(S) and Steroidogenesis

Perhaps the best known function of DHEA(S) is its role as a weak precursor to the sex steroids testosterone and estrogen as evidenced in the well-characterized human steroidogenesis pathway. Specifically, DHEA is converted via one major pathway to androstenedione, catalyzed by 3β-hydroxysteroid dehydrogenase [HSD]). Androstenedione is then converted to testosterone, catalyzed by 17β-HSD. The strength of relationship between DHEA(S) and testosterone concentrations in humans as evidenced by cerebrospinal fluid, serum, or salivary sampling, is surprisingly understudied. Likewise, the relative contributions of DHEA and DHEAS to testosterone production are not known. There is a need for translational research exploring these relationships in humans.

DHEA(S) and Neuroprotection

Other evident effects of DHEA(S) include neuroprotection, neurite growth, and neurogenesis. Regarding neuroprotection, DHEA(S) is believed to exert prosurvival effects by modulating GABA, glutamate, *N*-methyl-D-aspartate (which mimics action of glutamate), and/or sigma-1 receptors (implicated in brain plasticity); or possibly after it is converted to the sex steroids testosterone and estrogen. Recent preclinical evidence also suggests that DHEA operates in conjunction with and/or via direct action upon members of the neurotrophin family, such as neurotrophin-3, brain-derived neurotrophic factor, and nerve growth factor (NGF). At least two mechanisms describing the DHEA–NGF interface have emerged from the animal literature. In the first, DHEA binds with transmembrane NGF receptors tyrosine kinase-A (TrkA) and p75 neurotrophin receptor ($p75^{NTR}$) on target cells, the balance of which ignites a sequence of events modulating expression and function of proteins governing apoptosis (i.e., cell death

Evidence that DHEA binds directly to these receptors and prevents neuronal apoptosis has been shown in sensory neurons and sympathetic neurons in mice and rats, respectively. As Lazaridis et al stated (p. 10), the “decision between survival and death” among DHEA-responsive cells is determined by the balance of DHEA's interaction with these two receptors. In the second mechanism, DHEA is believed to upregulate NGF messenger RNA (mRNA) expression in target cells. Evidence for this fascinating process has been shown in primary rat hippocampal cultures, whereby DHEA upregulated NGF mRNA after 3 hours of exposure while opposite effects were noted for the stress hormone cortisol. This latter observation is consistent with the frequently reported but imperfectly understood antagonistic relationship between DHEA(S) and cortisol. Studies addressing relationships between DHEA(S) and NGF in humans are sparse. In one exception, Schulte-Herbrüggen et al showed no relationships between serum DHEAS and NGF concentrations in a study of 40 pregnant women. To this author's knowledge, the DHEA(S)–NGF association has not been quantified in healthy human male populations.

DHEA(S) and Neuroactivation

DHEA(S) is also believed to have neuroexcitatory properties, in part because of negative modulation of GABA, the chief inhibitory neurotransmitter in the mammalian nervous system that acts principally on norepinephrine, epinephrine, and neuroendocrine systems. Specifically, animal models

suggest that DHEA(S) interacts with the $GABA_A$ receptor complex on target neurons throughout the brain and central nervous system, inhibiting GABA-mediated neurotransmission, thus initiating a net "excitatory" effect.[7] Some of these studies further suggest that DHEAS modulates this receptor complex with greater potency than DHEA. Direct relationships between DHEA(S) and sympathetic nervous activity in humans are not well-characterized.

DHEA(S) Applications in Military Populations: Operational/Traumatic Stress and TBI

Recent studies demonstrate stress inoculation effects of endogenous DHEA(S) during military stress, specifically evidencing buffered acute stress symptoms and/or performance maintenance. Morgan et al, for example, showed that plasma DHEA(S) correlated to improved performance and fewer dissociative symptoms in a stressful underwater navigation exam in military members enrolled in a combat diver qualification course. Regarding exogenous (administered) DHEA, Taylor et al recently found that a brief, low-dose DHEA regimen yields dramatic increases in salivary DHEA(S) concentrations and enhances anabolic balance during military stress, but no effects were observed with respect to subjective distress.

Animal models also suggest exciting potential use for DHEA supplementation in the clinical treatment of TBI. Hoffman et al demonstrated in a rat model that delayed administration of DHEAS improves behavioral performance recovery from induced TBI on both sensory and cognitive tasks. Likewise, Malik et al showed convincing effects of a DHEA analogue (fluasterone) in improving functional recovery (e.g., balance, neurological reflexes) from induced TBI.

In sum, preclinical evidence suggests anabolic, neuroprotective, and neuroexcitatory effects of DHEA(S), but few studies have quantified these relationships in humans. The current study was designed to evaluate the anabolic, neuroprotective, and neuroexcitatory properties of DHEA(S) in healthy military men. Accordingly, it was hypothesized that DHEA(S) would positively associate with the anabolic hormone testosterone, the neurotrophin NGF, and the sympathetic analogue salivary alpha amylase (sAA).

METHODS

Subjects

Subjects included 42 healthy, male, active duty Navy and Marine Corps personnel (mean ± SD age 26.4 ± 4.6 years) who had reported to Naval Air Station North Island to begin Survival, Evasion, Resistance, and Escape (SERE) training. This same sample was also studied in a prospective evaluation of DHEA supplementation during survival training, and those findings are reported elsewhere. Subjects who were deemed medically fit to undergo SERE training and were enrolled in the SERE course were thus considered eligible for the current study, with two exceptions: women were excluded because of health concerns associated with DHEA supplementation, as were individuals who endorsed taking any anabolic or ergogenic supplement within the past 3 months or who were currently taking any over-the-counter medications. Those who expressed an interest in participating attended an in-person meeting to review the details of the study and provide written informed consent. This protocol was approved by the Naval Aerospace Medical Research Laboratory Institutional Review Board.

Salivary Sampling

For this study, a single salivary sample was obtained via the passive drool method between 1145 and 1247 under baseline, free-living conditions on the first day of academic (classroom) instruction for military survival training. Each subject was asked to rinse his mouth with water approximately 10 minutes before sample collection and to avoid the following: brushing teeth before collection, using salivary stimulants (e.g., gum, lemon drops), and consuming acidic or high-sugar foods within 20 minutes before collection. After data collection, all samples were immediately placed on dry ice and transferred to Salimetrics, LLC (State College, Pennsylvania) for storage and data processing. Samples were assayed for DHEA, DHEAS, testosterone, NGF, sAA, and cortisol.

DHEA and DHEAS

All samples were assayed for salivary DHEA in duplicate using a highly sensitive enzyme immunoassay. The test uses 50 µL of saliva per determination, has a lower limit of sensitivity of 5 pg/mL, standard curve range from 10.2 pg/mL to 1,000 pg/mL, an average intra-assay coefficient of variation of 5.6%, and an average interassay coefficient of 8.2%. Method accuracy determined by spike recovery averaged 102.2%, and linearity determined by serial dilution averaged 106.9%. The serum–saliva correlation for DHEA in a combined male/female normative database (Salimetrics, LLC) is high ($r = 0.86$, $p < 0.0001$, $n = 39$). Mean ± SE DHEA concentrations were 229.7 ± 14.7 pg/mL.

Similarly, samples were assayed for salivary DHEAS in duplicate using a highly sensitive enzyme immunoassay. The test uses 100 µL of saliva per determination, has a lower limit of sensitivity of 43 pg/mL, standard curve range from 189 pg/mL to 15,300 pg/mL, an average intra-assay coefficient of variation of 7.3%, and an interassay coefficient of variation of 7.6%. Method accuracy determined by spike recovery averaged 105.9%, and linearity determined by serial dilution averaged 98.2%. Mean ± SE DHEAS concentrations were 4390.8 ± 403.9 pg/mL.

Testosterone

This assay was performed in duplicate using a highly sensitive enzyme immunoassay. The test uses 25 µL of saliva per determination, has a lower limit of sensitivity of 1.0 pg/mL, standard curve range from 6.1 pg/mL to 600 pg/mL, an average intra-assay coefficient of variation of 4.6%, and an average interassay coefficient of variation of 9.8%. Method accuracy determined by spike recovery averaged 104.3% and linearity determined by serial dilution averaged 102.4%. Serum–saliva correlations from a normative database (Salimetrics, LLC) of male subjects is high ($r = 0.91$, $p < 0.001$, $n = 26$). Mean ± SE testosterone concentrations in this sample were 120.2 ± 5.6 pg/mL.

Nerve Growth Factor

This assay was performed in triplicate using a highly sensitive enzyme immunoassay. The standard curve measured NGF from 3.9 to 250 pg/mL. The assay has an intra-assay precision of 14.5% and an interassay precision of 15.5%. Recovery of NGF added to saliva samples averaged 95.3%. Linearity ranged from 82.3 to 127.2%. Mean ± SE NGF concentrations in this sample were 88.7 ± 13.3 pg/mL.

Alpha Amylase

Though mainly involved in starch digestion in the oral cavity, sAA increases under physically and psychologically stressful conditions and is a correlate of sympathetic nervous activity. In this study, all samples were assayed via kinetic reaction. The assay employs a chromogenic substrate, 2-chloro-*p*-nitrophenol, linked to maltotriose. The enzymatic action of alpha amylase on this substrate yields 2-chloro-*p*-nitrophenol, which is spectrophotometrically measured at 405 nm using a standard laboratory plate reader. The amount of alpha amylase activity present in the sample is directly proportional to the increase (over a 2-minute period) in absorbance at 405 nm. Results are computed in units per milliliter of alpha amylase using the formula: [Absorbance difference per minute × total assay volume (328 mL) × dilution factor (200)]/[millimolar absorptivity of 2-chloro-*p*-nitrophenol (12.9) × sample volume (0.008 ml) × light path (0.97)]. Intra-assay variation computed for the mean of 30 replicate tests was less than 7.5%. Interassay variation computed for the mean of average duplicates for 16 separate runs was less than 6%. Mean ± SE sAA concentrations were 101.6 ± 15.5 U/mL.

Cortisol

All samples were assayed for salivary cortisol in duplicate using a highly sensitive enzyme immunoassay. The test uses 25 µL of saliva per determination, has a lower limit of sensitivity of 0.003 µg/dL, standard curve range from 0.012 µg/dL to 3.0 µg/dL, an average intra-assay coefficient of variation of 3.5%, and an average interassay coefficient of variation of 5.1%. Method accuracy determined by spike recovery averaged 100.8%, and linearity determined by serial dilution averaged 91.7%. Serum–saliva correlations from a normative database show the expected strong linear relationship, ($r = 0.91$, $p < 0.0001$, $n = 47$). Mean ± SE cortisol concentrations were 0.13 ± 0.9 µg/dL.

Data Analysis

Preliminary analysis incorporated the use of normal probability and residual plots to assess compliance with the assumptions of linear regression. These plots revealed that NGF and sAA were positively skewed. These analytes were then log-transformed, which normalized each distribution. Next, bivariate correlations explored relationships between independent variables (DHEA and DHEAS), dependent variables (testosterone, NGF, and sAA), and potential covariates (age, body mass index [BMI], years of military service, sampling time, and salivary cortisol concentrations). Finally, to quantify the unique and combined influence of DHEA and DHEAS on each endpoint, separate multiple linear regression analyses were conducted with DHEA and DHEAS as independent variables, and testosterone, NGF, and sAA as dependent variables, respectively. Where warranted, covariates were included in the model. Where applicable, hypothesis tests were based on log-transformed data; untransformed means are reported for ease of interpretation. All hypothesis tests were two-sided and the probability of committing a type I error was set at 0.05. It was acknowledged when more stringent conventional alpha levels were achieved ($p < 0.01$ or $p < 0.001$).

RESULTS

Subject Characteristics

Mean ± SE age, BMI, and years of military service for this sample were 26.4 ± 0.7 years, 26.3 ± 0.6 kg/m^2, and 5.7 ± 0.7, respectively. Most subjects were Caucasian (78.6%). More than half had a high school education (57.1%), whereas the remainder possessed a 4-year or advanced degree. A broad cross section of military occupational specialties was represented. Combat experience was endorsed by 42.9% of subjects.

Selection of Covariates

Covariates are typically selected based on a theoretically supported influence upon the dependent variable of interest. Age ($r = -0.33$, $p < 0.05$), education level ($\rho = -0.41$, $p < 0.01$), and years of military service (-0.43 $p < 0.01$) were associated with lower salivary testosterone concentrations. As expected, years of military service was highly correlated to (and presumably a function of) age ($r = 0.83$, $p < 0.001$). Thus, age and education were selected as covariates in the regression model examining testosterone as the dependent variable. Sampling time (which was restricted to a 1-hour time frame, detailed above) did not influence any of the end points (all $p > 0.05$), nor did salivary cortisol concentrations (all $p > 0.05$). Thus, neither was included as a covariate in the regression models.

Anabolic, Neuroprotective, and Neuroactive Effects of DHEA(S)

In the first regression model, the independent variables (DHEA and DHEAS) and covariates (age and education) combined to explain 23.4% of variance in testosterone ($F = 4.0$, $p < 0.01$). Inspection of the standardized beta coefficients revealed that DHEA exerted an independent effect on testosterone ($\beta = 0.40$, $p < 0.01$), whereas the other predictors were not significant.

In the second regression model, the independent variables (DHEA and DHEAS) combined to account for 17.2% of variance in NGF ($p < 0.01$). Inspection of standardized beta coefficients showed that DHEAS exerted an independent effect on NGF ($\beta = 0.48$, $p < 0.01$), whereas DHEA was not significant. The unadjusted bivariate association of DHEAS to log-transformed NGF>. In the third regression model, DHEA and DHEAS explained 7.4% of variance in sAA ($p = 0.09$). Inspection of standardized beta coefficients demonstrated that DHEAS independently influenced sAA ($\beta = 0.36$, $p< 0.05$), whereas DHEA was not significant..

DISCUSSION

This study characterized anabolic, neuroprotective, and neuroactive properties of DHEA and DHEAS in military men. Salivary DHEA and DHEAS combined to substantially predict salivary testosterone, NGF, and, to a lesser extent, sAA concentrations. Moreover, DHEA independently influenced testosterone, whereas DHEAS independently influenced NGF and sAA.

The first model clarified an independent relationship of DHEA to testosterone, whereas DHEAS did not contribute significantly. This finding is consistent with the theorized role of DHEA as a precursor to the sex steroids, as reflected in the human steroidogenesis pathway and empirically supported throughout the preclinical literature. As noted earlier, DHEA is converted to androstenedione, which is then converted to testosterone. The observed strength of relationship suggests a central role of DHEA in the production of testosterone irrespective of age or educational level. It further suggests that its sulfated version—DHEAS—may not play a direct functional role in this process. More research is needed to characterize this relationship across sexes, under acute and chronic stress, and in clinical conditions such as posttraumatic stress disorder, TBI, and metabolic syndrome.

In the second model, an independent relationship of DHEAS to NGF was suggested, whereas DHEA did not contribute significantly. This finding differs from that of Schulte- Herbrüggen et al's human study showing no relationship between DHEAS and NGF in 40 pregnant women (who would

possess different hormonal profiles). As alluded to earlier, at least two possible mechanisms are supportive of an active relationship between DHEA(S) and NGF. In the first, DHEA(S) binds with NGF TrkA and $p75^{NTR}$ receptors to regulate apoptosis of target cells (e.g., sympathetic and sensory neurons). In the second, DHEA upregulates NGF mRNA expression in target cells (e.g., hippocampal cells). The first mechanism suggests shared biological "action" of DHEA(S) and NGF, whereas the second suggests that DHEA(S) may mediate the "production" of NGF. Specifically, mRNA is transcribed from a DNA template within the nucleus and then carries coding information to the ribosomes for protein synthesis. Although the observed positive association of DHEAS and NGF is supportive of this latter mechanism, the cross-sectional design and noninvasive methodology of this study preclude definitive conclusions.

The third model suggested an independent influence of DHEAS on sAA, whereas DHEA did not contribute significantly. Produced in the oral cavity, sAA is described as a reliable correlate of circulating catecholamines, particularly norepinephrine, under both baseline and stress-induced conditions. Thus, it is advocated as a noninvasive and easily obtained salivary analogue of sympathetic tone. The neuroexcitatory effects of DHEA(S) are believed to emanate partly from its role as a negative modulator of GABA (discussed earlier), which inhibits both norepinephrine and epinephrine. Inhibition of GABA-mediated neurotransmission, then, initiates a net excitatory effect. That DHEAS associated more substantially with sAA in this study complements some animal studies suggesting that DHEAS modulates the $GABA_A$ receptor complex with greater potency than DHEA. Interestingly, negative modulators of the $GABA_A$ receptor complex typically possess anxiogenic (i.e., anxiety-inducing) qualities, but this does not appear to be the case for DHEA(S). Several studies, in fact, document anxiolytic (i.e., anxiety-reducing) effects of DHEA(S) in chronically stressed individuals, which some authors attribute to its previously mentioned antiglucocorticoid properties.

Limitations of this study should be addressed. First, this translational study involves measurement of peripheral hormone concentrations in humans. Concentration of a given hormone, however, lacks precise mechanistic information regarding its functional status (e.g., action on target receptors). Also, a single sample gives limited information in analytes known to possess a diurnal rhythm. Testosterone, cortisol, and DHEA typically peak shortly after waking and reach a nadir in the evening. By contrast, sAA typically reaches a nadir approximately 30 minutes after awakening and then steadily increases throughout the day. DHEAS remains relatively stable across the day, whereas the diurnal pattern of NGF is not well understood. To mitigate this limitation, sampling occurred at a time point during which dramatic fluctuation is not expected, and was restricted to a single hour. Statistical analyses further showed that sampling time (within the single hour) did not associate with salivary concentrations of any of the analytes. Regardless, prospective studies evaluating these relationships across the diurnal cycle could provide more nuanced information.

In summary, this study examined unique and shared relationships of DHEA and DHEAS to biomarkers of anabolic, neuroprotective, and sympathetic nervous activity. It was demonstrated that DHEA and DHEAS possess anabolic, neuroprotective, and neuroexcitatory properties in military men, yet they appear to have distinct relationships with each end point. Thus, separate study of DHEA and DHEAS activity is warranted. This work has broad implications for stress inoculation, TBI rehabilitation, and regenerative medicine in military personnel. For example, DHEA(S)' antiglucocorticoid properties may help military personnel not only to buffer acute stress reactions but also to manage the deleterious effects of chronic stress which may include immunosuppression, depression, fatigue, cognitive decline, and sleep disruption. Likewise, the observed link between DHEAS and NGF is particularly exciting with respect to potential advancements in TBI treatment as well as regenerative medicine for sensory and sympathetic systems. The association of DHEAS to sAA (the sympathetic analogue) may have less obvious clinical implications;

coupled with its known covariance with cortisol, this may allude to a protective role within the complex, coordinated “fight or flight” response. Together, these relationships highlight the importance of not only characterizing endogenous DHEA(S) but also the potential impact of DHEA(S) supplementation in military personnel. In this author's view, well-designed randomized controlled trials documenting its efficacy and pinpointing its risks and side effects are needed to realize its preventive and therapeutic potential.

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Occurrence of Secondary Insults of Traumatic Brain Injury in Patients Transported by Critical Care Air Transport Teams From Iraq/Afghanistan: 2003–2006

Military Medicine
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Abstract

Traumatic brain injury patients are susceptible to secondary insults to the injured brain. A retrospective cohort study was conducted to describe the occurrence of secondary insults in 63 combat casualties with severe isolated traumatic brain injury who were transported by the U.S. Air Force Critical Care Air Transport Teams (CCATT) from 2003 through 2006. Data were obtained from the Wartime Critical Care Air Transport Database, which describes the patient's physiological state and care as they are transported across the continuum of care from the area of responsibility (Iraq/Afghanistan) to Germany and the United States. Fifty-three percent of the patients had at least one documented episode of a secondary insult. Hyperthermia was the most common secondary insult and was associated with severity of injury. The hyperthermia rate increased across the continuum, which has implications for en route targeted temperature management. Hypoxia occurred most frequently within the area of responsibility, but was rare during CCATT flights, suggesting that concerns for altitude-induced hypoxia may not be a major factor in the decision when to move a patient. Similar research is needed for polytrauma casualties and analysis of the association between physiological status and care across the continuum and long-term outcomes.

Introduction

Traumatic brain injury (TBI) is considered a signature injury of current military operations. The care of patients suffering a severe TBI is complex, as patients who survive the primary trauma are susceptible to secondary insults to the injured brain. Secondary insults, which are a delayed, physiologic response to the primary injury, are associated with worse short- and long-term outcomes. Over one-third of the patients transported by Critical Care Air Transport Teams (CCATTs) since the start of Operation Iraqi Freedom and Operation Enduring Freedom in Afghanistan have suffered a TBI. The CCATT, which comprised a physician with critical care experience, a critical care nurse, and a respiratory therapist, transports severely ill and injured patients on aeromedical evacuation (AE) flights from the area of responsibility (AOR;Iraq/Afghanistan) to Germany and the contiguous United States (CONUS). During the continuum of care from the AOR to CONUS, casualties pass through multiple hospitals and

undergo flights lasting from 8 to 14 hours onboard a military cargo aircraft. The austere AE environment poses challenges to the monitoring and care of patients with severe TBI, and the stresses of flight can potentially contribute to secondary neurological insults.

Explosive blast injuries create a complex clinical profile that may differ from penetrating or closed head injuries. This different profile and the prolonged transport results in a patient population that is different from patients injured in the civilian setting. No studies have examined the occurrence or timing of secondary insults in TBI in severely injured patients as they move across the continuum of care.

The secondary insults selected for analysis in this study were based on two considerations. First, a literature review identified secondary insults associated with the worse outcomes in patients with TBI. This information was then considered relative to the data collected as a routine part of care across the continuum. On the basis of these considerations, the following secondary insults were studied: hypoxia, hypotension, hyperthermia, hypothermia, and hyperglycemia. Year of transport was studied to control for potential changes in practice over time. Two aircrafts, the C-141 and C-17, were used between 2001 and 2006. It was not known whether the characteristics (e.g., noise, temperature, ambient lighting, and patient access) in the cargo compartment of these aircraft might affect the occurrence of secondary insults.

In patients with isolated TBI who were transported by CCATTs, the specific aims of this study were to (1) describe the occurrence of secondary insults (hypoxia, hypotension, hyperthermia, hypothermia, and hyperglycemia) and (2) determine if the occurrence of secondary insults was associated with severity of injury (Injury Severity Score [ISS] and Abbreviated Injury Score [AIS]), mechanism of injury (blast vs. nonblast), type of aircraft used for transport (C-17 vs. C-141), and year of injury (2003–2006).

Methods

A descriptive retrospective cohort study was undertaken following permission from the Institutional Review Board at the University of Maryland. Patients with isolated TBI (single body system injured) were identified from the Wartime Critical Care Air Transport Database (WCCATD),4 which allowed for identification of the frequency and timing of the secondary insults. Additional demographic and physiological data were also collected to characterize type and severity of injury. During post hoc analysis, hypertension, a potential sequela of TBI, and blood transfusions were also analyzed. Operational definitions of the variables used in this study can be found in Table I. This study followed patients through five time periods (or legs): leg 1, point of injury to AOR military medical treatment facility (AOR MTF); leg 2, care while at the AOR MTF; leg 3, CCAT from the AOR to Landstuhl Regional Medical Center in Germany (LRMC); leg 4, care while at LRMC, and leg 5, CCAT from LRMC to CONUS.

The WCCATD integrates data from multiple sources, including the Transportation Command and Control Evacuation System, CCATT Mission Reports, Joint Theater Trauma Registry, and a retrospective review of medical records from the AOR, LRMC, CCATT transports, and two CONUS MTFs (Walter Reed Army Medical Center, Washington, DC and National Naval Medical Center, Bethesda, Maryland). The entire database contains information on patients transported by USAF CCATT in support of Operation Enduring Freedom/Operation Iraqi Freedom from October 2001 through May 2006.4

Subjects in this study included any patient with a TBI or head injury who did not have any other body area injured except for minor abrasions, lacerations, or digit amputations and were transported by a CCATT. Patients with isolated TBI were used to explore secondary insults associated

with TBI while minimizing confounding variables found in patients with polytrauma. All eligible patients, aged 18 years and older, were included. Three patients with no physiologic study variables recorded were excluded, resulting in a sample size of 63 patients.

Missing variables are a common problem when using administrative data. Although there are missing data in the WCCATD, it is the only known database that has comprehensive data reflecting the patients' physiologic status and care across the continuum, including CCATT transport. To control for missing data, pairwise deletion was used when necessary.

Descriptive statistics were used to analyze the demographic data and the occurrence of secondary insults. A logistic regression model was used to analyze the binary occurrence for each secondary insult as the dependent variable with the independent variables of severity of injury (AIS), mechanism of TBI, type of aircraft, and year of occurrence.

Results

Sixty-three patients were included in this study. The demographic characteristics of these patients are summarized in Table II. Fifty-three percent of the injuries were caused by blasts. The mean ISS was 17 ± 8. Eighteen patients had a severe injury (ISS > 15) and 18 had a critical injury (ISS > 25). To avoid the potential confounding effect of facial trauma along with head trauma on the ISS, the AIS for head trauma was also analyzed. The AIS ranged from 1 to 5, with a mean AIS of 3.5 ± 1.2 (median 3), with 84% of the patients with a serious or critical head injury (AIS ≥ 3). The Glasgow Coma Scale (GCS) score was recorded for 60 patients in leg 1, and 41% of the patients had a GCS = 3; however, it was not clear if this GCS was obtained before or after intubation, which limits the utility of the GCS as an indicator of the severity of injury. Thirty-five patients had intracranial pressure (ICP) monitoring during at least one leg of care (total 64 legs where ICP was monitored). There was a documented occurrence of ICP > 20 mmHg during 27/64 (42%) legs, but in only one case was there a clinically significant increase in ICP during flight (leg 3) compared to preflight (leg 2). Although the WCCATD encompasses the period from October 2001 through May 2006, the earliest patient who met inclusion criteria for this study was injured in December 2002, with all the remaining patients transported in 2003 to 2006. For simplification, the patient transported in 2002 was analyzed with the data from 2003. Seventy-seven percent of the patients were injured in 2004 and 2005. The average time from injury to LRMC was 2.3 ± 2.2 days, with the median decreasing from 2.5 days in 2003 to 1 day in 2005 and 2006. The mean time from point of injury to arrival in CONUS was 6.8 ± 4.3 days, with the median days from injury to CONUS arrival decreasing from 8 days in 2003 and 2004 to 3.5 days in 2006. The ISS, AIS, age, and mechanism of injury did not vary by year.

The primary aircraft used for CCATT transports from 2001 to 2006 were the C-141 and the C-17. There was an approximately equal distribution of C-141 and C-17 aircraft used for transports from AOR to LRMC and from LRMC to CONUS. The C-141 was the primary aircraft for CCATT transport between 2001 and 2004. In 2005, the last C-141 was retired, and the C-17 became the primary aircraft for transport.

Fifty-three percent of the patients had at least one documented episode of a secondary insult. Hyperthermia was the most frequent (47%) secondary insult. There were 51 patients with oxygen saturation (SpO2) measurements. Among these patients, 13 (25%) had at least one episode of hypoxia. Eleven patients (17%) had at least one episode of hypotension and 17 patients (27%) had at least one episode of hypertension. The secondary insults with the lowest recorded frequency were hyperglycemia (13%) and hypothermia (8%).

Secondary insults were also examined by leg, which generally equates to time since injury (Table III). Hyperthermia was the secondary insult with the highest rate of occurrence for all legs except leg 2, ranging from 21 to 41%. The occurrence of hyperthermia increased over legs 2 through 5. Hypoxia was the most frequent secondary insult during leg 2 (AOR MTF).

Combinations of secondary insults were also explored.13,18,19 Twenty patients had documented combinations of secondary insults. The combinations of hyperthermia and hypoxia (n = 5) and hyperthermia and hypotension (n = 5) were the most common combinations documented. The combinations of hypotension and hyperthermia were the only insults documented during CCATT flights from the AOR to LRMC, whereas hypoxia and hyperthermia were the only insults documented during CCATT flights from LRMC to CONUS.

To better understand what factors may influence the occurrence of secondary insults, logistic regressions predicting any secondary insults were modeled with four independent variables: AIS, blast vs. nonblast injury, year of injury, and the aircraft used for transport from the AOR to LRMC. The model predicting hyperthermia was the only significant model ($\chi 2(4, N = 63) = 13.5, p < 0.05$). The AIS was the only significant predictor of hyperthermia (odds ratio [OR] = 2.3; 95% confidence interval [CI] = 1.3, 4.2), indicating that for every one point increase in AIS, patients were 2.3 times more likely to have documented hyperthermia, controlling for other factors in the model (Table IV). Hyperthermia was not associated with blood product administration.

Discussion

Several findings from this study add to our understanding of this unique patient population. First, over half the patients had at least one documented episode of a secondary insult, which is similar to the rates found in civilian studies (Table V). Compared to Mason's study6 of 113 patients transported by CCATTs in 2005–2006 from Iraq to LRMC, more patients in this current study underwent ICP monitoring and had a higher incidence of increased ICP (>20 mmHg). However, it was not possible to separate out the patients with isolated TBI in Mason's study to allow for comparison of the incidence of secondary insults. Second, hyperthermia was the most common secondary insult, with the occurrence rate increasing from leg 1 to leg 5. All other secondary insults had the highest occurrence rates documented while the patients were in the AOR. Finally, there was a decrease in median days from injury to arrival at LRMC and CONUS between 2003 and 2006. However, no significant differences in the documented occurrence of secondary insults were found by year or between the type of aircraft used for CCATT transport.

Forty-seven percent of the patients in this study suffered hyperthermia during at least one leg, compared to 73% reported in the first week post-TBI in civilian patients.21 The difference may be related to variations in documentation as the acuity of the patients is similar. Hyperthermia in the acute period after brain injury may be caused by post-traumatic cerebral inflammation, direct hypothalamic damage, or altered sympathetic tone.22,23 Hyperthermia exacerbates the cellular mechanisms of secondary injuries, and is associated with increased ICP24–26 and worse neurological outcomes.11 Of note, among the 35 patients in this study who had ICP monitoring, there was no association between hyperthermia and intracranial hypertension. Hyperthermia was the only secondary insult for which occurrence rates increased across the continuum of care (Table III), which may reflect a transition from postinjury inflammation and neurological dysfunction to infection. The likelihood of this transition is supported by the finding that among 408 patients with neurological injury admitted to Walter Reed Army Medical Center between 2001 and 2006, 46% had systemic infection and 9% had a CNS infection.27 The cause of hyperthermia is an important treatment consideration. For example,

antipyretic agents rely on intact thermoregulation and may not be effective in patients with neurogenic injury.23 The timing of the onset of hyperthermia also has implications for the initiation of targeted temperature management and the continuation of this therapy during flight. The clinical utility, feasibility, and safety of actively cooling a patient during flight must be carefully considered.23,28–32

The occurrence rate of hypoxia documented in this study was also consistent with civilian studies (Table V).11–13,14 Hypoxia was documented most commonly during leg 2 (26%), which is consistent with the acute phase reported in the literature. There were no documented cases of hypoxia during the CCATT flights from the AOR to LRMC; however, 14% of the patients who had SpO2 values recorded during the CCATT flights from LRMC to CONUS suffered hypoxia. Therefore, CCATT providers should closely monitor the oxygenation status of their patients, even if the patients have had no previous hypoxic episodes.

Hypotension was documented in 17% of the patients, which is in the range (3–68%) reported in civilian literature (Table V). Hypotension was most often documented during leg 2 (care at AOR MTF) and most likely reflects the early stage of resuscitation. It is possible that there was a higher occurrence during leg 1; however, there was a recording bias in the data as there was no systematic capture of vital signs during this phase of care during 2001–2006.

Early hyperglycemia exacerbates secondary brain injury,33,34 and it is an independent predictor of mortality in TBI.33,35,36 Although a single-channel point-of-care glucose monitor (i-STAT; Abbott, Abbott Park, Illinois) is approved for use in flight and far-forward operating areas, in this study, documentation of blood glucose outside the MTF seldom occurred. Of the 47 patients with documented blood glucose levels, the occurrence rate of hyperglycemia was 13% compared to the 28–42% found in the civilian studies (Table V).12,20 The low occurrence rate in this study may be due to limited monitoring and/or missing documentation. In patients with documented hyperglycemia, there was no documentation of insulin administration, which suggests missing data. The possible lack of monitoring or documentation is an area for improvement, as a glucose < 60 mg/dL or ≥160 mg/dL during the first 24 hours after TBI is associated with worse outcomes independent of the severity of the injury.35 In addition, tight glycemic control (glucose 80–110 mg/dL) is also associated with worse outcomes.37 The need for control of blood glucose emphasizes the need for consistent monitoring and documentation of glucose across the continuum.

Hypothermia had the lowest documented occurrence rate (8%), which is consistent with the 5–26% rate reported in civilian studies (Table V).12,13,16,17 In this study, hypothermia was documented most frequently during leg 2 (care at AOR MTF), which may reflect the early phase of resuscitation. The low occurrence rate may also reflect recording bias as described above. Another factor that may have affected the occurrence of hypothermia was the implementation in 2004 of the Joint Theater Trauma System Hypothermia Prevention Clinical Practice Guideline, which led to a system-wide effort to prevent hypothermia. Based on a study of the thermal characteristics of the cargo compartment of the C-141 and C-17, the average temperature was 59°F and 55°F, respectively (E. Bridges, personal communication). Despite this rigorous thermal environment, results of this study suggest actions to prevent hypothermia during CCATT transport are effective as there were no documented episodes of hypothermia during leg 3 or leg 5.

There were no differences in the occurrence of secondary insults based on the mechanism of injury. The documentation in the medical records does not allow for differentiation of the various types of head trauma. Specifically, it was not possible to isolate the effect of a primary blast injury

vs. secondary or tertiary blast trauma (penetrating or blunt injury). These various mechanisms of injury may be associated with different clinical outcomes. Further research and refinement of the differentiation of the cause of brain injury may allow for tailored care across the continuum to minimize secondary insults and TBI sequelae, such as post-traumatic vasospasm.10,38,39

The question remains, when is the best time to transport a patient with a severe TBI? This study is the first to describe the incidence and timing of secondary insults across the continuum of care and allows us to consider current literature regarding these unique patients and en route care. Fang7 noted that the first crucial decision in CCATT mission planning is the timing of patient movement. He reviews the factors that contribute to this decision, including consideration of the effect of the stresses of flight (e.g., hypoxia, gas expansion, vibration, noise) on the patient and logistical considerations including availability of aircraft, military operational considerations, and weather. He also notes that because peak brain edema occurs during postinjury days 3 to 5, transfer is avoided during this time if control of ICP is problematic.

Goodman9,40 describes the potential exacerbation of the neuroinflammatory response to TBI by altitude-induced hypobaric hypoxia. An animal model,40 found that early hypobaric hypoxia exposure (3 hours after TBI) was associated with increased cerebral cytokine expression and severity of brain injury in contrast to delayed hypoxia exposure (24 hours after TBI). However, there are no data on the effects of hypobaric hypoxia during intermediate periods (i.e., 12 or 18 hours after TBI). Two factors need to be considered when evaluating the implications of Goodman's40 study. First, oxygen was not administered, so it is not known if the effect of altitude-induced hypoxia can be ameliorated with supplemental oxygen. In the patients in this study with documented SpO2 measurements, 9/35 (26%) had a hypoxic event during leg 2 (AOR MTF). In contrast, there were no documented cases of hypoxia during the flight from the AOR to LRMC (leg 3) and 3/22 (14%) of patients had a documented episode of hypoxia during the flight from LRMC to CONUS (leg 5). The veracity of these results are supported by a similar low incidence rate of hypoxia during leg 3 in Mason's study6 of a 113 trauma and medical patients transported by CCATTs from the AOR to LRMC in 2005–2006. The relatively low incidence of hypoxia during flight suggests that concerns for altitude-induced hypoxia may not be a major factor in the decision when to move a patient as long as supplemental oxygen is available and SpO2 is carefully monitored. Second, the median time from injury to arrival at LRMC decreased from 2.5 days in 2003 to 1 day in 2005–2006, which is similar to the results of a study by Mason6 where the mean time from injury to CCATT flight was 28 hours (median: 27.6 hours; range: 8.0–68.3 hours). Based on the timing of transport, it is possible that some patients in these studies were transported during the early critical phase as described by Goodman. In total, these articles suggest a narrow window for transport (i.e., after the acute period of susceptibility to the effects of hypobaric hypoxia and before peak edema).

The occurrence of secondary insults may be underreported in this study. Despite this limitation, the results of this study suggest that safe transport can be provided for this unique patient population. This assertion is supported by Mason's study,6 which found similar results regarding safe CCATT transport.

Conclusion

This is the first study to describe the occurrence rates of secondary insults in patients with TBI as they move across the continuum of care. A better understanding of secondary insults in patients with TBI may inform preventive measures and contribute to improved outcomes for these unique military combat casualties. Similar analysis of patients with polytrauma is ongoing. The results of this study, in concert with current

literature, suggest a window for safe transport and the need for preventive or protective interventions specific to the needs of these patients within the context of the continuum of care. Efforts are needed to systematically integrate data from all points along the care continuum into one data source and to link the patient's physiological status and care across the continuum with long-term outcomes.

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Other

Unintended Pregnancy Among Active-Duty Women in the United States Military, 2008

Obstetrics & Gynecology
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February 2013

OBJECTIVE: To estimate unintended pregnancy rates among a representative sample of 7,225 active-duty women in the U.S. military in 2008 and to compare these rates with 2005 and with the U.S. population.

METHODS: Cross-sectional data came from the 2008 Department of Defense Survey of Health Related Behaviors among Active Duty Military Personnel (Health Related Behaviors Survey). For all women and by key subgroups, unintended pregnancy rates per 1,000 women were calculated and compared with rates reported in the 2005 Health Related Behaviors Survey. Univariable and multivariable logistic regression to test for associations between unintended pregnancy and key subgroups was also performed. Finally, an age-standardized unintended pregnancy rate was calculated to adjust for differences in age composition between the military and U.S. populations for better comparison with the general U.S. rate.

RESULTS: Eleven percent of women reported an unintended pregnancy in the prior 12 months. The 2008 self-reported unintended pregnancy rate was 105 per 1,000 women, an increase from 2005 (97/1,000 women). Younger, less educated, nonwhite, and married or cohabitating women had significantly higher rates of unintended pregnancy compared with their counterparts. Rates did not differ between women deployed in the prior 12 months and nondeployed women. The age-standardized rate was 78 per 1,000 women (95% confidence interval 77–79), which is 50% higher than the general U.S. population (52/1,000 women).

CONCLUSION: Unintended pregnancy rates in the military are high and have increased in most key subgroups since the 2005 survey. Efforts are needed to help servicewomen prevent unintended pregnancy, including during deployment.

LEVEL OF EVIDENCE: II

In the United States, 49% of pregnancies are unintended, meaning that they are mistimed, unplanned, or unwanted. Unintended pregnancy is an important public health issue, because it may lead to negative maternal and child health outcomes, including low birth weight and preterm birth,

lower rates of breastfeeding, and postpartum depression. For these reasons, the U.S. Department of Health and Human Services identified reducing unintended pregnancy as a national goal in its Healthy People campaign, a set of 10-year national benchmarks and objectives for health promotion and disease prevention.

Unintended pregnancy among women in the U.S. military may have additional consequences, affecting both women's careers and negatively affecting troop readiness because pregnant women cannot be deployed and must be evacuated from theater if already overseas. With 97% of women in the U.S. military of reproductive age and a growing proportion of active-duty personnel that is female, these issues are particularly salient. Data from the 2005 Department of Defense Survey of Health Related Behaviors among Active Duty Military Personnel (Health Related Behaviors Survey) indicate that unintended pregnancy rates are very high, with 54% of pregnancies unintended. The self-reported annual unintended pregnancy rate was 97 per 1,000 women, and the rate adjusted for underreporting of abortion was 117 per 1,000 women. Factors found to be significantly associated with unintended pregnancy in univariable analysis included being younger, having a lower education level, cohabitating (compared with being married), being non-Hispanic black or Hispanic (compared with non-Hispanic white), serving in the Marine Corps or Army (compared with the Air Force), and being enlisted personnel (compared with an officer).

This analysis was conducted to estimate unintended pregnancy rates among a representative sample of active-duty women in the U.S. military in 2008. In addition to updating the findings from the 2005 survey and gauging progress toward reducing unintended pregnancy, the data presented here are the first to include all military branches and information about deployed women. We also performed a multivariable analysis to identify covariates associated with unintended pregnancy, and we calculated an age-standardized rate that adjusts for differences in the age composition between the military and U.S. populations, thereby facilitating comparison with the general U.S. population.

MATERIALS AND METHODS

Data from the 2008 Department of Defense Survey of Health Related Behaviors among Active Duty Military Personnel were used to calculate rates of unintended pregnancy in the prior 12 months among active-duty women. The survey was conducted by RTI International under the guidance of the Office of the Assistant Secretary of Defense (Health Affairs), TRICARE Management Activity, and the U.S. Coast Guard. This survey, conducted every 2–4 years, aims to assess potential health issues among active-duty military personnel with an emphasis on substance use and abuse, mental health, sexual health, gender-specific issues, oral health, gang involvement, hearing protection, and the military's progress in meeting the Healthy People 2010 objectives. The relevant variables used for this analysis were obtained from TRICARE as part of a request under the Freedom of Information Act.

Data were collected from May through July in 2008. The survey used a two-stage sample design. Each service branch (Air Force, Army, Coast Guard, Marine Corps, and Navy) selected major commands (ie, service branch subdivisions organized on a functional or geographical basis) from which to draw the first-stage sampling frame. Within each command, installations (ie, bases, posts) were selected with probability proportionate to size. Individual personnel were then sampled from each of the selected installations. Replacements for personnel unavailable at the time of data collection were drawn from a second list and were matched to the original sample members on gender and rank. Eligibility for survey participation

included all active-duty military personnel except recruits, service academy students, personnel absent without official leave, and personnel who were incarcerated at the time data were collected.

Data were collected using group survey administration at large installations, including aboard afloat ships (n=40,600) or through the mail for remote personnel (n=5,200). The total sample size was 45,800, of which 28,546 surveys were completed for an overall response rate of 62.3%. Sample weights were applied to make the sample representative of the entire active-duty military population. The survey was self-administered using a paper-and-pencil questionnaire designed for optical-mark reader scanning. Participants were informed that all responses were anonymous and confidential. We restricted our sample to women aged 18–44 years, resulting in a final sample size of 7,225 participants.

Analyses were performed with Stata Statistical Software 12.0 using the *svy* command to account for complex sampling design. Our outcome of interest was unintended pregnancy in the prior 12 months, measured by the question, "In the last 12 months did you cause or have an unintended pregnancy?" Based on this self-report, for all women and by key population subgroups (including age, education, race and ethnicity, union status, service branch, pay grade, and whether the participant was deployed in the prior 12 months), we determined the weighted number of unintended pregnancies and then divided this number by the weighted total population to obtain an unintended pregnancy rate per 1,000 women. For the overall rate and rates by service branch, 95% confidence intervals (CIs) based on the Wilson procedure without a correction for continuity were also calculated. For all women and by key subgroups, we also reported the self-reported unintended pregnancy rates per 1,000 women from the 2005 Health Related Behaviors Survey for comparison with the rates in 2008.

In the U.S. civilian population, the unintended pregnancy rate among women aged 18–24 years is twice that of the national rate for all ages combined. Because there is a greater proportion of younger women in the military compared with the civilian population, we therefore calculated an age-adjusted unintended pregnancy rate using the technique of direct standardization to increase comparability with the rate reported for the general population. U.S. population estimates were obtained from the U.S. Census Bureau population projections for women in 2006, the year on which the unintended pregnancy rate for the general U.S. population is based. This adjustment provides an indication of the expected unintended pregnancy rate that the military would have if its population had the same age distribution as the general U.S. population. A directly standardized rate and 95% CI based on the gamma distribution were calculated.

Finally, we conducted univariable and multivariable tests of association between unintended pregnancy in the prior 12 months and key subgroups using logistic regression. All variables were used as binary or categorical variables with reference groups selected based on sample size, meaningful comparison, or both. Missing data were excluded from these analyses. This study was approved by the Allendale investigational review board.

RESULTS

Roughly half (49%) of respondents were aged 18–4 years, 22% were 25–29 years, and 29% were 30–44 years. Most (52%) had completed some college but did not have a college degree, whereas one-fourth had a high school degree or less, and one-fourth had a college degree or higher. Fifty-two percent identified as non-Hispanic white, 26% non-Hispanic black, 11% Hispanic, and 11% as other race. Forty-eight percent of women

were unmarried, 43% were married, and 9% were cohabitating. The majority (83%) of women were in the enlisted pay grade, and 17% were officers. Thirty-five percent of women reported being deployed in the prior 12 months. Eleven percent of women (n=806) reported an unintended pregnancy in the prior 12 months. Half (48%) of these women with an unintended pregnancy in the prior 12 months and 11% of women overall were unable to deploy in the prior 12 months as a result of a pregnancy.

In 2008, the self-reported unintended pregnancy rate in the prior 12 months among active-duty women was 105 per 1,000 women (95% CI 103–106). This rate overall and by most key subgroups increased in 2008 from 2005 when the self-reported rate was 97 per 1,000 women. The age-adjusted unintended pregnancy rate for military women was 78 per 1,000 women (95% CI 77–79), which is 50% higher than the general U.S. population (52/1,000 women).

In multivariable logistic regression, the self-reported unintended pregnancy rate in 2008 was significantly higher among younger women, women with less education, non-Hispanic black and Hispanic women (compared with non-Hispanic white women), married or cohabiting women (compared with unmarried women), and women in the Army, Marine Corps, or Navy (compared with those in the Air Force). In univariable analysis, pay grade was also a predictor of unintended pregnancy, with enlisted women having significantly higher unintended pregnancy rates compared with officers; however, in multivariable analysis, pay grade dropped from significance because it was confounded by education. Women who were deployed in the prior 12 months did not have significantly different rates of unintended pregnancy compared with nondeployed women.

DISCUSSION

Unintended pregnancy increased in the military between 2005 and 2008 when the last Health Related Behaviors Survey was conducted, especially for certain branches of the military. Younger, less educated, nonwhite, and married or cohabitating women in the military had significantly higher rates of unintended pregnancy compared with reference groups; these findings are similar to data from the general U.S. population. Unintended pregnancy rates were also significantly higher for women in the Army, Marine Corps, and Navy compared with those in the Air Force. These findings highlight an important public health problem within the military that has not been adequately addressed.

Our findings also illustrate how unintended pregnancy affects deployment and ultimately troop readiness. There is little information on pregnancy or unintended pregnancy during deployment; however, a longitudinal analysis of a deployed U.S. Army Brigade Combat Team over 15 months during Operation Iraqi Freedom found that 10.8% of women were medically evacuated for pregnancy-related reasons. Half of women with an unintended pregnancy in the prior 12 months and 11% of women overall in the 2008 Health Related Behaviors Survey reported being unable to deploy in the prior 12 months as a result of pregnancy. Furthermore, women deployed in the prior 12 months did not have significantly different rates of unintended pregnancy compared with nondeployed women. These data indicate that unintended pregnancy occurs among women in all phases of their military careers, while stationed at their home base, while preparing for deployment, and during deployment, and that efforts to improve pregnancy prevention among all active-duty servicewomen are needed.

Although one might anticipate unintended pregnancy rates to be lower in the military compared with the general U.S. population as a result of better access to most health care services at no cost, the opposite appears to be true. The age-adjusted unintended pregnancy rate in 2008, 78

per 1,000 women, is 50% higher than the rate for the general U.S. population, 52 per 1,000 women, which is already high in comparison to other countries. These high rates of unintended pregnancy in the military are particularly worrisome given the limited options available to servicewomen. In the general U.S. population, 43% of unintended pregnancies end in abortion. Federal law only allows abortion to be performed at military facilities and covered under TRICARE military insurance when the pregnancy threatens the life of the woman or results from rape or incest. Women who are deployed, especially in countries like Afghanistan, where abortion is legally restricted, cannot access abortion services off-base in most cases and must be evacuated out of theater if they wish to terminate an unwanted pregnancy. Faced with a desperate situation, some women deployed abroad even consider unsafe means of self-inducing an abortion.

There are a number of factors that likely contribute to the high rates of unintended pregnancy in the military. Although most forms of contraception are covered under TRICARE, a survey of women's health experiences during deployment found a number of barriers to access. The majority of respondents were not counseled on contraception for pregnancy prevention or menstrual suppression as part of their predeployment preparations, and some faced barriers to accessing a method while overseas. These overseas barriers included care-seeking stigma and logistic obstacles that made it challenging to visit a health care provider as well as a limited amount of contraceptive supplies given at a time to women for deployment. Another factor deterring some women from seeking contraception was confusion about prohibition of sexual activity. Although consensual sexual activity among members of the same rank is legal, current military regulations make sexual relationships a chargeable offense in a number of circumstances. Confusion or concern about these laws led some women to believe they could not access contraception or would not need contraception. Another factor that may contribute to the high rates is the high prevalence of sexual assault. An estimated 20–43% of servicewomen experience rape or attempted rape during their military career, and the Department of Defense estimates that 86% of incidents are never reported.

Some branches of the military have begun to address the high rate of unintended pregnancy. For example, in the Navy and Marine Corps, the Sexual Health and Responsibility Program was created to reduce the occurrence of sexually transmitted infections and unplanned pregnancies among Navy members and families to levels specified in the Healthy People 2010 Objectives. Efforts to address unintended pregnancy within all military branches are needed. Additionally, clinicians outside of the military should be sensitized to this issue, because servicewomen do not always receive all medical care through military health care providers. For example, research has shown that servicewomen sometimes access predeployment contraception from private clinicians, yet they may not be given supplies that last their full deployment or they may not be able to access the prescribed method through the military once overseas.

This study has several limitations. The 2008 Health Related Behaviors Survey did not ask about any pregnancy in the prior 12 months, so we were unable to calculate the proportion of pregnancies that were unintended. However, unless the overall pregnancy rate increased substantially among active-duty servicewomen since the 2005 Health Related Behaviors Survey, which is unlikely, we see no evidence to suggest a reduction in the proportion of pregnancies that are unintended. Additionally, unlike the previous analysis of the 2005 Health Related Behaviors Survey data and estimates from the general U.S. population, we did not adjust our unintended pregnancy rates for abortion underreporting and so our rates likely underestimate the true incidence of unintended pregnancy. The strengths of this study include its large, representative sample from across all branches of the military.

Unintended pregnancy is a serious public health issue that has bearing on a woman's right to choose when and if she has a child. Unintended pregnancy among active-duty servicewomen has the additional effect of adversely affecting troop readiness, because pregnant women cannot be deployed or must be evacuated from theater. All branches of the military need to address this problem in a comprehensive manner that includes education and evidence-based provision of contraception in the context of confidential health services as well as improved access to abortion care, a right to which all U.S. women are entitled.

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The Association of Self-Reported Measures With Poor Training Outcomes Among Male and Female U.S. Navy Recruits

Military Medicine
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Abstract

This prospective study evaluated the association of self-reported health habits and behaviors in 2,930 Navy recruits with poor training outcomes, defined as graduating late or separating from training. Although 17% of the men and 21% of the women had a poor training outcome, results suggest that some self-reported measures were associated with poor training outcomes. Men who did not run or jog at least 1 month before basic training or had a previous lower limb injury without complete recovery and women reporting the same or less physical activity compared with their same-age counterparts were more likely to have a poor training outcome. An important first step in decreasing poor training outcomes is encouraging incoming recruits to participate in physical activity and taking steps to identify and rehabilitate recruits who are not completely healed from a lower limb musculoskeletal injury before reporting to basic training.

Introduction

All U.S. Navy enlisted sailors are required to graduate from 7 weeks of basic training at the Naval Recruit Training Command (RTC), Great Lakes, Illinois, before assignment to specialized schools. RTC is the sole entry-level training command for the U.S. Navy and trains male (30,000 per year) and female (8,000 per year) Navy recruits. Candidates must meet minimum physical standards to qualify for enlistment to ensure that the Navy enlists only those applicants who are capable of successfully completing basic training1(http://www.cnrc.navy.mil/publications/1130.8J.htm).

Some recruits can take longer than 7 weeks to complete basic training if they are required to repeat a training cycle before eventually graduating. U.S. Navy recruits who do not graduate on time negatively impact the Fleet Marine Force by slowing down the time it takes for a recruit to matriculate into the Fleet Marine Force (accession pipeline). Poor training outcomes (failing to graduate or graduating late) increase the recruiting

and basic training costs, and negatively affect military operational readiness2 (http://handle.dtic.mil/100.2/ADA460104). There is evidence of an association between the risk of musculoskeletal injury during basic training and baseline level of health and fitness before basic training, and that injury accounts for increased medical costs, a higher first-term active duty attrition rate, and poor long-term military outcomes.

The purpose of this study is to identify Navy recruits who are likely to have a poor training outcome by examining self-reported measures before training. Identification of simple self-reported measures to predict poor training outcomes could lead to cost-effective screening and interventions. These results could also benefit other U.S. military services and nonmilitary populations who participate in a required physical training program to improve job performance.

Methods

Participants

Subjects were male and female RTC basic trainees. There were 3,272 Navy recruits briefed about the study, and 2,956 (90%) consented to participate. We excluded 22 subjects who had prior service or were enlisted trainees from another service branch and 4 who were lost to follow-up. The final sample for univariate analyses included 2,312 men and 618 women and for multivariate analysis 2,297 men and 617 women (Table I).

Study Design

This prospective study enrolled subjects from January to April 2007. All participants received the Privacy Act statement and signed a consent form in accordance with the guidelines of the Naval Health Research Center Institutional Review Board (Protocol NHRC.2007.0025) before completing the baseline questionnaire. The baseline questionnaire included factors decided by a multiservice panel of Army, Air Force, Navy, and Marine Corps investigators for a study with the purpose of identifying and reducing injuries and attrition in basic training across the services. The Bureau of Naval Personnel approved the trainee survey (BUPERS Navy Survey Approval RCS 1513-1).

To avoid sampling error, male recruits who were identified as being in the Naval Special Warfare Preparatory School pilot program, who were integrated into standard training divisions, were not approached to volunteer for this study because their training takes longer and incorporates additional physical requirements (they would all take longer than 7 weeks to graduate, and they would be mistakenly considered to have had a poor training outcome).

Outcome Variables

This prospective study enrolled subjects before officially starting recruit training, and graduation status was determined at the end of training. Recruits were divided into 2 groups based on their graduation status: those who graduated late or were separated from training (poor training outcome) and those who graduated on time. Graduation dates were collected and on-time graduation was determined from RTC administrative records.

Exposure Variables

Shortly after arrival at RTC, a few days before training commenced, incoming recruits were briefed on the nature and purpose of the study. Consenting recruits were administered a baseline questionnaire, 1 time only, that asked about tobacco use, physical activity, injury history, and (for women) menstrual history; uniformed personnel and the authors were not present.

The questionnaire asked about the recruit's smoking status, self-rated fitness, physical activity level, prior injuries sustained, and menstrual history. A current smoker was a recruit who had smoked during the past 30 days. The reference group for current smoker status was those who reported not having smoked cigarettes in the past 30 days.

Self-rated fitness was divided into 3 categories: excellent/very good (reference group), good, and fair/poor. Several physical activity questions assessed exercise or sports participation and running behavior, including average frequency (per week) during the previous 2 months and length of time (months) before recruit training. For all exercise and sports questions, the group with the highest level of activity was the reference group.

History of previous lower limb injury was used as a categorical variable with 3 levels: those with a previous lower limb injury that had not completely healed, those with a previous lower limb injury that had healed, and, the reference group, those without a history of previous lower limb injury.

Women answered 5 additional questions based on menses during the 12 months before basic training. From these questions, several variables were created: primary amenorrhea (women whose age at menarche was ≥16 years), menstrual regularity (≥10 menses in the past 12 months as the reference group), secondary amenorrhea (≥6 consecutively missed menses during the past 12 months), birth-control hormone use (No as the reference group), and months since last pregnancy.

Additional exposure data collected from RTC administrative records included age, height, weight, and race/ethnicity. Age was used as a categorical variable (<19, 19–23, >23 years), with those aged 19 to 23 as the reference group. Height and weight were measured by the medical clinic staff 1 or 2 days after recruits had completed the questionnaire. Body mass index (BMI) was derived from weight (kg) and height (m) as weight/height2. BMI was categorized using Centers for Disease Control and Prevention guidelines: low (≤18.4), normal (18.5–24.9), and high (≥25), with normal BMI as the reference group. Race categories were White/Caucasian alone (the reference group), Black/African American, Asian, and other (some other race or 2 or more races).

A number of studies support use of recruits' initial physical fitness run time as strong determinant of basic training success. RTC administrative records provided recruits' initial physical fitness test run times; however, this variable was excluded as a covariate because the initial run test was administered during the third week of training and does not represent the recruits' incoming fitness level. The physical activity, injury history, and physical fitness questions were designed to provide information about the recruits' baseline fitness in the absence of the recruits' initial run time and to determine factors associated with poor training outcomes by administering a simple questionnaire before sending the recruit to RTC.

Statistical Analyses

SPSS statistical software, version 17.0.2 (SPSS, Chicago, Illinois) was used to analyze the prospectively collected data. Univariate analyses, t tests for continuous variables and $\chi 2$ tests for categorical variables, and unadjusted odds ratios (ORs) examined the association between poor training outcomes and each potential risk factor by sex. For multivariate analysis, the measure of association was the adjusted OR, which was generated from a multiple logistic regression analysis. The backward elimination logistic regression procedure began with all the exposure variables and removed each factor that was not statistically significant, reassessing the model after the removal of each factor.16 In all cases, statistical significance was determined by a p value less than 0.05. Separate logistic regression models were run for men and women with respect to poor training outcomes, adjusting for age and race.

Results

Approximately 17% of the men and 21% of the women graduated late or failed to graduate (Table I). Mean (±SD) age was 21.4 (3.1) years for men and 21.4 (3.3) years for women. Among the men, the mean (±SD) height, weight, and BMI were 68.6 (2.8) inches, 173.7 (30.4) pounds, and 25.9 (4.0), respectively; 77.6% were self-identified as White/Caucasian, 16.5% as Black/African American, 3.8% as Asian, and 2.1% reported being some other race or 2 or more races. Among the women, the mean (±SD) height, weight, and BMI were 63.6 (2.7) inches, 143.4 (24.1) pounds, and 24.9 (3.6), respectively; 64.9% were self-identified as White/Caucasian, 26.1% as Black/African American, 6.0% as Asian, and 3.0% reported being some other race or 2 or more races. Forty-two percent of men and 46% of women were in the normal BMI range (18.5–24.9). Age, height, weight, BMI, and race did not vary by graduation status for either men or women; however, there was a weak association with increased poor graduation outcomes among female recruits in the low-BMI category (n = 16 represents only 2.8% of the population studied) (OR = 3.06; 95% confidence interval [CI]: 1.00–9.36). Thirty-six percent of the men and 29% of the women reported having smoked in the previous 30 days. Smoking status was not associated with poor training outcomes in either men or women.

Unadjusted logistic regression models were used to calculate crude ORs and 95% CIs with respect to poor training outcomes (Tables II and III). Both male and female recruits who self-rated being somewhat or much less active than their same-age counterparts were less likely to graduate on time than those who reported being much or somewhat more active: men (OR = 1.33; 95% CI: 1.02–1.73) and women (OR = 2.83; 95% CI: 1.66–4.81). In addition to female recruits who self-rated being less physically active than their same-sex counterparts, those who reported having about the same activity level were more likely to have a poor training outcome compared with those who reported being much or somewhat more active (OR = 2.18; 95% CI: 1.25–3.78).

Male recruits who self-rated their current physical fitness as fair or poor (OR = 1.35; 95% CI: 1.00–1.82), their exercise or sports physical activity participation ≤1 time/week in the past 2 months (OR = 1.46; 95% CI: 1.05–2.02), or ≤1 month of running or jogging in the past 2 months (OR = 1.47; 95% CI: 1.05–2.05) were more likely to have a poor training outcome compared with the group with the highest level of activity. Male recruits who reported previous lower limb injury with incomplete recovery were 6 times more likely to have a poor training outcome compared with those who reported never injuring a lower limb (OR = 6.05; 95% CI: 2.24–16.37).

The factors displayed in Tables II and III were candidates for the final multivariate model of independent factors for poor training outcomes (Table IV). The strongest predictors of poor training outcome using baseline information from the self-reported questionnaire were different for men and

women. Men who reported running or jogging ≤1 month before basic training were 76% more likely to have a poor training outcome compared with those who reported running or jogging 7 months to 1 year before basic training, and men who had a previous lower limb injury with incomplete recovery were over 7 times more likely to have a poor training outcome compared with those who reported never having had a lower limb injury.

Men who reported a previous injury with complete recovery were no different in poor training outcome from those who reported no injury. Women who reported being less active than their same-age counterparts were 3.1 times more likely to have a poor training outcome compared with those who reported being more active than their same-age counterparts. Similarly, women who reported the same activity level as their same-age counterparts were 2.5 times more likely to have a poor training outcome compared with those who reported being more active than their same-age counterparts.

Discussion

The basic training attrition literature identifies factors associated with basic training discharge or factors associated with basic training success. This study demonstrated that a brief questionnaire could identify factors associated with poor training outcomes (delayed graduation or separation) in Navy recruits. Previous attrition research identified extrinsic and intrinsic risk factors for injury because injury is a strong determinant of graduating from basic training. Prospective studies that identified injuries that occur during basic training as an independent factor for graduating are consistent with the present study.

Risk factors for discharge from basic training include low aerobic fitness, low physical activity level before basic training, low muscular endurance,and cigarette smoking before training. Studies conducted among female athletes and female Marine Corps recruits have suggested that a history of menstrual dysfunction may be a common risk factor for stress fracture and musculoskeletal injuries, which could lead to discharge from basic training. Our baseline questionnaire addressed these potential risk factors.

Two prospective studies assessed factors associated with discharge in the Air Force and Marine Corps by analyzing self-reported and medical clinic data using multiple logistic regression to determine their independent effects and relative importance. The Air Force study developed models for 4 categories of discharge: medical, psychiatric/behavioral, legal, and performance related. Less incoming physical activity was an independent factor in all 4 categories of discharge. Smoking (current smoker, ex-smoker, never smoked) was an independent factor only in the legal discharge category. We found that male recruits reporting less physical activity, specifically those who reported running or jogging ≤1 month before basic training, were more likely to have a poor training outcome. The study of Marine Corps recruits also developed a multiple logistic regression model to evaluate independent factors for discharge. Recruits older than 23 years, poor incoming self-reported physical fitness, no history of competitive sports participation, and a lower limb injury before basic training without complete recovery were independent factors associated with discharge. In contrast, we found that self-reported current fitness level and sports participation were not independent factors for poor training outcomes in either men or women. However, in agreement with the Marine Corps study, we found that male recruits reporting incomplete recovery of a previous lower limb injury were more likely to have a poor training outcome, and there was no increase in poor training outcome for those who reported a previous injury with complete recovery for either men or women. The distinguishing factor was complete or incomplete recovery.

An Army study looked for predictors of training success, defined as graduating from basic training. Trainees completed a baseline survey self-reporting previous injuries that limited participation in organized sports; quantified the frequency and duration of running, aerobic exercise, and weight training in the 6 months before basic training; and whether they smoked. Results of the recruits' initial physical fitness test were obtained from the training companies. The univariate predictors of training success were the recruit's performance on the initial physical fitness test and history of cigarette smoking; multivariate models were not analyzed. We found that smoking status was not an independent factor for poor training outcomes in either men or women.

Factors suggested to impact poor training outcomes in women include primary and secondary amenorrhea, irregular menstrual activity (oligomenorrhea), and birth control use. Female recruits in our study answered questions based on menses during the 12 months before basic training, primary amenorrhea (age at menarche ≥16 years), irregular menstrual activity (<10 menses), secondary amenorrhea (≥6 consecutively missed menses), and birth-control hormone use. We found that self-reported menstrual history was not associated with poor training outcomes.

There are several limitations of our study. We relied on self-reported physical activity, which Adams et al has shown to be influenced by social desirability bias. Social desirability is the defensive tendency to portray oneself in keeping with perceived cultural norms, in this case a military environment, and could result in over reporting positive responses. It is also possible the questionnaire lacks construct validity and does not accurately assess information; in general, the respondent could have misinterpreted a question or deliberately given misleading answers. However, to improve construct validity, the questionnaire was developed through evidence-based consensus of subject matter experts from the Air Force, Army, and Navy, and to improve comprehension of the questionnaire, each question was read aloud to provide clarity by a study investigator without uniformed personnel present. Volunteers were also encouraged to ask questions to clarify their understanding of a question, hopefully minimizing this bias.

A history of alcohol consumption might have an influence on poor training outcomes. Alcohol consumption questions were not asked because more recruits might have declined to enroll in the study or after enrolling in the study and seeing alcohol questions might intentionally provide misinformation.

Survey questions about alcohol consumption might be misinterpreted by the recruit as disclosing a practice that could lead to legal separation because the minimum age to consume alcohol is 21years for all Navy personnel and most of the incoming recruits are too young to legally drink alcohol (http://doni.daps.dla.mil/allinstructions.aspx). Other potential factors for poor training outcomes include diet, nutritional status, and psychological factors. It is possible that these factors could increase the predictive ability by accounting for more recruits with poor training outcomes, but these factors were not addressed in the questionnaire.

Literature suggests basic training graduation rates vary by season, specifically the rate of poor training outcomes is higher during the summer months. Our study enrolled subjects from January to April 2007 and does not represent the annual enrollment at RTC Great Lakes, Illinois. If the current study enrollment occurred during the summer months, more recruits may graduate late (a poor training outcome) and seasonal conditions might become a confounding factor.

This study has several strengths. The questionnaire is simple and easy to administer with respect to time and recruit comprehension. Most of the basic training attrition literature discusses logistic regression models with injury or stress fracture as an exposure variable. Gathering medical information requires time-consuming data collection methods, such as medical record screenings, or medical evaluations and separate recordkeeping methods to document an event that occurs while basic training is already under way. The simple baseline questionnaire can be administered at the recruiting office, before sending the recruit to RTC, as a screening tool and could be effective in reducing basic training attrition. The questionnaire was developed through evidence-based consensus of subject matter experts from the Air Force, Army, and Navy and perhaps could be used by all the services as a universal screening tool. The study sample size is large, and has good statistical power, and uses multivariate analysis to better separate data, which adds clarity to the issues involved with basic training attrition.

In summary, the results of the current study suggest that some simple self-reported measures can be strong independent factors associated with poor training outcomes in both men and women. The male model consists of 2 objective modifiable factors, whereas the sole factor in the female model consists of a subjective comparison of her individual physical activity level compared to others of her same age. Men who did not run or jog at least 1 month before basic training or who had a previous lower limb injury without complete recovery were more likely to have a poor training outcome. In contrast, the sole independent factor for women was a subjective report of the same or less physical activity compared with her same-age counterpart. In conclusion, an important first step in decreasing poor training outcomes is encouraging incoming recruits to participate in physical activity before arrival and taking steps to identify and rehabilitate recruits who are not completely healed from a lower limb musculoskeletal injury before reporting to basic training.

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