Army Medicine Peer Reviewed Publications

December 2012

Executive Summary

December 2012 – Journal coverage for December focused primarily on post-traumatic stress disorder and traumatic brain injury with a significant number of pertinent articles also discussing medical protocol and training. Coverage of PTSD noted the success of various cognitive therapy programs, peer-based interventions as well as physical indications of trauma susceptibility. TBI research focused on spinal cord injury, white matter abnormalities, health perceptions and intracranial-pressure monitoring. Journals this month published opinions on the future of medicine with one article from *Military Medicine* suggesting the country adopt the Army's primary care system. Other articles discussed the trend toward centralized medicine and social media's role in medical training.

Military Medicine continued to publish a significant number of articles relevant to Army medicine. This month it published a four-part series on dietary supplement use in the military that researched perception, safety and use. Separately, *The Lancet* published its groundbreaking study of the global burden of disease that was a result of collaboration between 302 institutions across 50 countries. This comprehensive study may outline ways in which military medical research can contribute to civilian health.

Several journal articles received coverage in the traditional media market including two studies from *Medical Surveillance* on the financial medical cost of the wars in Iraq and Afghanistan and a ten-year review of substance abuse in the military. The estimated financial medical cost of the wars in Iraq and Afghanistan, as well as projections about the future cost of veteran healthcare, drew critical coverage this month.

Medical Journal Coverage

Nutrition and Fitness

Military Medicine: Dietary Supplements and Warfighters: A Challenge for Military Providers

As an introduction to a series of four articles on dietary supplements, this article explains that the risks of using supplements outweigh the potential benefits. It discusses several case studies were Soldiers have collapsed and in some cases died after using dangerous but legal supplements. Concern has been growing in the civilian and military medical community regarding health supplements, and this author's conclusion is to fully educate service members on the risks associated with dietary supplements.

Military Medicine: Cost-Minimization Analysis of the U.S. Army Accession Screening and Immunization Program

In an effort to determine the most cost-effective delivery of immunizations, researchers estimated just over $400,000 in savings through the use of the Accession Screening and Immunization Program (ASIP) as opposed to a universal immunization program. As the Army may be required to lay out cost-cutting behaviors with Congress expected to cut the DoD budget, it is important for Army Medicine to determine where money can be saved without sacrificing care.

Military Medicine: Case Reports: Death of Active Duty Soldiers Following Ingestion of Dietary Supplements Containing 1,3-Dimethylamylamine (DMAA)

This article examines the risk that DMAA may pose to service members. One case study examines a death that occurred after a service member ingesting a dietary supplement containing DMAA, β-alanine, arginine α-ketoglutarate, caffeine, creatine monohydrate and Schizandrol A. While most ingredients are relatively well established, little is known about the effects of DMAA. It was initially developed in 1944 as a nasal decongestant, but was ineffective and today is used in some dietary supplements. There is no causal relationship between the two service members' deaths and DMAA, and few studies have been conducted regarding DMAA.

Military Medicine: Third-Party Certification of Dietary Supplements: Prevalence and Concerns

Over 70 percent of military personnel report using dietary supplements, despite little being known about their effectiveness and the associated risks. Uniquely, service members may be more susceptible to the adverse effects of dietary supplements due to certain stressors, including extreme heat, altitude and sleep deprivation. This study determined that 12 percent of dietary supplements sold at installations are certified by a third party, which may lead service members to wrongly believe this ensures their safety. Consumers should be aware of the issues surrounding dietary supplement use.

Military Medicine: Dietary Supplements in the Department of Defense: Possible Solutions to Optimizing Force Readiness

Seventeen to 20 percent of service members use high-risk weight loss, performance enhancing or bodybuilding supplements. Because there is no standard policy or program to inform Soldiers about the risk of such supplements, this article considers the viability of various education or prevention initiatives including monitoring dietary supplement use, regulating supplement purchases on installations or regulating its use. Many of these ideas rely on expanding the authority of the Dietary Supplement Subcommittee (DSSC) to create a DoD certification seal, ban certain substances and implement targeted education.

Physiological Injuries and Surgery

Military Medicine: A Large-Scale Study of Respiratory Virus Infection Over 2 Years Using the Luminex xTAGRVP Assay

In order to effectively diagnose respiratory viruses, the study introduces the Luminex xTAGRVP Assay to determine whether viral cultures or the assay produced faster results. The mean return time on viral cultures was 10.5 days while the assay produced adequate results in 1.3 days. The study conducted by Landstuhl Regional Medical Center highlights the Army's leadership on issues of productivity in healthcare.

Military Medicine: Improving Compliance with Malaria Chemoprophylaxis in Afghanistan

In an attempt to encourage service members to continue malaria treatment, briefings and medical consultations were implemented in order to determine why Soldiers had discontinued treatment. Based on the results, a discussion of side effects increased the likelihood of continued malaria treatment amongst 90 percent of participants.

Military Medicine: The Effects of QuikClot Combat Gauze and Movement on Hemorrhage Control in a Porcine Model

Determining the effectiveness of certain materials used during medical operations is the objective of the evaluation of QuikClot combat gauze. QuikClot was determined to be better at controlling hemorrhage and it produces a more robust clot, offering a greater ability for movement. Improvements in healthcare for combat positively reinforce the dedication to modernization amongst military medical entities.

Medical Surveillance: Outbreak of Gastrointestinal Illness During Operation New Horizons in Pisco, Peru

In studying an e-coli outbreak in *Operation New Horizons* in Pisco, Peru, researchers determined Soldiers contracted the bacteria from food prepared in their hotel kitchens, despite being informed that these kitchens were not sanitary. Fewer than half of deployed Soldiers received medical training prior to their deployment while less than one third mentioned diarrheal illness and personal hygiene when asked if they were aware of potential medical issues before this deployment. Regarding treatment, medications would only be able to counteract several types of bacteria, and it is likely the majority of Soldiers would continue to have diarrheal illness. This issue has been challenging for the U.S. Military, as

the outbreak resulted in the loss of a day of work per Soldier and, if cases such as this continue, could affect the overall mission. Gastrointestinal illness is best addressed by implementing both prevention and treatment initiatives.

Clinical Infectious Diseases: Invasive Mold Infections Following Combat-related Injuries

Invasive fungal wound infection is an emerging issue in trauma-related infections, and it can lead to significant morbidity. Soldiers who received their injury in an agricultural setting, motor vehicle accident, natural disaster or blunt crash have the greatest risk of developing fungal infections. In order to help prevent amputations and early mortality, special attention should be paid to train military personnel who treat Soldiers in these circumstances on techniques regarding early identification and repeated surgical debridement.

European Journal of Physical and Rehabilitation Medicine: Residual limb wounds or ulcers heal in transtibial amputees using an active suction socket system. A randomized controlled study

This study attempts to fill the void in research regarding residual limbs and open ulcers post amputation. Results determined that the vacuum assisted socket system (VASS) allows Soldiers to walk independently before and for longer than the control group, but the margin narrowed after six months. This suggests that VASS allows Soldiers to adapt to a prosthetic faster than alternatives. Despite predictions, VASS had no affect on residual limb health.

TBI

Journal of Musculoskeletal and Neuronal Interactions: Heterotopic ossification following traumatic brain injury and spinal cord injury: insight into the etiology and pathophysiology

The presence of heterotopic ossification (HO), or the formation of bone-like tissue, occurs in various instances such as around fractured bones, after traumatic brain injuries (TBI) and in comatose states. The research behind HO following combat-trauma or a TBI is extensive and suggests an increased incidence after these events. The study concludes, however, that HO is not clearly definable and thus renders it difficult to treat until it is more fully understood.

American Journal of Psychiatry: White Matter Abnormalities in Veterans With Mild Traumatic Brain Injury

In studying the short- and long-term effects of mild TBI on veterans, researchers were unable to determine a difference using diffusion tensor imaging (DTI). They were able, however, to discover an increased incidence of “potholes” in those veterans who suffered from a mild TBI with the frequency of the potholes correlating with the severity of the injury, not other factors such as age or non-deployment related TBI. These white matter potholes may be a biomarker for axonal injury.

International Journal of the Care of the Injured: Blast-related mild traumatic brain injury is associated with a decline in self-rated health amongst US military personnel

Soldiers suffering from mild TBI were five times more likely to report major health issues six months after their injury than Soldiers who had other mild injuries. This association was consistent across all population subsets including age, rank, service branch and mental health diagnosis. The article pointed to the need for more research on the short and long term effects of mild TBI as well as Soldiers’ perceptions of health. Previous studies and articles from traditional media have been critical of categorizing TBI as mild, moderate and severe given the severity of some mild TBI symptoms.

New England Journal of Medicine: A Trial of Intracranial-Pressure Monitoring in Traumatic Brain Injury

Intracranial brain pressure monitoring is not generally utilized during guided imagery sessions, despite its availability and potential usefulness. Researchers set to determine if intracranial monitoring improved outcomes and determined that patients who had intracranial monitoring had longer hospital stays and were administered more high-dose barbiturates. Patient outcomes, however, were not affected by intracranial-pressure monitoring.

PTSD

The Lancet: Cognitive behavioural therapy as an adjunct to pharmacotherapy for primary care based patients with treatment resistant depression: results of the CoBalT randomised controlled trial

With fewer than 40 percent of patients responding effectively to antidepressant medication, the study tries to determine the best “next step therapy” when antidepressants alone prove ineffective. The study found a 46 percent criteria-match in the group exposed to cognitive behavioral therapy (CBT), while only 22 percent had the same results in the usual care group. The determination was that pharmacotherapy, especially when

it involves CBT, has a multiplier affect on the treatment of depression can help the Army to treat Soldiers suffering from depression and to reorient treatment to center on CBT and antidepressants.

Biology of Mood & Anxiety Disorders: The relationship between Hippocampal asymmetry and working memory processing in combat-related PTSD -- a monozygotic twin study

With increased media coverage of research advances related to combat PTSD, Army Medicine can now point to the study of hippocampal asymmetry as a possible precursor to PTSD susceptibility and the necessary resources for PTSD treatment. Researchers found that the hippocampus's structure and function are susceptible to the effects of trauma.

Military Medicine: Group Exposure Therapy Treatment for Post-Traumatic Stress Disorder in Female Veterans

Eight-eight female veterans with PTSD participated in group therapy sessions that consisted solely of repeated imaginal exposure, exposing a Soldier repeatedly to images of their trauma. The women met in groups of three for several sessions and filled out a checklist to evaluate their symptoms prior to each session. Researchers found that 40 percent of participants experienced a 10-point drop in symptoms. This validation of imaginal exposure therapy can help expand therapists' treatment options. This research is particularly important given the media's recent focus on female service members' issues, the need for alternative PTSD treatments and treatments that avoid the heavy use of addictive pain medication.

Cognitive Therapy and Research: How Disorder-Specific are Depressive Attributions? A Comparison of Individuals with Depression, Post-Traumatic Stress Disorder and Healthy Controls

The study focused on the tendency of depressed individuals to assign causes from internal, stable and global factors to negative events. Through the investigation of this tendency, researchers sought to determine how major depression (MD) and post-traumatic stress disorder (PTSD) factor into this habit. Results allow for medical professionals to distinguish how to treat patients suffering from one of the two forms of depression going forward.

Neuropsychopharmacology: Preclinical evaluation of reconsolidation blockade by clonidine as a potential novel treatment for posttraumatic stress disorder

In continued research of animals and traumatic memories, the study seeks to determine whether clonidine is capable of blocking reconsolidation, or the recollection of traumatic memories. The study found that two administrations of clonidine were successful in impairing one's ability to retrieve traumatic memories.

Journal of Consulting and Clinical Psychology: Manualized therapy for PTSD: Flexing the structure of cognitive processing therapy

Modified Cognitive Processing therapy (MCPT) is an intervention that allows mental health practitioners to adjust therapy protocols based on the progress of the Soldiers they are treating. Research indicates that MCPT treatment is more effective than symptom-monitoring delayed treatment, with only 2 out of 50 participants displaying PTSD symptoms after a three-month follow-up.

Military Medicine: Peers and Peer-Based Interventions in Supporting Reintegration and Mental Health Among National Guard Soldiers: A Qualitative Study

Research indicates that some, but not all, peer networks can help lessen the stigma against mental health therapy. Thirty National Guard Soldiers who recently returned from deployments and are currently displaying high levels of mental health symptoms expressed three common themes when interviewed. First, that their personal acceptance of mental health symptoms prevents them from seeking treatment. Second, Solders in tightly knit peer networks display fewer signs of stigma against mental health treatment. An exception to this, however, is an impoverished peer network where stigma tends to be stronger. Third, Soldiers react positively to participating in peer-based therapy programs.

Sexual Health

Military Medicine: Evaluation of HIV Postexposure Prophylaxis for Occupational and Nonoccupational Exposures at a Deployed U.S. Military Trauma Hospital

The review of care for 31 cases of HIV exposure who were prescribed PEP over the 65-month timeframe with 18 out of 23 evaluative cases adhering to CDC guidelines. The study highlights the effectiveness of combat medics despite the high intensity and high risk of combat environments.

Substance Abuse

Armed Forces Health Surveillance Center: Substance Use Disorders in the U.S. Armed Forces, 2000-2011

This comprehensive study of substance abuse in the military examined hundreds of thousands of service members over a 12 year period. Substance abuse became less prominent as Soldiers age, spend more time in service, increase rank and deploy more often. Cannabis was the most commonly used drug, but opioid drug abuse became more common over the study period, potentially reflecting an increase in prescription drug misuse. For the purposes of this study, substance abuse did not include alcohol or tobacco related addictions. This article received some coverage in the traditional media market.

Medical Protocol and Training

The Lancet: GBD 2010: Understanding disease, injury, and risk

The Lancet's in-depth study of the global burden of disease involved collaboration from 486 scientists from 302 institutions in 50 countries, and it sought to enhance understanding of current and future health priorities for the global community. Briefly, findings indicate that life expectancies for men and woman are increasing, death by HIV and malaria is decreasing, fewer children under the age of 5 are dying and infectious diseases are being controlled. Eight million people died from cancer in 2010, representing over a third more deaths than 20 years ago, and death from road traffic accidents increased by 50 percent. Blood pressure is the biggest global risk factor for disease, followed by tobacco, alcohol and a poor diet. All factors have been noted in traditional media as medical issues for service members. The study also found that young adults are more medically neglected than previously, as they, especially men, are dying in a higher number. Africa remains the most medically afflicted country.

Military Medicine: A Model for Patient-Centered Army Primary Care

Establishing a patient-centered care model was the objective of this study, which established a patient management team to oversee patients' primary care. Using myriad measures, the results indicate that a patient-centered model, complete with shifts in staffing objectives, significantly improves access to outpatient care and general healthcare. As the US adjusts to the long-term effects of the Affordable Care Act, changes or shifts in the procedures of primary care will factor into the national debate; Army Medicine has the potential to unilaterally implement new approaches and present the results, reinforcing the identity as an industry leader.

Mayo Clinic Proceedings: Using Social Media to Improve Continuing Medical Education: A Survey of Course Participants

The goal of this study was to determine how continuing medical education students felt about using social media in an educational setting. Results indicate that confidence level was associated with age and frequency of use. Despite many students believing that social media is an acceptable and professional education method, professors are resistant to utilize it in lectures. The use of social media is increasing in educational settings, and Army Medicine can continue to integrate it in medical education.

American Journal of Medicine: The Anatomy and Physiology of the US Health Care System in 2050? An Exercise in Prognostication, Fantasy, and Hope

This journal article explores what the authors feel will be emerging trends in medical care including the move to a centralized system, fewer independent doctors, decentralization away from Washington, D.C. and a patchwork of state, local and private entities working together toward healthcare. The authors predict that most if not all Americans will have health insurance with many receiving healthcare from plans paid for in part or in whole by the government. Notably, the authors predict that medicine will become increasingly digital with microchips embedded in individuals to keep track of medical information. They did note that a more centralized system may stymie innovation.

Military Medicine: The Promises and Perils of the MHS' Implementation of the Patient-Centered Medical Home

With increasing healthcare costs for civilians and Soldiers and little improvement in overall care, few initiatives have focused on reintroducing the primary care physician as the center of healthcare. Previous studies indicate that primary care providers lower healthcare costs and improve quality. The Army's Patient-Centered Medical Home (PCMH) has breathed new life into the primary healthcare provider model and, this article argues, should be implemented throughout the MHS. Coverage of this subject could help mitigate criticism of inefficiencies and increases in military medical healthcare costs.

Sleep

Journal of Thoracic Disease: Excessive daytime sleepiness in sleep disorders

With an increased focus on sleep as a potential root cause of various other functions, the study determines that poor oxygenation and irregularity of autonomic function often cause sleep interruptions. The authors argue that shift work, obesity, depressive symptoms and poor sleep hygiene may contribute to the phenomenon of poor quality/quantity of sleep. In understanding what causes poor sleep habits, the Army has the potential to refocus certain schedules and processes to better accommodate Soldiers' needs.

Primary Care Respiratory Journal: Body mass index and obstructive sleep apnoea

In an exhaustive study of the relationship between obstructive sleep apnoea (OSA) and body mass index (BMI), age, gender, and economic identity, the editorial highlights possible deficiencies in the methodology of the study. Despite the deficiencies, the journal finds a decrease in weight correlates with a therapeutic benefit in reducing OSA risk. With recent media coverage on the Army's problem with overweight Soldiers, the editorial offers a unique light on the correlated issue of obesity and sleep apnoea.

Other

Medical Surveillance: Costs of war: excess health care burdens during the wars in Afghanistan and Iraq (relative to the health care experience prewar)

As troops withdraw from theaters of war, health care costs are of significant concern both to the military and the civilian population. The report compares real instances of care during war (October 2001 to June 2012) as compared with the estimated incidence if pre-war habits continued during the same period. The study found a significant contribution of these excesses by Army and Marine Corps personnel and those older than 30 years old with mental disorders accounting for the majority of cases. This research received some critical coverage in traditional media, which quoted a drastic shift of cause for hospitalization and the rise of mental disorder hospitalizations, 63 percent.

Military Medicine: Providing Support Through Life's Final Chapter for Those Who Made It Home

With a focus on the transition from combat to civilian life, the study details efforts by the Department of Veterans Affairs to provide long-term care for "those who served." The information points largely to hospice and palliative care provided or supported by the VA. With impending budget cuts, the authors suggest that cuts in Medicare may impact the VA's ability to offer veterans' services.

Military Medicine: Promoting Reintegration of National Guard Veterans and Their Partners Using a Self-Directed Program of Integrative Therapies: A Pilot Study

National Guard veterans and their partners who used self-directed, integrative therapy programs administered through CD and DVD saw significant improvements in symptoms for PTSD and depression. Veterans reported reductions in pain, tension, irritability and anxiety after watching and participating in simple massage technique (DVD) and relaxation exercises (CD). The success level, however, may be attributable to the participants, namely couples who were already willing and eager to partner to decrease symptoms.

Military Medicine: Anxiety, Social Support, and Physical Health in a Sample of Spouses of OEF/OIF Service Members

Media coverage has focused on the burden that military spouses undertake and this research set to evaluate the actual effects of the anxiety, social support and physical health on spouses. Of the 86 spouses who participated in the study, 38 had generalized anxiety disorder (GAD). Those who had GAD were less likely to report social support and were more likely to have poorer overall health. Interestingly, heightened anxiety has a stronger influence on health than social support, indicating that anxiety-related health is a key factor in addressing the health of military spouses.

Military Medicine: Mammography Screening by Race/Ethnicity Among U.S. Servicewomen, 2009–2010

In an effort to understand the impetus to mammography screening, researchers set out to confirm the notion that access is the primary barrier in the variation of ethnic habits related to screening. Research determined that non-Hispanic women with equal access to healthcare do not exhibit substantial differences in mammography screening. For Army Medicine, it is important to pay specific attention to the promotion of access to mammography screening for all ethnic groups, especially groups traditionally prone to limited access.

JAMA: Prevalence of and Risk Factors for Autopsy-Determined Atherosclerosis Among US Service Members, 2001-2011

Based upon autopsies of service members who deployed, the incidence of atherosclerosis varied largely by age and risk factors. Of the study group, approximately 8.5% exhibited signs of atherosclerosis and the mean age was nearly 26 years old. There was a correlation between a diagnosis of dyslipidemia and the prevalence of atherosclerosis, while smoking did not show correlative properties with the disease. The study offers insight into the age range and potential causes of atherosclerosis in military members, especially for Soldiers in combat.

Medical Journal Clips

Nutrition and Fitness

Dietary Supplements and Warfighters: A Challenge for Military Providers

Military Medicine
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This month's issue of Military Medicine includes four manuscripts that address the continuing and concerning utilization of dietary supplements by warfighters, and the challenges that confront policy makers and providers who care for them. Although many dietary supplements may be helpful in promoting health and performance, there are disturbing trends emerging that suggest some may potentially be harmful. Dietary supplement use is ubiquitous among warfighters, with previous studies demonstrating a high rate of use both at home and when deployed. Although supplement use by warfighters mirrors that of the civilian population, the environmental conditions do not. Like athletes and other civilian groups, warfighters seek any advantage to assist with weight control, strength gains, improved performance, and health. However, dietary supplements do not face the same regulatory standards that medications (both prescription and over the counter) do, and as demonstrated in the three case reports described in this journal, and may lead to significant morbidity and mortality. This issue specifically addresses the emerging concern with the dietary ingredient 1, 3-dimethylamylamine, known as DMAA.

Young et al describe a 26-year-old warfighter who was injured presumably while working out during a deployment. The use of prework dietary supplements is a common practice among civilians and military athletes; these agents are thought to enhance the quality of the workout, despite limited data. As demonstrated in this case, the addition of the supplement with DMAA may have been a contributing factor for a hemorrhagic stroke. DMAA has not been previously identified in the literature as causal for an ischemic stroke; however, this agent is a sympathomimetic and is known to elevate blood pressure. Fortunately, in this case, the warfighter survived and was evacuated out of theater for further management to include rehabilitation.

Eliason et al describe two fatalities in warfighters, both of whom succumbed from what was described as exertional heat stroke complications. In the first case, a 22-year-old male warfighter in excellent health collapsed 10 minutes into a unit run; toxicology reports demonstrated the presence of both DMAA and caffeine. In the second case, a 32-year-old female, African American and sickle cell trait positive, was using dietary supplements to lose weight. At the completion of a 2-mile run she collapsed with leg cramps and dyspnea. Although she successfully survived resuscitation, she died 5 weeks after the initial collapse from sepsis while awaiting liver transplantation. Although exertional heat stroke is a known cause of sudden death in warfighters, in the majority of cases, contributing factors can be identified. Importantly, the average wet bulb globe

daytime temperatures over the 3 days before, day of, and day after the exercise were not high: 75°F and 62°F, respectively. These are not common temperatures for hyperthermia in the absences of other factors. In both cases, evidence of DMAA use was clear although a causal relationship between supplement use and cause of death cannot be confirmed. That being stated, the pharmacology of DMAA, based on it being a "look-alike" to other stimulants, is consistent with potentiating increases in metabolic rate and inherent risk for metabolic hyperthermia. It is clear that DMAA could increase the risk for exertional heat stroke through several mechanisms: increasing cardiovascular strain from vasopressor effects; impairing thermoregulation by adversely affecting skin vasodilation to facilitate conduction; increasing catecholamine secretion, lipolysis, and metabolic rate; and diminishing the athlete's sense of fatigue as a central nervous stimulant to perpetuate a continued "pushing," when they should be cutting back.

As concern over dietary supplement safety has grown over the last decade, one strategy that emerged to assist consumers is third-party certification. Accredited third-party certification is currently provided by two independent laboratories, USP and NSF International, and they attempt to establish that products are safe and pure, but this process does not ensure effectiveness. Cancio et al investigate the utilization of third-party certification in military and civilian stores within proximity of military bases. Unfortunately, this study demonstrates that a minority (12%) of dietary supplements available to military service members on base or at commercial shops are or have been independently certified by a third party for quality and purity.

The final article in this series on dietary supplements addresses strategies designed to improve safety while clearly recognizing that warfighters will use supplements. Gonsalves et al outline a number of potential practical solutions to address dietary supplement safety. Principal among these interventions are strategies that build upon the third-party certification processes, and include the possibility of a DoD seal that would recognize certification by an independent entity, based on clearly defined standards. There is a call for more research and education specifically focused on warfighters. Finally, and perhaps most importantly for the Military Medicine readership, there is a call for provider training and education to increase vigilance for dietary supplement complications and reporting of adverse events.

Dietary supplement use will undoubtedly continue at a high utilization rate for those who serve. These articles, however, serve as a wake-up call to both military providers and leadership that much can be done to avert the morbidity and mortality previously described. The cornerstone of this effort should be policy and education. Joint policy is critical to the services, so a consistent message and approach for minimizing potential harmful effects is sent, and such policy would send a message to civilian manufacturers that DoD demands high-quality products. Educational programs should provide opportunities for warfighters to learn about the risks and benefits of dietary supplements, and likely suitable alternatives to address performance, health, and weight loss needs. Currently, the Uniformed Services University Consortium for Health and Military Performance (CHAMP) (http://www.usuhs.mil/mem/champ.html) through the Human Performance Resource Center (HPRC) website—(http://hprc-online.org)—provides access to evidenced-based information on dietary supplements. The HPRC website maintains up-to-date information on tainted supplements, newly released information, the safety of dietary supplements, and provides direct access to state of the art information through the Natural Medicines Comprehensive Database for warfighters and health care professionals.

Most importantly, health care providers should conclude from these articles that dietary supplement use is common, and potentially dangerous, and that we are the potential focal point for closing the gap. Providers need to be vigilant asking about dietary supplement use in routine daily

care, and in scenarios that would raise suspicion, e.g., heat stroke, exertional rhabdomyolysis, palpitations, syncope, liver damage, cerebrovascular events, myocardial infarction, and unexplained sudden death. We need to be on the alert for use of problematic supplements, proactive in reporting adverse events, and equally attentive to informing about third-party certification. Only with adverse event reporting can we identify signals and bring attention to authorities the supplements that may cause harm. Such focus can assist in preventing scenarios, such as occurred with ephedra; we do not want to wait years before action is taken. Once again, the HPRC and the Natural Medicines Comprehensive Database provide tools to assist in warfighter and provider education and adverse event reporting.

Although many dietary supplements on the market can potentially improve both health and performance, others, as clearly identified in this issue, are potentially dangerous in the context of military training and operations. This landmark issue of Military Medicine serves as a call to action for military providers, and leaders, and effectively lays out a “way ahead” to assist us in caring for those who serve.

BACK TO TOP

Cost-Minimization Analysis of the U.S. Army Accession Screening and Immunization Program

Military Medicine
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Abstract

Objectives: Significant Army resources are utilized to identify nonimmune recruits for targeted vaccinations against hepatitis A, hepatitis B, measles, rubella, and varicella. Therefore, a cost-minimization analysis between the Accession Screening and Immunization Program (ASIP) and the previously utilized universal vaccination program will assist military public health policy makers in decisions that enhance force health protection. Methods: Serological immunity data on 41,146 Fort Leonard Wood, Missouri, Army basic training recruits aged 17 to 42 years from October 1, 2007 to September 30, 2009 were utilized. Vaccination, serology, and other direct and indirect costs were determined using the Federal Supply Schedule and local base immunization data. TreeAge Pro 2009 version 1.0.2 was used for the analysis. Results: The cumulative annual cost for the universal vaccination program totaled $1,504,587, whereas the cumulative costs for the ASIP totaled $1,094,025, for a cost-savings of $410,561 annually at this basic training site. Conclusions: Over $400,000 of annual savings was realized from the ASIP compared to universal vaccination at Fort Leonard Wood, thus confirming the cost-savings theorized by the implementation of the ASIP.
Introduction

In 2005, the U.S. Army instituted a system wide immunization program called the Accession Screening and Immunization Program (ASIP).1 The purpose of the ASIP was to ensure the highest level of immunity against hepatitis A, hepatitis B, measles, rubella, and varicella, while reducing overall vaccination costs. This program was focused on incoming enlisted military recruits at all five Army basic combat training sites: Fort Benning, Fort Knox, Fort Sill, Fort Jackson, and Fort Leonard Wood. The standards for immunization delivery are outlined in the ASIP policy and direct training posts to perform serological screening associated with these five vaccine-preventable diseases. Current Army vaccination dosing

schedules follow the recommendations of the Centers for Disease Control and Prevention and the Advisory Committee on Immunization Practices: measles/mumps/rubella (MMR)—two doses (0, 4 weeks), hepatitis A—two doses (0, 6 months), hepatitis B—three doses (0, 1, 6 months), and varicella—two doses (0, 4 weeks).2

ASIP sites serologically test for hepatitis A, hepatitis B, varicella, measles, and rubella immunity. If the recruit shows serological immunity, he/she does not receive that respective vaccination and evidence of immunity is recorded in the Army's electronic immunization tracking system, Medical Protection System. If the recruit does not show evidence of serological immunity, he/she receives the vaccination during basic training. Serological testing for mumps did not occur because of the high level of concurrent immunity of mumps in recruits who were immune to measles and rubella (92.2% to 96.1%).3 Nonimmunity for either measles or rubella will result in required vaccination with MMR. Vaccination of MMR was only averted when both measles and rubella immunity was evident. Recruits who were 18 years or older and required both hepatitis vaccines received the bivalent hepatitis A and hepatitis B vaccine. Younger recruits, along with those who required only hepatitis A or B, received the respective monovalent hepatitis vaccine. Adult doses of monovalent hepatitis A vaccines were given to those who were 19 years and older. Adult doses of monovalent hepatitis B vaccines were given to those who were 20 years and older. If the recruit was younger than these ages, then pediatric doses of monovalent vaccines were given. Because of the length of basic training, recruits only receive the 0 (initial) and 1 month doses of any vaccine series started. Subsequent doses were given when due, usually during advanced training or at their next duty station.

Before the implementation of the ASIP, the Army administered MMR, hepatitis A, and hepatitis B vaccines universally to all incoming recruits without screening for pre-existing immunity. Varicella vaccine administration before the implementation of ASIP, however, was based on a questionnaire for a negative history of varicella vaccine or disease.4

With approximately 120,000 new Army recruits annually, the cost expenditures for vaccines are substantial, and the projected decrease in unnecessary vaccinations, based on pre-existing immunity, should result in cost-savings to the Army compared to the universal vaccination program. Previous estimates for unnecessary vaccines (MMR, hepatitis A, hepatitis B, and varicella) for Army basic combat training sites were approximately $41 million in cumulative costs for fiscal years 2006–2011.4 In 2007, approximately 1 year after implementation of the ASIP, an economic analysis was performed, supporting the assertion that the vaccine cost-savings exceeded the cost of implementing local serologic screening programs.5

It has been several years since full implementation of the ASIP in 2006 and with 2 years of retrospective data from one site, a comprehensive cost comparison of the ASIP to the universal vaccination program can determine whether the ASIP policy is producing the cost savings anticipated. To accomplish this, a cost-minimization analysis was conducted between the ASIP and the universal vaccination programs by evaluating the results of one Army basic combat training site as a surrogate for the remaining four basic combat training sites. This operational evaluation of the ASIP will update previous analyses and the results of this study will provide military public health leaders with the data and an evidence-based analysis to construct future vaccination policies.

Methods

Alternatives and Assumptions

The efficacy of the two vaccination strategies (ASIP and universal) were assessed using a cost-minimization analysis over a 2-year time period.6,7 Assumptions include equal immunogenicity in both strategies and the cost of vaccination, antibody serology testing, labor, and adverse events resulting from vaccinations.

Construction of Decision Tree

A decision tree was constructed using standard software TreeAge Pro 2009 version 1.0.2 (TreeAge Software, Williamstown, Massachusetts) and analyzed to model the current ASIP vaccination algorithm (64 possible vaccination combinations, based on age and immunity status) and compared it to universal vaccination method (eight possible vaccination combinations based on age and theoretical reported history of varicella immunity). A simplified schematic of the decision model is shown in Figure 1

Data

Under an approved research protocol by the Uniformed Services University of the Health Sciences Institutional Review Board, deidentified serological immunity data (hepatitis A, hepatitis B, measles, rubella, and varicella antibodies) and demographic data (gender, race, and age at time of serology) on 41,164 basic training recruits from Fort Leonard Wood, Missouri, were obtained from the Military Vaccine (MILVAX) Agency from October 1, 2007 to September 30, 2009. Serological results of varicella zoster, measles, and rubella IgG antibodies, hepatitis A virus IgG/IgM antibody, and hepatitis B virus surface antibody (IgG Ab) were analyzed. The serological data were categorized by MILVAX as immune, nonimmune, or equivocal; per ASIP guidelines, equivocal results were categorized as nonimmune.

The proportions of the study population by demographic variables (i.e., gender, age, and ethnicity) and serological immunity status for the five vaccine-preventable diseases were analyzed using SPSS for Windows version 16.0 (IBM, Armonk, New York).

Vaccine-specific rates of adverse events were obtained from the scientific literature. Mild vaccine-related side effects from hepatitis A and B vaccinations include localized redness, mild fever, or headaches, but are rare.8–11 Severe adverse events such as respiratory distress and anaphylaxis from monovalent and bivalent hepatitis A and B vaccines were similar at less than 1 per 100,000 doses.8–11 The attenuated live-virus vaccines, MMR and varicella, have a higher rate of mild side effects at 50 and 1,000 per 100,000 doses, respectively, but with severe adverse events rarely occurring.12–16

Cost Calculation of ASIP and Universal Vaccination Program

The cost of vaccination per recruit was calculated for each of the 64 possible vaccination combinations for the ASIP and eight possible vaccination combinations for the universal vaccination program. Vaccine costs were obtained through the Federal Supply Schedule for August 2008.17 Additionally, the ASIP costs included universal serological testing for hepatitis A and B, measles, rubella, and varicella and included laboratory equipment contracts, reagents, reagent storage, supplies, and laboratory personnel costs.4,5 No laboratory costs were incurred in the cost calculation of the universal vaccination for hepatitis A and B, measles, rubella, and varicella since vaccinations were administered for hepatitis A and B, measles, and rubella regardless of prior immunity status. Varicella vaccinations were determined based on a self-reported varicella exposure questionnaire; however, the costs of these questionnaires were negligible and not included in the cost analysis. Table II details all costs utilized in the model in 2011 adjusted dollars (Bureau of Labor and Statistics, http://data.bls.gov/cgi-bin/cpicalc.pl.). This included costs of vaccine-related adverse events from hepatitis A, hepatitis B, MMR, and varicella that were obtained from scientific literature.8,13,14,17,18 A sensitivity analysis6,7 was conducted to test the robustness of the economic model using various vaccine-related adverse event rates, serological testing costs, and personnel labor costs.

Results

Seroprevalence and Demographics

A total of 41,164 recruits at Fort Leonard Wood during October 1, 2007 to September 30, 2009 were analyzed. Age ranged from 17 to 42 years (mean = 20.8 years, SD 4.2 years). Males and females represented 76.2% and 23.8%, respectively. Caucasians represented the largest proportion of the study population at 73.8%, followed by African Americans at 13.2%.

As displayed in Table III, 6.4% of recruits were serologically immune to hepatitis A only, 43.7% were immune to hepatitis B only, 13.0% were immune to both hepatitis A and B, and 36.9% were nonimmune to both hepatitis A and B. Although the majority of recruits were serologically immune to both measles and rubella (63.3%), 8.1% were nonimmune to both, 22% were immune to measles only, and 6.6% were immune to rubella only. Frequencies of the vaccination combinations under the ASIP and universal vaccination program of the recruit population are summarized in Table IVASIP and Universal Vaccination Program Costs and Sensitivity Analysis
The cumulative annual cost for the universal vaccination program totaled $1,504,587, whereas the cumulative costs for the ASIP totaled $1,094,025. This equals a cost-savings of over $400,000 annually from utilizing the ASIP over the universal vaccination program at one basic training site, Fort Leonard Wood, Missouri. Not surprisingly, the largest cost burden for both programs was the cost of vaccinations, which accounted for half of the ASIP costs and over 90% of the universal vaccination program costs. When analyzing the full range of variables for the ASIP and universal vaccination program, the cost of vaccine-related adverse events accounted for the largest range (Table V), but the total cost of both programs fluctuated minimally.

Discussion

The overall seroprevalence for measles antibodies among the recruits was 85.3%, which is comparable to previous studies (84.6%).19–21 Rubella immunity was measured at 69.9% and was lower than rates noted in previously published literature (73.3% –93.2%).19,20,22 The data demonstrate increased immunity to hepatitis A and B over time, which is understandable as a result of the introduction of hepatitis A and B vaccinations in routine childhood immunization schedules in 1999 and 1991, respectively.23–25 Studies among recruits in 2001 and 2004 showed that 12.5% were seropositive for hepatitis A antibodies, and 31.5% were seropositive for hepatitis B antibodies.23,24,26 Hepatitis A and hepatitis B immunity in this 2008–2009 recruit population was 19.4% and 56.7%, respectively. Varicella immunity in this study population was similar to a U.S. Navy recruit cohort from 1997 to 2000, which showed an immunity level of 93%.27

The cost-savings estimated in this study was $410,561 annually for one basic combat training site. Compared to the immunity rates among earlier recruit populations, the cost-savings of averting unnecessary vaccinations offsets the costs associated with serological screening. If immunity rates remain stable or increase for recruits, overall cost-savings are expected to continue. Similar cost-savings are anticipated at the remaining basic combat training sites for the Army, where serological immunity levels of recruits are thought to be comparable.

With a large proportion of the program costs originating from vaccines, this is an important area to focus further cost containment. Based on the sensitivity analysis, the model fluctuated minimally. This was largely attributable to the homogenous labor cost and low rates of vaccine-related adverse events. The initial investment cost of the serological diagnostic testing platform was stable regardless of the number of recruits tested; therefore, a greater cost-savings would be anticipated at larger basic training sites.

Conclusion

The ASIP was implemented in 2005 at all five Army basic combat training sites to decrease costs and avoid unnecessary vaccinations for recruits. This cost-minimization analysis indicates that annual cost-savings was $410,561 (27% of the total cost of the universal vaccination program) with the implementation of ASIP at Fort Leonard Wood during the study period.

This analysis provides information for policy and decision makers of the Army and other services (Navy, Air Force, Marine Corps, and U.S. Coast Guard) on the value of the ASIP. Findings of this study support the continuation of the ASIP across all five Army basic combat training sites. In a time when cost containment is increasingly important for the Army, this study demonstrates substantial cost-savings while also decreasing the number of unnecessary vaccinations given to recruits.

BACK TO TOP

Case Reports: Death of Active Duty Soldiers Following Ingestion of Dietary Supplements Containing 1,3-Dimethylamylamine (DMAA)

Military Medicine
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December 2012

ABSTRACT

Dietary supplements and their associated adverse events are not uncommon in the U.S. military, and selected dietary supplements have been associated with a number of nontraumatic deaths in service members. Specific ingredients and dietary supplement products in the civilian community are often associated with multiple adverse events and some have subsequently been removed from the marketplace; the most notable in the last decade is ephedra. We present case reports for two soldiers who were taking commercially available dietary supplements containing multiple ingredients to include the sympathomimetic, 1,3-dimethylamylamine (DMAA); both collapsed during physical exertion from cardiac arrest and ultimately died. A presentation of their clinical courses and a discussion of the history and pharmacology of dietary supplement ingredients, including DMAA, are provided. Our cases highlight concerns that DMAA in combination with other ingredients may be associated with significant consequences, reminiscent of previous adverse events from other sympathomimetic drugs previously removed from the market.

INTRODUCTION

Most nontraumatic deaths of military service members occur during exertion, with the two primary causes being cardiovascular events followed by heat injury. Sudden death in this population has been reported several times in association with various dietary supplements, most notably in the last decade from ephedra. The multiple adverse events associated with ephedra ultimately led to its removal from the U.S. market, although it is

still readily available. Ephedra and other dietary stimulants, alone and in combination with caffeine, can induce a sympathomimetic toxidrome as well as increase metabolic rate. When taken in combination with strenuous exercise, the results can be very serious and even fatal.

One ingredient of concern in dietary supplements is 1,3-dimethylamylamine (also known as methylhexanamine) or DMAA. This sympathomimetic ingredient was first used commercially in 1948 as a nasal decongestant, but was removed from the market in 1983 at the request of its manufacturer. It has since reappeared in over-the-counter dietary supplements, first as “Geranamine” (a “constituent of flower oil” according to the trademark application), then simply as geranium oil or extract, and now more recently as 1,3-dimethylamylamine or by various other synonyms. DMAA continues to be available in dietary supplements despite the lack of evidence that it qualifies as a dietary ingredient.

An early study on methylhexanamine (DMAA) noted that “The systemic toxicity of DMAA in animals is greater than that of ephedrine and less than that of amphetamine, its vasopressor action is more prolonged than that of epinephrine.” Also, an early animal study showed DMAA exerted a pressor effect 3.5 times that of epinephrine. We present here two case reports of military personnel who were taking a commercially available dietary supplement containing DMAA combined with other ingredients, and subsequently collapsed during exercise from cardiac arrest and ultimately died.

CASE REPORTS

Case 1

A 22-year-old male infantry soldier, who was in excellent physical condition (last physical fitness test placed him above the 85th percentile), experienced leg cramps followed by loss of consciousness while running in formation with his battalion for about 10 minutes. The soldier was found to be pulseless; bystanders initiated CPR and he was transported via ambulance to the emergency department. Upon arrival at the hospital, physical examination was remarkable for hyperthermia (40.8°C/105.5°F) and dry hot skin. Initial laboratory values were remarkable for renal insufficiency (potassium 7.4 mEq/L, sodium 149 mEq/L, carbon dioxide 9 mEq/L, creatinine 2.3 mg/dL, glucose 188 mg/dL), anion gap metabolic acidosis (pH 6.91, PCO_2 112.5 mm Hg, PO_2 205 mm Hg, lactate 38.2 mg/dL), and elevated cardiac and muscle enzymes (creatine kinase MB 7.3 U/L, myoglobin 6227.2 µg/L, troponin I cardiac 0.069 ng/mL). Aggressive resuscitation efforts were applied including active core cooling via an endovascular device, endotracheal intubation, and fluid restoration. Return of spontaneous circulation was achieved several times, but the patient eventually devolved into refractory asystole and resuscitative efforts were terminated after a 4-hour course. Autopsy results were consistent with the clinical evidence of shock and heat stroke, but otherwise unrevealing. As the ambient temperature at the time of collapse was approximately 23.9°C/75°F and the humidity was less than 40%, and the average wet bulb globe temperatures (composite temperature used to estimate the effect of temperature, humidity, wind speed/wind chill and solar radiation on humans) 3 days before death were below 70°F, environmental temperature alone is an unlikely explanation for cause of death. Toxicology analyses of antemortem blood were remarkable for the presence of DMAA = 0.22 mg/L and caffeine = 2.9 mg/L, with no findings of drugs of abuse or ethanol. He was taking only one dietary supplement and according to persons in his immediate community, he was taking the supplement according to the recommendations on the product label; he had been taking it for about 4 weeks.

Case 2

A 32-year-old female, African American female soldier with a history of mild obesity and sickle cell trait (SCT) had recently started dietary supplements for the purpose of losing weight. She was nearing completion of a 2-mile physical fitness test when she experienced dyspnea and leg cramps, went to lie down, and subsequently became unresponsive. She was found to be in asystole; CPR was initiated and she was emergently transported to the local military hospital. The patient responded to standard advanced cardiac life support measures with a return of spontaneous circulation. Initial physical examination demonstrated that the patient was in shock and hypotensive (77/36 mm Hg), tachycardic (109 beats per minute), hyperthermic (core temperature 105° F), unresponsive to noxious stimuli, and with dry mucous membranes. Initial laboratory values were remarkable for anion gap metabolic acidosis (pH 6.67, PCO_2 46.1 mm Hg, PO_2 292 mm Hg, HCO_3 5.0 mmol/L, lactate 21.5 mmol/dL), renal insufficiency (potassium 5.2 mEq/L, sodium 133 mEq/L, creatinine 1.8 mg/dL, glucose 261 mg/dL), liver dysfunction (GGT 56 IU/L, AST/ALT <5 IU/L, albumin 3.3 mg/dL), and suggestion of disseminated intravascular coagulation (PT 20.2 seconds, INR 1.72, PTT 52.2 seconds). The ambient temperature at time of collapse was approximately 23°C/73°F and thus an unlikely explanation for cardiac arrest. Toxicology analysis performed 4 days after admission revealed a DMAA level of 0.04 mg/L and caffeine level of 1.9 mg/L, but was negative for acetaminophen, ethanol, salicylates, or drugs of abuse. Two different supplements were found in her car and it is assumed she was taking both, which contained DMAA. The quantities of the various supplements she was taking and the time period over which she was taking them are unknown.

Upon transfer to the intensive care unit, the patient remained in a comatose state and developed progressive multiple organ failure to include rhabdomyolysis (creatine kinase peaked at 161,000 U/L), renal failure, liver failure, pancreatitis, disseminated intravascular coagulopathy, and pulmonary edema. One week following initial presentation, her liver failure significantly worsened so she was transferred to a regional transplant center. During the ensuing weeks, the patient's condition briefly improved as she regained consciousness and was at one point extubated and communicating with her family. However, she developed ultimately refractory sepsis and died 5 weeks after the initial collapse.

DISCUSSION

In the case studies presented, both patients had ingested the same product marketed as a dietary supplement containing (among other ingredients) DMAA, β-alanine, arginine α-ketoglutarate, caffeine, creatine monohydrate, and Schizandrol A. Whereas the toxicological profiles of creatine, arginine, β-alanine, Schizandrol A, and caffeine have been relatively well established, little is known about DMAA. As with any case report, no causal relationship between the supplement ingredients and deaths can be confirmed. However, based on the structure and biochemistry of DMAA as a drug, the symptoms and toxidrome that developed in these two cases are in line with what could be expected of DMAA alone or in combination with the other ingredients.

DMAA was originally developed in 1944 for topical use for nasal decongestion. In early efficacy studies, local application of DMAA via nasal route of administration produced little or no effect upon the pulse rate or blood pressure in adult humans although potential side effects were known including headache, nervousness, mental stimulation, and tremors. The Council of Pharmacy and Chemistry of the American Medical Association recommended the occurrence of such side effects warrant discontinuing use of the drug. The systemic toxicity of DMAA lies on a spectrum between ephedrine and amphetamines. Over time, the actions of DMAA on the body were established to be similar to amphetamine and

ephedrine, and in vitro studies demonstrated it was ~200 times less potent than epinephrine as a vasopressor, but had a longer duration of action. DMAA eventually fell out of favor and was removed from the market in 1983 at the request of the manufacturer. DMAA reappeared in dietary supplements as early as 2005. Since then the number of products containing DMAA as a supplement has increased and have become best sellers in mainstream nutrition stores. It appears DMAA gained acceptance as a dietary ingredient on the (now discredited) premise that it was extracted from *Pelargonium graveolens*, a plant in the Geranium family. Numerous groups publicly dispute the methodology and conclusions of the article, and no other published evidence exists to establish DMAA as a dietary ingredient. However, DMAA continues to be available in dietary supplements so it is important for clinicians to query service members who have experienced adverse events such as those described here for the use of dietary supplements.

Caffeine is an analeptic or central nervous system stimulant. Similar to the serious adverse events occurring with combination ephedra–caffeine products, caffeine combined with DMAA may be synergistic, producing a more powerful stimulant effect and a lower dosage threshold for adverse events. In addition to the caffeine that is included in supplements, consumers may ingest caffeine from other sources further increasing the risk of adverse events.

The dietary supplement product in these case studies also contains two amino acid substances (β-alanine and arginine α-ketoglutarate) as well as creatine, all of which could contribute to adverse effects in both kidney and liver. Although creatine is generally believed to be safe at low doses, supplementation can increase urinary excretion of creatinine 10% to 30% and creatine up to 100 times greater than normal. The long-term effects of this combination of ingredients have not been investigated, but the possibility for a variety of nephrotoxic effects exists, particularly in those with compromised kidney function. Interestingly, Bailes et al presented evidence that amphetamine derivatives and creatine together may contribute to dehydration and heatstroke by shifting water out of the extracellular space into muscle cells. Such an effect may also occur in response to DMAA/creatine combinations.

Since the only known source of DMAA in the United States is from products marketed as dietary supplements, it is likely that the DMAA discovered in the patients' blood and urine samples was from the dietary supplement they were using at the time. Caffeine was also found in the blood of both, although there are many potential sources of caffeine other than the supplements. Levels of caffeine found in the soldiers' blood were not within the range associated with caffeine fatalities (79–344 mg/L), although as stated earlier, the presence of DMAA and caffeine together might produce a toxic effect at a lower dose, given the known interactions between caffeine and ephedra. Although toxic levels of DMAA are unknown, Gee et al have published three cases of cerebral hemorrhage following DMAA ingestion with plasma DMAA values of 0.75, 1.09, and 2.31 mg/L as compared to our values of 0.22 and 0.02 mg/L. The critical cutoff for toxicity is unknown.

One of the case study patients had SCT, which has previously been associated with fatal exertional heat stroke and rhabdomyolysis. DMAA and caffeine could have contributed to catecholamine neurotransmitter persistence and adenosine receptor antagonism in this patient, and mutual potentiation of the stimulant effects might have resulted in excessive metabolic heat production, and possibly hypokalemia. Previous studies have demonstrated increases in metabolic rate when caffeine and sympathomimetics, such as ephedra, synephrine, and/or yohimbine, are combined. Unfortunately, data on stimulant effects in persons with SCT are limited, but such ingredients may exacerbate any intrinsic complications of SCT.

At least nine other case reports published or reported have shown a possible association between an adverse event and DMAA. All of the case reports list one or more of the following symptoms: hypertension, agitation, headache, vomiting, bradycardia, and/or stroke following the use of DMAA and bear hallmark similarity to those observed for ephedrine.

Some government agencies around the world are taking regulatory action to curb the availability of DMAA. The New Zealand Health Ministry in 2008 issued a request for the voluntary suspension of the sale of pure DMAA powder by retailers following adverse reactions to this substance, and all products containing DMAA will effectively be banned, removed from shelves, and no longer sold over the Internet in New Zealand from April 9, 2012 forward. In August 2011, Health Canada classified DMAA as a drug and it is now subject to their Food and Drug Regulations. Authorities in France and Italy are in the midst of investigations with regards to banning products with this ingredient entirely, and the UK division of the Council for Responsible Nutrition has pointed out that DMAA is not authorized for use in food supplements in the European Union.

The fact that at least two previously healthy soldiers died after ingesting a product marketed as a dietary supplement that contained DMAA raises questions, especially since only a few studies funded by industry have been conducted on this stimulant. Thus, the safety of DMAA remains an open question. Importantly, the types of adverse findings in these cases are consistent with known effects of sympathomimetic drugs and this entire scenario is reminiscent of ephedra, which ultimately was banned by the FDA. Otherwise, healthy individuals who present for medical treatment with exertional rhabdomyolysis, exercise-related syncope, heat injury, hypertension

BACK TO TOP

Third-Party Certification of Dietary Supplements: Prevalence and Concerns

Military Medicine
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ABSTRACT

According to recent studies, over 50% of the general population (and nearly 70% of military personnel) report regular use of dietary supplements (DS). Military personnel may be at greater risk for adverse reactions to DS because of operational environments and stressors (extreme heat, altitude, or sleep deprivation) associated with military deployments and training. As a recent example, the Department of Defense placed a medical hold on all DS containing the ingredient 1,3-dimethylamylamine in response to several fatalities linked to the use of this product. This study investigated product certification for DS in military commissaries (grocery stores), exchanges (department stores), and civilian retail stores. Overall, only 12% of the available products were certified by an independent scientific agency. Consumers should be aware that most over-the-counter DS do not have independent certification of product integrity. Although “third-party certification” does not ensure DS safety or

effectiveness, it is important that consumers and health care providers are made aware that such product screening takes place, to help patients make more informed decisions about the purchase and use of DS.

INTRODUCTION

Dietary supplement (DS) use is quite common in the United States. Based on data from the 1999–2000 National Health and Nutrition Examination Survey, 52% of adults take DS on a monthly basis. Other data from athletic, military, and general population samples suggest that over 50% of adults regularly take some form of DS. DS use is particularly widespread in the military. Current data suggest that 69% of military personnel use at least one DS and 22% use three or more DS. Military personnel typically purchase their products from one of the three sources: military commissaries/exchanges (35.6%), nutrition/health food stores located on post/base (25.3%), and nutrition/health food stores off post/base (25.3%). Other products (13.2%) are purchased either through mail order or the Internet.

Currently, the U.S. Food and Drug Administration (FDA) does not require premarket review of DS for safety or purity. Similarly, the FDA does not provide formal regulatory oversight for DS product development or marketing. The Dietary Supplement Health and Education Act of 1994 requires DS manufacturers to ensure that the (1) “supplement facts” labels are accurate, (2) dietary ingredients are safe, and (3) contents match the amounts declared on the label.

To bridge this regulatory gap, organizations such as U.S. Pharmacopeia (USP) and National Sanitary Foundation International (NSF) have developed independent certification procedures for individual DS products. These third-party entities conduct scientifically rigorous, independent product reviews for safety and purity. If independent testing standards are satisfied, DS are provided with a “stamp” of certification. However, because such third-party certification is not required, many DS manufacturers forego the added scrutiny and expense associated with independent product certification.

The present study was designed to assess the percentage of independently certified DS available for purchase in a cohort of military commissaries (grocery stores), exchanges (department stores), and similar civilian retail stores. The study focuses on military personnel because they may be at greater risk for adverse reactions to DS as a result of the operational environments and stressors (extreme heat, altitude, or partial sleep deprivation) common in military deployments and training. Although “third-party certification” does not ensure DS safety or effectiveness, it is important that consumers and health care providers are made aware that such product screening takes place, to help patients make more informed decisions about the purchase and use of DS.

METHODS

Following approval from the Uniformed Services University of the Health Sciences Institutional Review Board, six military commissaries (grocery stores), four military exchanges (department stores), and two different commercial vitamin specialty stores were chosen to quantify the numbers, types, and percentage of independently certified DS available on-the-shelf for consumer purchase. Military exchanges and commissaries in the Greater Washington DC area and on Oahu, Hawaii, were sampled. The civilian stores selected from the Washington DC area were within a 10-mile radius of nearby military installations. To determine on-the-shelf availability of certified DS, study investigators went to the stores and

recorded all DS available for consumer purchase. Primary outcomes of interest included the name of the DS manufacturer, the primary ingredient listed on the product label, the USP-defined DS category and the presence of product label certification. Based on this label review, products were listed as being either “third-party certified,” “self-certified,” or “not certified.”

For the purposes of this study, DS were designated as third-party certified if they displayed the USP or the NSF certification seals of approval. The USP Verification Program issues a product seal after confirming that the product (1) contains the ingredients listed on the label in the declared potency and amounts, (2) does not contain harmful levels of specified contaminants, (3) will break down and be released into the body within a specified amount of time, and (4) has been made according to FDA current good manufacturing practices by using sanitary and well-controlled procedures.

Using a process analogous to USP, the NSF certification process has a specific NSF Certified for Sport Program to ensure DS do not contain banned substances and have met stringent certification criteria. The NSF Prohibited Substances List is used by Major League Baseball and the National Football League as the official list of banned supplements. NSF certification verifies that the (1) identity and quantity of dietary ingredients declared on product labels are accurate; (2) products do not contain undeclared ingredients or unacceptable levels of contaminants (heavy metals, microbial, aflatoxins, and if applicable, pesticides, polychlorinated biphenyls, and dioxins); and (3) manufacturer conforms to currently recommended industry manufacturing practices.

Products were assigned as “self-certified” if they relied on in-house product labeling. Some companies stamp their DS products with a generic seal of approval that may say “guaranteed quality,” “quality assured,” or conform to FDA current good manufacturing practice standards. Products listed as “self-certified” may use internal certification processes to document adherence to published FDA standards and utilize statements such as “conforms to USP <2091> for weight” on the product label, which means the DS “pill” conforms to USP standards with regards to the stated weight. These self-certified products have no documentation, however, of independent testing to ensure product purity. Self-certification is scientifically less rigorous for ensuring consumer safety/quality because this process does not screen for banned substances, test for ingredient dissolution and disintegration, or both. Self-certified products do not utilize a nonbiased, independent agency for product verification.

If a product had no clearly identifiable certification stamp, and it was unclear to the consumer as to whether or not the product had been tested for content and/or purity, the product was classified as “not certified.”

Some of the products that NSF and USP have listed as “independently certified” on their websites do not have the seal on their product label. To avoid misattribution of product certification, an additional cross-check of all products against posted lists of certified products published by both NSF and USP was done. Products listed as NSF/USP certified but lacking verification on the label were considered to be third-party certified for purposes of analysis.

We also evaluated differences in cost based on third-party certification. Cost comparisons were difficult because of confounding differences in ingredients, dosing, and manufacturers. As such, comparable pricing was calculated on a “per pill” basis by comparing DS that were third-party certified to DS that were either self-certified or not certified.

After all product labels were reviewed, data were entered into a Microsoft Excel spreadsheet for analysis. Basic descriptive statistics were used to describe product certification categories.

RESULTS

A total of 2,315 DS products were available for on-the-shelf purchase in the 12 stores. Of these, 12.1% (280/2,315) were found to be “third-party certified,” 28.5% (659/2,315) were classified as “self-certified,” and 59.4% (1,376/2,315) were “not certified.” Amino acid supplements had the highest percentage of third-party certifications (24.4%), followed by vitamins (23.8%). Vitamin and multivitamin/mineral products were the most prevalent of all types of supplements and therefore had the highest absolute number of third-party certifications.

Certified DS were most commonly available in military exchanges. Third-party certification was least common in civilian stores. Only 4.0% of DS products available at commercial specialty stores were third-party certified. When self-certification was included as a valid form of DS certification, military commissaries had the greatest total percentage of certified products (57%), followed by military exchanges (35%) and commercial vitamin stores (29%).

Statistical tests were not run; but, no trend suggesting a higher cost for third-party certified products relative to noncertified products was noted.

DISCUSSION

Our study indicates that the majority of DS available in retail stores for purchase by military personnel are not independently certified for quality or purity. This finding is particularly important given the recent medical hold the Department of Defense imposed on all DS products containing the ingredient 1,3-dimethylamylamine. This hold was put in place in response to two fatal outcomes potentially associated with DS use. These unfortunate cases have increased attention on potential adverse events associated with DS use and call safety and purity issues into question. Prior studies have shown that the potential for contamination of DS is high. Reports suggest that at least 15% of DS are contaminated or adulterated in some way. Third-party DS certification is intended to mitigate this problem by ensuring the integrity of the manufacturing process and by establishing a baseline standard of quality and purity.

Military personnel and athletes often take DS to enhance performance. Our study shows that at venues where DS are commonly purchased by military personnel, very few products are independently certified. This potentially places unknowing consumers at risk. It is likely that few consumers (and health care providers) understand the risks associated with DS failing to meet purity or quality control standards, nor recognize that some DS are independently certified. Dodge and Kaufman reported that most consumers have little knowledge regarding the role the FDA serves in regulating DS. Interestingly, consumers who are educated about current FDA regulations regarding DS manufacturing and distribution processes rate DS as less safe and less effective than consumers who are not aware of the regulatory standards. Another area of concern for consumers is the fact that many DS interact with commonly prescribed pharmaceuticals. In 2008, the Center for Food Safety and Applied Nutrition Adverse Event Reporting System documented 1,080 health anomalies that could be tracked specifically to DS use.

Unlike highly regulated prescription medications, our results showed 15 to 24% of DS sold on military installations and less than 5% of those sold in sampled civilian stores undergo any type of independent, third-party certification process. As the DS industry continues to expand, the number of adverse reactions associated with their use can be reasonably expected to increase.

Our study has several limitations. First, online suppliers were not included in this survey. Many military members anecdotally report purchasing DS through Internet sources. Another limitation is that our geographic sampling was one of convenience. It is possible that different products are available at different stores in different geographic locations across the country. This is unlikely in the military setting, however, since most commissaries and exchanges offer comparable products because of business standardization protocols. It is expected that national chains of civilian vitamin stores do likewise, with perhaps local product exception. Another limitation is that our analysis was limited to products available on-the-shelf at the time of the survey. Newer products continually emerge to replace older products. However, given the broad number of products sampled, we feel that our results likely generalize to military members and civilian consumers throughout United States.

In summary, our results suggest that a minority (12%) of DS available to military service members on base or at commercial shops that sell DS are independently certified by a third-party for quality and purity. Military commissaries and exchanges were more likely to carry independently certified DS compared to civilian vitamin specialty shops. Based on increasing reports of adverse events associated with DS use, promoting the sale of independently certified DS is one way to improve quality and purity control and enhance patient (consumer) safety. Although “third-party certification” does not ensure DS safety or effectiveness, it is important that consumers and health care providers understand issues surrounding DS manufacturing processes to make more informed decisions regarding DS use.

BACK TO TOP

Dietary Supplements in the Department of Defense: Possible Solutions to Optimizing Force Readiness

Military Medicine

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ABSTRACT

Dietary supplement use is common among military service members; approximately 17 to 20% report using high-risk weight-loss, performance-enhancing, and bodybuilding supplements. To date, no overarching policy or program has been approved or implemented to inform service

members or educate health care providers on the potential adverse consequences of using multiple combinations of supplements or the pros and cons of supplements per se. A review of regulations, concerns, and possible solutions is provided. Importantly, the role of third-party certification and education is emphasized.

INTRODUCTION

Dietary supplement (DS) use by military service members is high. In 2010, Lieberman et al reported that more than 50% of soldiers used DS one or more times per week and 22% consumed three or more different ones each week. Two 2012 publications on military populations found weight-loss and bodybuilding supplement use ranged between 17 and 20%. Moreover, use of such supplements was associated with high-risk behaviors—steroid use, heavy drinking, and riding a motorcycle without a helmet.

The accessibility of DS in many retail stores on military bases may give the impression of active endorsement for their use and safety, and requirements to meet body composition and fitness standards and personal desire to improve performance may contribute to use. Although some DSs might improve physical or mental performance, others may interfere with or otherwise compromise mission success. Service members are frequently required to perform highly specialized and potentially dangerous tasks under extreme environments (high temperature, altitude) and interactions between combinations of ingredients under such conditions are unknown. Likewise, service members are also a target for DS manufacturers. Thus, DS use by Military personnel raises a number of unique concerns. This article reviews the history of DS regulations, describes issues of concern, introduces concepts related to quality, and proposes solutions that might enhance the health and safety of service members.

HISTORY AND REGULATIONS

DSs are regulated by the Dietary Supplement Health and Education Act (DSHEA) of 1994, which defined them as those products (except tobacco) containing one or more of the following dietary ingredients: vitamins, minerals, herbs or other botanicals, amino acids, and other substances (e.g., enzymes, organ tissues, glandulars, and metabolites); and they are intended to supplement the diet by increasing the total dietary intake of that ingredient. Regardless of form, DSs were placed in a special category under the general umbrella of “foods,” not drugs—they are exempt from U.S. Food and Drug Administration (FDA) drug approval standards. As a result, the FDA does not evaluate the safety, efficacy, or quality of DS ingredients or products. This exemption may have been suitable in 1994 when about 4,000 DSs were available, but likely not in 2012 when an estimated 55,000 products are on the market.

The enactment of DSHEA not only decreased barriers for consumer access to DS but also presented various safety, efficacy, and quality issues—DHSEA permitted products to be marketed with limited content labeling, no documented health benefits, and little or no safety data. Structure–function claims that may appear on product labels have confused consumers as the number and types of natural health products have burgeoned. Although the FDA is responsible for claims on product labels and promotional materials distributed at the point of sale, the Federal Trade Commission oversees claims in advertising; for example, marketing on the Internet, television, and the like. In 2009, a U.S. Government Accountability Office report found that consumers were not well informed about the safety and effectiveness of DSs and had difficulty interpreting

product labels. In addition, Dodge et al highlighted deficits in consumer knowledge about FDA regulation and effectiveness of DSs. Without a clear understanding of the safety, efficacy, and labeling of DSs, consumers are exposed to risks, which include potentially harmful drug–supplement interactions, taking DSs instead of prescription medications, and using “megadoses” of various vitamins and minerals.

Once a DS is on the market, the FDA must demonstrate that it poses an unreasonable health risk. The FDA can restrict a DS only after it has been proven to be unsafe. Thus, the FDA cannot act swiftly to protect the public, and it may take years after a product has been marketed and harm occurs before it is finally removed from the market. For example, the FDA took approximately 10 years after issuing its first advisory about ephedra—a popular weight-loss supplement in the 1990s reported to have caused heart attacks, seizures, and deaths—to gather sufficient data to meet the statutory burden of proof before banning it from the market in April 2004. The Department of Defense (DoD) banned the sale of DSs containing ephedrine alkaloids from military commissaries worldwide in 2002—2 years before the FDA ban—because of safety concerns.

Several states in the United States (Illinois, California, and New York) acted independently to regulate ephedra. For example, in 2005, the New York State Task Force on Life and the Law, an independent body created with a mandate to develop public policy on difficult bioethical questions, recommended that New York impose its own supervision to provide consumers with basic DS information and protect them from dangerous DSs. Although New York State's far-reaching actions are commendable, they had little impact on the DS industry and intense lobbying by DS manufactures.

Inadequate federal oversight of the DS industry is seen as a serious public health matter for many and a great concern for the U.S. military because of the diverse occupational demands and environmental exposures of service members. It is increasingly clear that multi-ingredient, adulterated, and contaminated DSs may pose a significant risk to our service members and compromise readiness.

A landmark report by the Institute of Medicine (IOM) in 2008 suggested that without appropriate guidance on DS use, certain DSs have the potential to negatively impact mission readiness and performance. The IOM recommended developing service-wide military policies (e.g., education or regulations) and implementation of a system to actively monitor DS use and adverse events (AEs). The DoD Instruction 6130.05 specifically states that it is the policy to provide appropriate education and training to service members to ensure they can make healthy lifestyle choices regarding DSs, but the lack of formal policies related to DS use has raised concerns.

QUALITY CONTROL STANDARDS

Some DSs are manufactured by established pharmaceutical and nutrition companies, and all are required to follow the FDA current good manufacturing practice (cGMP) regulations. However, companies with 20 or fewer employees did not have to comply with or meet this regulation until June 2010. Regardless of regulations, quality control standards for DSs may range from nonexistent to very high quality; contamination, adulteration, false labeling, and incomplete labeling are not uncommon problems.

Contamination and Adulteration

Many weight-loss, bodybuilding, sexual enhancement, performance boosting, and diabetic DS products are contaminated with prescription/nonprescription medications. The literature suggests that 15 to 25% of DSs touted to increase physical performance may contain banned or prescription drug ingredients that are not listed on the label. Hidden ingredients found in various products between 2009 and 2012 include steroids, sildenafil analoges, aromatase inhibitors, sibutramine, tadalafil, and others. The FDA has removed many such products from the market. These contaminants/adulterants may cause minor to serious injury or illness by themselves, or when they interact with DS ingredients. Injuries and illnesses associated with DSs include, but are not limited to, cardiac events, exertional heat stroke, seizures, rhabdomyolysis, liver and kidney failure, syncope, and death.

Contaminated products are not merely a peripheral problem from selected “black-market” suppliers, as they can also be found within the major supply chains. The major chains—GNC and Vitamin Shoppe—withdrew StarCaps from their stores in 2009 after the papaya-based supplement was shown to contain bumetanide, a powerful diuretic with serious side effects. StarCaps was only one of 72 weight-loss supplements the FDA reported in December 2008 to be contaminated. Thus, the quality of DS products is neither assured nor uniform; those of low quality could potentially result in injury.

Third-Party Certification of DSs

The need for improved oversight over DSs led the FDA to implement regulations requiring cGMP and truth in labeling. Third-party certification consists of an independent “third-party” agency/organization conducting a quality review of a manufacturer's products and processes—they examine the manufacturing plant where the ingredients originate, the conditions and facilities where the ingredients are manufactured into the final product, and test the ingredients and final products for multiple factors. The FDA published guidelines for third-party certifiers in 2009, and since then increasing numbers of manufacturers are voluntarily taking part in certification programs. Products that pass all verification requirements may receive recognition and a seal of participation.

Some key elements to require from a third-party certifier include demonstrating that (1) the ingredients used come from a reputable source; (2) the ingredients are consistent with those listed on the label in the declared potency and amounts; (3) the product does not contain harmful levels of specified contaminants; (4) the product will dissolve, disintegrate, and be released into the body within a specified period; (5) the product was made according to the FDA cGMP, under sanitary and well-controlled procedures; and (6) the manufacturing plant has passed FDA inspections for GMP. Some certifiers also screen for banned substances and conduct random off-the-shelf tests on approved products. This screening process would be very important for service members, as some DSs can even cause positive drug urinalysis tests because of adulteration and the presence of banned/illegal substances. Although certification does not ensure effectiveness or even safety, such programs do help curtail “the Wild West nature of the dietary supplement industry” as described by Larimore and O'Mathuna, and promote integrity in the manufacturing process.

The five primary third-party certifiers include: (1) National Sanitation Foundation (NSF) International; (2) U.S. Pharmacopeia (USP); (3) Informed Choice; (4) Banned Substances Control Group; and (5) Consumer Labs. These third-party certification organizations have developed their own, specific approaches, criteria, and processes for evaluating and authenticating products; each one differs in some ways, but all follow current FDA

guidelines. USP and NSF International are nonprofit, nongovernmental organizations, both of which have developed manufacturing standards to ensure the consumer receives a quality product, provide annual and/or biannual certification, conduct safety reviews, have scientific advisory boards, and have established reputations for developing standards for pharmaceutical drugs and DSs.

ADVERSE EVENTS REPORTING

Over the past 15 years, service members have experienced mild to serious AEs in association with taking DSs. Some have died and others were hospitalized or suffered serious consequences after combining exercise with DSs. At least 33 service members taking ephedra died during exercise. Unfortunately, AE reports (AERs) from DSs and botanicals are limited at best. The FDA passed regulation in 2008 mandating all manufacturers, packers, and distributers submit all serious AERs to the FDA (FDA 3500A, Mandatory Reporting Form). Interestingly, 1,080 AEs were submitted to the FDA the year the regulation was implemented, as compared to only 350 in 2007.

These AERs represent only a small fraction as the FDA has estimated that total numbers of AEs—including mild, moderate, and serious, related to DS per year—are over 50,000, which emphasizes that underreporting of AEs limits the FDA's ability to identify and act on safety concerns. Some reasons for underreporting include assumption by consumers that DSs are safe, reluctance to report DS use to physicians, failure to recognize chronic or cumulative toxic effects from DS use, unfamiliar with AER process by providers, and a cumbersome reporting process.

The DoD has no formal, centralized process or mechanism for AER from DS; it relies on the FDA MedWatch Adverse Event Reporting System, which provides no real-time signals to the DoD. A recent study of over 600 DoD physicians found that the majority (>60%) had witnessed an AE in association with a DS, but less than 25% of them knew how or where to report the AE. Thus, a centralized process for AER from DS is critical for detecting signals to remove dangerous DSs.

PROACTIVE APPROACHES/POSSIBLE SOLUTIONS

The recognition that some DSs may pose a threat to force readiness is real. The current regulatory structure for DS leaves service members insufficiently protected and DoD-level actions are warranted to help protect the force until adequate standards and enforcement for manufacturing, safety, and effectiveness are implemented government wide. The process of identifying and choosing solutions to this problem will require careful weighing of the evidence of harm, and then appropriate action among the services.

Many possibilities for increasing the safety and quality of DSs exist, and solutions range from targeted education and training to making decisions about what products should be authorized for sale on military installations. One potential approach is to implement a screening process for products available for sale on military installations. For this article, “military installation” includes the commissary, the exchange, kiosks, fitness centers, and specialty concession stores within the continental United States and overseas.

Previous studies have suggested that service members typically purchase 35.6% of DS products from military commissaries/exchanges and 25.3% from nutrition/health food stores on base; the remaining products are purchased off base (25.3%) or through mail order/the Internet (13.2%). If over half of all DS products are purchased on military installations, a process to ensure quality and safety would send a strong

message to service members and their families and to manufacturers of DSs. Cancio et al reported that less than 12% of all DSs sold on military installations are third-party certified. Although no quantitative data are available, it is generally assumed that service members believe DSs sold on installations are safe. Possible solutions to protect service members and their families from potentially harmful DSs are described next.

Monitor DS Use Patterns

The IOM strongly supported monitoring patterns of use. The most common DS, identified by brand name or ingredients, could be monitored on a regular basis for sales and use patterns. These patterns could be assessed for risk through cooperation with the DoD Dietary Supplement Subcommittee (DSSC), the Center Alliance for Dietary Supplement Research (CADSR), and other national partners (e.g., Office of Dietary Supplements [ODS], FDA, USP, NSF, and the U.S. Anti-Doping Agency). New data on the safety and efficacy of DSs emerge continually from scientific research and AERs. The DSSC could evaluate available safety data on DSs sold on installations to estimate potential risk. These evaluations could result in specific policy or regulatory recommendations to the DoD and might range from a public advisory to banning the sale of a particular DS or ingredient on a military installation. A clear process would need to be set up, but is certainly feasible.

Regulate Point of Sale—Product Quality and Safety

The military does not currently regulate, or control to any extent, which DSs are sold on installations. However, several options could be implemented to improve the quality and safety of DSs sold. First and foremost, the DoD could require all DSs sold on military installations to have undergone third-party review by selected nonprofit, certifying bodies that have multiple predefined criteria in place. Requiring third-party certification sends a clear message and would greatly enhance product integrity. In addition, third-party certification would have the added benefit of removing the evaluation process from the consumer, as well as any potential conflict from the military installation to a more impartial source. Implementing such a policy/requirement would require coordination and collaboration, but would be both feasible and important.

Regulate Use

Another possible approach would be implementation of premarketing requirements based on known safety/efficacy profiles or potential risks of consumer harm. Two tiers could be used to classify DSs as lower (Tier I) and higher (Tier II) risk based on the number and combinations of ingredients, currently available research literature, and existing AERs. Then third-party certification might be required for all Tier II DSs, and encourage voluntary third-party classification for Tier I DSs, still keeping in mind that all DSs may pose some risk when not used or manufactured appropriately.

Tier I, the least restrictive category, would encompass single ingredients, multivitamins and minerals, fish oils, α-linolenic acid, single amino acids, creatine monohydrate, probiotics, and the like. However, if a herbal ingredient were added to a commonly used multivitamin product, the product would be considered higher risk. For example, a DS containing creatine monohydrate as the only ingredient would be considered Tier I, whereas a DS containing a “proprietary” creatine complex, such as creatine phosphate or creatine nitrate plus D-Ribose and ginseng, would no longer be considered Tier I.

Tier II would include known categories of problematic DSs, such as weight-loss, performance-enhancing, testosterone boosting, sexual enhancing, bodybuilding, and diabetes products. Also, products with nonnutritive ingredients other than caffeine (e.g., superoxide dismutase, yohimbine, synephrine), combinations of ingredients, herbals, botanicals, specialty multivitamin supplements, and products labeled as containing "Proprietary Ingredients/Blends" would be Tier II. Although manufacturers do want to protect their special formulations, the user of DSs with proprietary ingredients has no way of knowing the actual amount of each ingredient in the protected blend.

Expand Authority of DSSC

The DSSC, a joint DoD subcommittee under DoD (Health Affairs), was chartered in February of 2012. This diverse body of experts—including dietitians, pharmacists, family medicine physicians, and clinical pharmacologists—is aware of the FDA regulations, understands the issues, and interacts with the FDA and ODS. Health Affairs could expand the authority and mission of the DSSC to organize internal and/or external safety and efficacy reviews of commonly used and potentially problematic DSs and help monitor DS safety. Further, it could help develop unified messages on DSs through education and training.

Establish Conditions of Use

The use of any DS during basic and/or any other military training could be prohibited, particularly when use might pose a risk (i.e., basic training, dive school, aviation, special operations). All services currently prohibit the use of DSs during basic training, but similar policy statements could be developed for other training venues and deployment locations deemed high risk. In addition, the military could establish specific "conditions of use" for DSs that pose the greatest risk and prohibit military facilities from stocking products whose ingredient contents are of concern. This approach is comparable to the system used by the U.S. Navy's Aeromedical Reference and Waiver Guide, which categorizes DSs into three classes (A, B, and C) based on specific limitations of use. Under this system, Class A DSs could be used without limit, Class B DSs would be limited to individuals cleared by a provider, and Class C DSs would be prohibited.

Certain exceptions could be acknowledged. For example, service members currently under the care of a physician for medical or metabolic conditions who had been prescribed a DS would be able to continue use, unless it was clearly problematic. In addition, the service member would be able to continue such use when a dietary deficiency/inadequacy (e.g., vitamin D, iron, essential amino acids, and essential fatty acids) had been established by a dietitian or a health care provider.

Develop a DoD Seal

Another possible solution would be a DoD Seal to demonstrate third-party certification. This could be a color code (green/red), with green signifying third-party and red indicating no independent certification. Alternatively, the seal could be based on the Tier I/II approach described earlier or the Human Performance Resource Center's Dietary Supplements Classification Table. This classification system was developed based on recommendations from the IOM report, wherein the risks (minimal, low, moderate, or high concern) and benefits (low, moderate, or high) of particular DS were considered based on available evidence and use during operational conditions. Considerable thought would be needed to effectively implement a seal/logo system for DSs.

Section-off Supplements

Another solution is to create a special section in the sale venues to identify products that have undergone third-party certification. Certain shelves would be marked to indicate all products were third-party certified, which would inform/notify service members those DSs are free of illegal/controlled substances and of high quality. As noted above, making high-quality DSs available and prominent on military installations would assist our population in making informed choices and hopefully encourage other DS manufacturers to have their products third-party certified. Third-party certification of DSs, if the appropriate criteria are met, will help ensure products sold on our installations are of high quality, unadulterated, and likely safe.

Surveillance and Research

The IOM has recommended additional research be conducted to evaluate the safety and efficacy of DSs. Clinical research on DSs has been slow and cannot keep up with the new products reaching the market annually. Importantly, methodologies for evaluating multi-ingredient products have not been established, and various issues need to be addressed. The CADSR is examining various approaches to studying multi-ingredient products, but given some DSs contain as many as 50+ ingredients, the methodology becomes increasingly more complex. The DoD could conduct selected clinical trials with special emphasis on DSs identified by the DSSC as most relevant, with a focus on potentially beneficial, but high-risk combinations. The military operational environment is unique, so other governmental organizations are not likely interested in conducting safety and efficacy trials in such environments.

Targeted Education and Training

A DoD-wide DS education program should be implemented to include interactive modules, videos, social media advisories/educational messages, and general information aimed at helping service members make informed choices regarding DSs. Curricula could be specifically targeted for different groups (special operations operators, aviators, divers, physicians, dietitians, nurses, and other health care professionals) and organizations (training schools, military hospitals, and health care facilities), with dissemination of cohesive, consistent messages—ranging from best resources to AERs. Both professional and consumer education about AER were recommended in both IOM reports.

Service Members

DS education could be incorporated through established training at entry into service and as a part of annual training. The education should inform about potential risks and adverse effects; the importance of discussing DS use with their health care providers; and how to read a “Supplement Facts” label, third-party certification, the basics of DS regulations, the potential for drug/DS interactions, and the DS categories of greatest concern. In addition, high-quality resources on DSs, such as http://hprc-online.org and ODS (http://ods.od.nih.gov), would be communicated.

Health Care Personnel

Health care personnel could be encouraged to participate in Continuing Education Unit-based, interactive training modules, wherein they would be instructed how to gather and document DS information from their patients, informed about professional sources of evidence-based information on DS, and taught how to report suspected AEs associated with DS. Such a module is currently available at http://hprc-online.org/ and provides 2 Continuing Education Units. Reporting of AEs related to DSs could be mandatory, which would greatly enhance the ability of the DoD to detect signals. Although no formal mechanism for AER from DS currently is in place, the information should flow to the local preventive medicine service and to Natural Medicines Watch at https://www.therapeuticresearch.com/nd/adverseevent.aspx?s=ND until a DoD system is in place. This will ensure positive information flow to DoD and the FDA, so new signals can be detected.

Military dietitians can be of great assistance to service members in the safe and appropriate use of DSs and an important resource for gathering and disseminating DS information. An online password-protected forum for rapid communication and sharing experiences on popular DS products would be useful. Over the past several years, the ODS has allowed the DoD health care professionals to participate in their annual Dietary Supplement Practicum. This opportunity has allowed approximately 25 dietitians and other providers (pharmacists, physicians) to become familiar with the key issues relating to DSs.

Personal Trainers/Exercise Specialists

The DoD could require (or incentivize) persons working as personal trainers, strength and conditioning specialists, physical fitness experts, and others to have completed a DoD-certified course in DSs. This would ensure a basic foundation of knowledge and better equip them to more critically review marketing materials continually imposed on the military by DS manufacturers. The DSSC could lead in the development of such a course, in collaboration with others particularly interested in this topic.

Smart Phone/iPad/Kiosk Application

With the advent of new technologies and rapid access to information, an application wherein every service member could select the DS he/she is taking from a pick list of all DSs on the market would be useful. The information could be transmitted to his/her personal health record and merged with individual medical and pharmacy records. The DoD could track the prevalence and patterns of use electronically and, in the case of an AE, be able to quickly determine other concomitant prescription medications. Given we already have this, the primary barrier would be maintaining an up-to-date label database for DSs on the market.

SUMMARY

Several solutions have been proposed that strike an appropriate balance between respecting the freedom of service members to purchase potentially beneficial products and protecting their health and safety. Processes to ensure quality and safety are desired to protect service members while still allowing choice. Service members, through their purchasing actions, can encourage DS manufacturers to embrace public quality standards, and the DoD would serve a helpful role in encouraging development of, and conformance to, the FDA standards. The proposed solutions would also ensure health care professionals have the necessary resources for information about benefits, risks, and quality to effectively counsel patients about the health, benefits, and risks for all DSs.

BACK TO TOP

Physiological Injuries and Surgery

A Large-Scale Study of Respiratory Virus Infection Over 2 Years Using the Luminex xTAGRVP Assay

Military Medicine
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Abstract

Traditional methods of detecting and identifying respiratory viruses like cell culture and immunofluorescence are labor intensive, often slow, and are dependent on specimen viability. As a result, there has been a shift in laboratory practices from these methods to molecular-based techniques such as polymerase chain reaction, which can be faster, more sensitive, and less labor intensive than traditional methods. The Food and Drug Administration approved version of the Luminex xTAG respiratory viral panel (RVP) assay detects 12 respiratory viruses simultaneously. We evaluated the performance of the RVP assay, on over 8,000 nasopharyngeal specimens during a 2-year period. Approximately 70% of all specimens tested were positive for at least one respiratory virus. Influenza A (Inf A) was the most prevalent, followed by respiratory syncytial virus. The RVP assay also detected the newly emerging Inf A porcine H1N1 that started to circulate in 2008. However, it could not identify it to subtype level and required further confirmatory tests. This study shows that the RVP assay is an invaluable tool in monitoring seasonal outbreaks and pandemic events. It not only detects newly emerging influenza strains, but also allows the throughput of thousands of clinical specimens in a timely manner, reducing the turnaround time from weeks to days, when compared to cell culture.

Introduction

The timely and accurate detection of respiratory viruses is important for both surveillance and the clinical diagnosis of disease. Respiratory tract infections are among the most common infectious diseases worldwide and result in considerable morbidity and mortality. Clinically, it is important to distinguish between a bacterial or a viral infection to ensure the patient receives appropriate treatment in order to improve patient outcome and reduce the unwarranted use of antibiotics. Detection of respiratory viruses, as part of an active surveillance program, is imperative in order to identify potential outbreaks, and for the detection of emerging diseases or novel strains such as the 2009 strain of Inf A porcine pH1N1. Viral culture, the gold standard for viral identification, is time-consuming, and detection is generally limited to the most common viruses.2 In addition, viral culture depends on short transportation times of specimens to ensure viruses remain viable until the specimen is received by the laboratory.3 Rapid antigen tests for select individual pathogens are available. Although these tests provide a quick result, the testing is relatively expensive,

has a limited sensitivity,4,5 and is unable to subtype Inf A infections. These rapid antigen tests are therefore of limited value for use, either clinically or for surveillance. Since the development of real-time polymerase chain reaction (PCR), molecular testing is quickly becoming the new gold standard as it is both faster and more sensitive than viral culture.6 Traditional PCR testing is limited, however, in that only one to four different virus types may be tested for in a single experimental set up.

Multiplex PCR-microsphere flow cytometry systems, like the xTAG respiratory viral panel assay (RVP assay) from Luminex, are able to overcome many of these challenges, providing high sensitivity and specificity coupled with a rapid turnaround (TAT) time for test results. Multiple viruses can be detected in a single experimental set up. The Food and Drug Administration approved version of the RVP assay can test for 12 different viral types simultaneously including some viruses that are difficult to isolate, are not detectable by cell culture,7 or that are rendered nonviable because of extended specimen transportation times. Traditionally, only respiratory syncytial virus (RSV) and influenza viruses were monitored for their activity. Using the RVP assay, however, monitoring of outbreaks and seasonal activity can easily be expanded to adenoviruses (ADV), rhinoviruses/enteroviruses (REV), the parainfluenza viruses (PIV), and human metapneumovirus.8

Located in Germany, the Landstuhl Regional Medical Center (LRMC) provides clinical laboratory support to active duty service members, Department of Defense (DoD) civilians and dependents throughout Europe, as well as treating personnel evacuated primarily from Iraq and Afghanistan. LRMC also conducts active surveillance for influenza and other respiratory viruses as part of the DoD's global disease surveillance program administered by the Armed Forces Health Surveillance Center, Division of Global Emerging Infectious Surveillance and Response System.4,9

In this article, we discuss the performance and results of the RVP assay, over two influenza seasons at LRMC. Implementation of the RVP assay has had a dramatic effect on laboratory performance as the detection of viruses in submitted specimens is no longer dependent on specimen viability and the availability of appropriate cell lines for culture. In addition, TAT times have been reduced from 2 weeks to days, and in some cases hours.

Methods

Patient Specimens

Specimens were collected as described by Kallstrom et al from patients meeting the DoD case definition for influenza-like illness, or otherwise suspected of having influenza. Following receipt by the laboratory, specimens that were contaminated or improperly sampled were rejected. Specimens used in this study were collected from the onset of the 2007 influenza season through week 53 of the 2010 season.

Nucleic Acid Extraction

Specimens were vortexed for about 30 s to ensure homogeneity. Extractions were performed on one of two automated nucleic acid extraction platforms: an MagNA Pure Compact Instrument (Roche) using the MagNA Pure Compact Nucleic Acid Isolation Kit I (Roche) with the “Total_NA_Plasma_100_400_V3_1” protocol or a Roche MagNA Pure LC instrument using the MagNa Pure LC Total Nucleic Acid Isolation kit

with the “Total NA Variable_Elution_Volume” protocol. For the MagNA Pure Compact, 200 µL of specimen suspension was extracted and suspended into 50 µL of elution solution. For the MagNA Pure LC, 200 µL of specimen suspension was extracted and suspended into 100 µL of elution solution. Extracted nucleic acids were stored at −80°C. The MagNA Pure Compact extracts eight specimens at a time, whereas the MagNA Pure LC extracts 32 specimens. Both systems extract nucleic acids to the same standard. The MagNA Pure LC was used when increased throughput of specimens was required.

xTAGRVP Luminex Test

The principle of the Luminex xTAG system (Luminex Corporation, Austin, TX) has been described in detail.7,8 Testing was performed following the manufacturer's guidelines. Briefly, 5 µL of extracted nucleic acids were added to a reaction mix consisting of water, one-step real-time RT-PCR enzyme mix (either included in the kit or purchased from Qiagen [Hilden, Germany]) buffer, and primer mix. An MS2 (Bacteriophage DNA) internal control is added before the extraction process. The RT-PCR products were treated with exonuclease I and alkaline phosphatase followed by PCR with Takara hot start Taq (Lonza, Verviers, Belgium), buffer, and biotin-labeled primers. The PCR product was hybridized to fluorescent beads and stained with phycoerythrin. Detection was performed on a Luminex 200 system (Luminex Corporation, Austin, TX) and the data evaluated using the Luminex 100 IS software.

CDC Swine Influenza Virus Real-Time RT-PCR Detection Panel

The CDC Swine Flu RT-PCR was performed according to manufacturer's instructions10 using a 7500 FAST Dx (Applied Biosystems, Darmstadt, Germany). Each extracted nucleic acid sample is tested by separate primer/probe sets; Inf A, universal Swine flu, Swine H1, and RNaseP. The RNaseP primer/probe set targets the human RNaseP gene, so is used as an internal control for human nucleic acids. Reaction mixtures were made consisting of nuclease-free water, forward and reverse primers, probe, master mix, and enzyme mix. Once dispensed into a 96-well reaction plate, 5 µL of extracted nucleic acid and negative or positive controls were added to the appropriate wells. The plate was sealed and centrifuged briefly before being placed in the ABI 7500 FAST Dx for detection and analysis.

Results

This study evaluates the performance of the RVP assay over an approximate 2-year period at LRMC. The RVP assay was introduced at the end of 2007–2008 influenza season. Over 8,000 specimens were tested as part of this study. Approximately 2,000 specimens from the 2007–2008 season were tested, including 1,000 archived specimens that were tested retrospectively. During the 2008–2009 influenza season, over 4,500 specimens were collected, and an additional 2,700 specimens were received during part of the 2009–2010 season. The majority of specimens were received from patients aged 45 and under with the largest number (35%) coming from patients age 26 to 45. Only 1.3% (59) of all specimens submitted were from patients older than 60 years.

During the 2007–2008 influenza season, the submission of specimens to the laboratory were elevated from approximately February through April (weeks 6 through 15), with the maximum submission numbers occurring during week 9(n = 170). Almost no specimens were submitted during the summer months. For the 2008–2009 season, specimen submission began to increase in January (week 1), with peak specimen submission occurring in week 5 (n = 240). Initially, the numbers of submitted specimens began to decrease following the peak; however, specimen

submissions began to increase again in week 19, with higher than typical specimen submissions being received throughout the spring and summer. Elevated specimen submissions were observed into the 2009–2010 season with the peak occurring during week 45 (n = 495).

Detection of Viral Respiratory Pathogens

Approximately 70% of all specimens submitted tested positive for at least one viral respiratory pathogen, whereas the remaining 30% were resulted as negative with no further testing being performed. Inf A was detected among all of the age groups, and was the most prevalent respiratory virus detected in patients aged 6 to 55 over the 2 years of this study (Table I). During the 2007–2008 season, the seasonal H1N1 subtype was most common, whereas the H3N2 subtype dominated during the traditional influenza period. However, toward the end of the season 2008–2009, the emerging novel strain of Inf A H1N1 was the most frequently detected influenza strain. The total number of influenza B (Inf B)-posit ive specimens received by the laboratory decreased approximately 65% from the 2007–2008 to the 2008–2009 seasons. Inf B was observed mainly in children aged 6 to 18.

REV were the predominant virus type detected in the youngest as well as the oldest age groups and was the second most common respiratory pathogen detected among all the others (Table I). Although REV can be detected throughout the whole year, detection appears to peak as the occurrence of influenza begins to rise (data not shown). RSV was detected in 11.3% of specimens submitted from patients aged 5 and under, and was only rarely detected in all other age groups. In general, detection of RSV peaked in the winter and early spring months. During the period of this study adenovirus was identified infrequently. There were no outbreaks and only sporadic cases occurred, with slightly more identified in children aged 5 and under than in adolescents or adults. A similar trend was observed for the PIV (types 1, 2, and 3). Although PIV was detected most frequently in specimens from children aged 5 and under, it was identified among the other age groups as well. As with the other noninfluenza viruses, human metapneumovirus was most frequently detected in children aged 5 and under, although it was detected at low frequency among all age groups.

In adults and adolescents, multiple viral detections are not common (1% and 2%, respectively). However, about 8% of all positive specimens in children under the age of 8 are positive for more than one viral pathogen. There is no predominant combination of double infections, although most include REV (data not shown).

Detection of the 2009 pH1N1 Strain

Following the end of the typical influenza season, approximately week 25, the laboratory received a surge of specimens that were positive for Inf A but could not be subtyped (NOS) (Fig. 2). The RVP assay will not specifically identify the 2009 pandemic strain of H1N1 (pH1N1). These specimens are identified by the assay as Inf A positive, but cannot be further subtyped (NOS). A number of Inf A (NOS) (n = 317) positive specimens were submitted to the Bundeswehr Institute of Microbiology in Munich for confirmation of pH1N1. Approximately 88% of these specimens were confirmed by the Bundeswehr as pH1N1. These specimens were tested retrospectively using the CDC developed Human Influenza Virus Real-Time RT-PCR Detection and Characterization Panel for confirmation of the pH1N1 virus, which confirmed 87% were positive for pH1N1.

System Performance

Before introduction of the RVP assay, the laboratory relied on viral culture as the primary means of testing for influenza. Using viral culture, TAT times ranged from 6.5 to nearly 14 days with a mean TAT time of 10.5 days. Following the introduction of the RVP assay during week 1 of the 2008–2009 influenza season, an immediate decrease in TAT was observed. The TAT using the RVP assay ranged from 1 to 3.7 days with a mean TAT of 1.3 days. This represents an eight times decrease in TAT based on the mean values.

Discussion

In this study, we evaluate the performance of the RVP assay over an approximate 2-year period, analyzing over 8,000 specimens. This study demonstrates the improved standard of care the LRMC laboratory is able to offer by using the RVP assay, as opposed to other more traditional methods. Detection of respiratory viruses increased from around 10% to approximately 70%. This increase reflects the advantages that are inherent to the RVP assay. Foremost, the multiplex capability of the RVP assay allows for the simultaneous detection of 12 viral species and subtypes. By increasing the breadth of viruses tested for, the percentage of positive specimens has increased. It is not unusual for patient specimens submitted to the LRMC laboratory to have been collected under austere conditions or subject to extended shipping times. These and other factors may severely decrease specimen viability, which is required for cell culture methods. Also, not all viruses are easily cultured in vitro making them nondetectable by cell culture. The diversity of testing available using multiplex technology was previously not possible because of the technical difficulties and constraints on labor and cost. Although cell culture is considered to be the gold standard, testing is limited as cell culture requires specialized equipment and expertise. By implementing the RVP assay, the LRMC laboratory is able to provide accurate and timely results that are vital to reducing the misdiagnosis of patients, and subsequently, incorrect treatment and elevated patient care costs.7,11

In general, our findings were consistent with other disease surveillance data.12,13 With the exception of influenza, the other viral respiratory diseases identified were most often found in children (0–5 years). This is due in part to the fact that many of these viruses are normally found in children; however, the unique population served by LRMC is likely a contributing factor as well. Adenovirus, which is most often associated with children and military recruits, was largely absent from all age groups except young children (0–5 years).14 It is important to note, however, that there are no large recruit populations (U.S. forces) in the European theater. RSV, MPV, and PIV are all common respiratory infections among children, although they can readily infect immunocompromised adults who are generally not found among the LRMC patient population. 15–17 As expected, influenza was the most common respiratory pathogen detected among all age groups, except in children aged 5 and under, in which case influenza was second to REV. Although these numbers highlight the frequency of influenza infection, particularly attributable to the 2009 pH1N1 pandemic, they should be interpreted with some caution. The vast majority of specimens are received as part of the influenza surveillance program, and therefore the majority of specimens are from patients with clinical symptoms consistent with influenza. During the 2007–2008 and 2008–2009 seasons, only a few Inf B strains could be detected. The distribution of influenza between children and adults is the same. Inf A H1N1 was the most detected subtype during season 2007–2008. Inf A H3N2 was the most detected subtype during 2008–2009 season with seasonal H1N1 being detected sporadically. These data are representative of the seasonal activity of influenza in Germany during both 2007–2008 and 2008–2009 seasons (http://influenza.rki.de/agi/index.html?l=de).

Toward the end of the 2008–2009 season, the new emerging novel porcine Inf A H1N1 was detected using the RVP assay, and confirmed by the Bundeswehr Institute of Microbiology in Munich. The literature suggests that the RVP assay, coupled with regional and local surveillance data, is sensitive enough to detect this novel pH1N1 Inf A strain.18 Similar results were obtained in this study, where only 2% of the unsubtypeable Inf A specimens (NOS) could not be confirmed as pH1N1.

Despite the robust nature of the RVP assay, there remain instances where a specimen could not be definitively resulted. During the course of this study, 2,255 positive Inf A specimens were tested; of these, 1,801 were influenza (NOS) according to the RVP assay. Although the vast majority of these specimens were pH1N1, approximately 5% (n = 100) of these specimens were received outside of the pandemic timeframe (Fig. 2) and are therefore presumed not to have been pH1N1. In some cases, the inability to subtype Inf A specimens may reflect limits of the test, others18 have noted that Inf A H3 specimens can be difficult to subtype using the RVP assay. This may result from a problem with the specimen such as a low viral load because of the specimen being collected either too early or too late in the infection. However, the possibility exists that a result of Inf A NOS, particularly those with a high Inf A signal, may represent a novel strain of Inf A and laboratories using the RVP assay should therefore have procedures in place for either additional testing or referring suspect specimens to a reference laboratory.

Multiple infections occur more often during the winter season, probably because more viruses are in circulation and because the cold weather increases the risk of viral infection.13 Most multiple infections happen in children. Possible explanations include increased contact to different viruses in child care facilities and the children's immature immune systems. It has been reported that multiple infections are more common in children less than 5 years old, and that the younger age is associated with larger viral quantity.14 Similarly, we found that children under 8 years old were positive for more multiple infections than any of the other age groups tested. Multiple infections can be difficult to detect using traditional methods such as immunofluorescence.19 The use of PCR not only increases the detection of multiple infections, the technique is much less labor intensive than traditional methods.7 Through using the RVP assay, we are capable of detecting multiple and triple infections that would otherwise be extremely difficult to detect using traditional methods. The multiplex nature of the RVP assay allows testing of 12 different viruses in the one test ultimately reducing the cost of supplies if the laboratory were to perform a single PCR test for each virus. Using a lean methodology, Dundas et al20 have shown the RVP assay to be not only more cost-effective than direct fluorescent analysis backed with tissue culture, but also much less labor intensive. Similar results were obtained when direct fluorescent analysis and the RVP were compared as part of hospitalization cost.21 Although the RVP assay was more expensive per test, it resulted in better patient outcomes, thereby lowering overall costs.

The RVP assay has proven invaluable in our large-scale study of respiratory viral infections of military members and their families throughout Europe and the Middle East. This test has proven to be accurate, sensitive, and fast, allowing the throughput of many thousands of specimens in a timely manner. As we have demonstrated here, the RVP assay can detect newly emerging strains of the influenza virus, something that has become invaluable in recent years. This assay is sensitive enough to detect coinfections and can be used as a powerful surveillance tool to monitor seasonal outbreaks as well as pandemic events.

BACK TO TOP

Improving Compliance with Malaria Chemoprophylaxis in Afghanistan

Military Medicine
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December 2012

Abstract

Objective: Historically, compliance with malaria chemoprophylaxis by military service members (MSM) has been notoriously low, ranging from 30 to 56%. Since 2002, 28 to 85 cases per year of malaria have occurred in MSM deployed to Afghanistan. During their deployment to Afghanistan, the authors identified a low compliance rate with malaria chemoprophylaxis. A performance improvement project was developed to improve compliance. Methods: In July 2011, a performance improvement plan was developed to improve malaria chemoprophylaxis compliance in MSM arriving on a remote base in western Afghanistan. The plan included a 15-minute briefing and a medical consultation for MSM who had discontinued their chemoprophylaxis because of side effects. At the conclusion of their deployment, the MSM were surveyed on their compliance. Results: Ninety-four MSM attended the briefings. Eighty (85%) MSM completed the survey in October 2011. Ninety-eight percent were taking doxycycline (n = 78). Ninety percent (n = 72) reported that they were compliant with their chemoprophylaxis. One entire unit (n = 29) was identified to be critically short of doxycycline, which initiated an emergency order for medication. Two noncompliant soldiers requested a consultation concerning side effects and were able to continue their chemoprophylaxis. Conclusion: Personalized in-theater briefings and consultations by knowledgeable providers may improve compliance with malaria chemoprophylaxis in MSM in Afghanistan.

Introduction

Army researchers have reported that military service members' (MSM) compliance with malaria chemoprophylaxis is “notoriously low.”1 Historically, the compliance rates for deployed soldiers have ranged from 30 to 56%.2–5 According to the U.S. Army Force Health Protection directive, unit commanders and their medical officers are responsible for the health and welfare of their soldiers, including malaria chemoprophylaxis.6 The individual soldier also bears responsibility per Central Command policy, which mandates compliance.7

Upon deployment to a remote base in western Afghanistan, the authors noted poor compliance of MSM with malaria chemoprophylaxis. An informal survey of MSM presenting to sick call identified less than 50% compliance with malaria chemoprophylaxis. A performance improvement plan was developed, which included a malaria prevention brief and medical consultations for soldiers with symptoms related to their chemoprophylaxis.

This is the first report to evaluate the efficacy of in-theater malaria briefings intended to improve compliance with malaria chemoprophylaxis in healthy MSM.

Methods

In July 2011, the authors developed a performance improvement plan intended to improve malaria chemoprophylaxis compliance in MSM on a remote base in western Afghanistan. Because of busy work schedules and outpost assignments, only newly arrived soldiers met in groups for briefings and in processing. The authors mandated that newly arrived soldiers attend a 15-minute brief entitled, “The Prevention of Malaria in Afghanistan.” The briefing included details concerning the risks of malaria in our province, the pathophysiology of malaria and the action of antimalaria medications. The MSM were also encouraged to obtain a consultation with a medical provider if they had discontinued their chemoprophylaxis because of symptoms that they felt was related to their antimalaria medication. At the conclusion of their deployment, the MSM were surveyed on their compliance with malaria chemoprophylaxis. The surveys were anonymous, on paper, and were distributed and collected by unit leaders. We informed the unit leaders that we were concerned about the issue of their influence on the survey results and asked that the completion of the surveys not be directly observed. Chemoprohylaxis compliance was defined by a single survey question “Are you taking your malaria medication as directed?”

Results

Ninety-four MSM attended the briefings. Six briefings were presented over a 2-month period. At our Forward Operating Base, MSM were commonly assigned to local outposts immediately upon arrival. We estimated that approximately 20 MSM did not attend the briefings because of prolonged assignments at the outposts. Eighty MSM were available to complete the survey in October 2011. Those unavailable for the completion survey were again assigned to outposts, had been reassigned to other areas, or had been redeployed because of injury or illness. At the time of one briefing, one entire unit (n = 29) was identified to be critically short of doxycycline. This finding initiated an emergency order for medication. In the absence of our briefing, this shortage would not have been identified. Two soldiers requested a consultation concerning symptoms related to doxycycline. One soldier qualified for a change in medication and the other soldier required a change in dosing schedule. Ninety-eight percent (n = 78) of those completing the end of tour survey were taking doxycycline. Ninety percent (n = 72) of those surveyed reported that they were compliant with their malaria chemoprophylaxis. We found that directly observed therapy (DOT) was not utilized by any command. U.S. Army Preventative Medicine was unable to provide any data regarding the rate of malaria in MSM originating in our province.

Discussion

Cases of malaria in MSM in Afghanistan continue to occur in significant numbers. During the period from 2002 to 2011, MSM in Afghanistan have accounted for 20 to 91 cases of malaria per year.8 In 2011, the 91 malaria cases in MSM in Afghanistan was the highest number since the start of the war.8 Historically, MSM have reported various reasons for poor compliance. Forgetting to take their chemoprophylaxis was the primary

etiologic factor in the poor compliance of U.S. Marines returning from Liberia.2 The overwhelming focus on mission requirements and a high operational tempo was the reported cause of poor compliance in a unit of U.S. Army Rangers returning from Afghanistan.3

Force Health Protection is defined as all measures taken by commanders, supervisors, individual service members, and the Military Health System to promote, protect, improve, conserve, and restore the mental and physical well-being of service members across the range of military activities and operations.6 The published literature is lacking as to descriptions of interventions utilized by commanders to improve malaria chemoprophylaxis compliance. An intervention available to commanders includes DOT.9 The Navy recommends DOT for all malaria chemoprophylaxis medication regimens. Chain of command support is required to carry out this method. MSM are directly observed taking their daily or weekly chemoprophylaxis medication. In the authors' combined 30 months of deployment experience in Afghanistan, DOT is an uncommon practice.

In the opinion of the authors, the malaria prevention briefings contained a number of unique strengths. Utilizing data from the Afghan Ministry of Health,10 the soldiers were briefed on the risk of malaria in their province. The authors also emphasized the large number of malaria cases still occurring in MSM in Afghanistan. In addition, the authors explained in simple terms the pathophysiology of malaria and the mechanism of action of doxycycline. Questions were answered concerning various possible side effects, and personal medical consultations were offered to any soldier who felt he/she was experiencing side effects related to their chemoprophylaxis. At the conclusion of the brief, all those in leadership positions were encouraged to add daily reminders to their morning reports and briefings.

The authors observed that the majority of soldiers briefed demonstrated intense interest in the subject material, and many soldiers related that this was their first exposure to information concerning malaria. The briefing and subsequent question and answer session offered the authors an opportunity to dispel myths regarding chemoprophylaxis. This interaction also allowed the authors to identify an entire unit that had been deployed with only a 1-month supply of doxycycline and mistakenly thought that they did not need to take the medication while deployed but only upon their return. The base Aid Station provided an interim supply while an emergency resupply was ordered.

The brief enabled the authors to interact with every soldier coming onto the Forward Operating Base and established a relationship in which the soldiers felt comfortable approaching the physicians with all types of health-related questions. Following the briefings, 2 soldiers did request a medical consultation. Each had discontinued doxycycline because of side effects. One soldier had been taking doxycycline late in the evening and also developed gastrointestinal symptoms. He was advised to resume his doxycycline but on an altered dosing schedule, i.e., taking the doxycycline in the morning following breakfast. A second soldier, also with persistent GI symptoms, qualified for a change in medication and was started on Mefloquine. The prescription of Mefloquine is highly restricted. In 2009, the Army Surgeon General issued updated guidance on the use of Mefloquine. In addition to the usual restriction of its use in patients suffering from depression, anxiety, psychosis, or schizophrenia, an additional restriction was placed on soldiers with a recent history of traumatic brain injury.11

The strengths of this performance improvement project include a simple, low-cost public health intervention and the high response rate to the survey. Weaknesses of the project include the use of historical benchmarks and the inherent disadvantages of self-reporting. An additional weakness includes the bias introduced by the use of paper surveys distributed to relatively small groups and collected by the leadership.

This is the first report of a public health intervention utilized to improve malaria chemoprophylaxis compliance in MSM in Afghanistan. Although our numbers are small, 90% chemoprophylaxis compliance far exceeds all previous reports. Had all MSM who were unavailable to complete the final survey been noncompliant, the compliance rate would still have been a respectable 77%. Although DOT initiated by a unit commander is considered the gold standard for ensuring chemoprophylaxis compliance, this performance improvement project suggests that a personalized in-theater malaria prevention brief, in the absence of or in addition to DOT, presented by knowledgeable providers, could possibly improve compliance with malaria chemoprophylaxis in Afghanistan. The authors feel that further study with larger populations is certainly indicated.

BACK TO TOP

The Effects of QuikClot Combat Gauze and Movement on Hemorrhage Control in a Porcine Model

Military Medicine
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Abstract

The purpose of this study was twofold: (1) to examine the effectiveness of QuikClot Combat Gauze (QCG) compared to a control group and (2) investigate the effect of movement on hemorrhage control when QCG is employed. This was a prospective, experimental design employing an established porcine model of uncontrolled hemorrhage. The minimum number of animals (n = 11 per group) was used to obtain a statistically valid result. There were no statistically significant differences between the groups ($p > 0.05$) indicating that the groups were equivalent on the following parameters: activating clotting time, the subject weights, core body temperatures, amount of 1 minute hemorrhage, arterial blood pressures, and the amount and percentage of total blood volume. There were significant differences in the amount of hemorrhage ($p = 0.018$) and the number of movements ($p = 0.000$) between the QCG and control. QCG is statistically and clinically superior at controlling hemorrhage compared to the standard pressure dressing control group. Furthermore, it produces a more robust clot that can withstand significant movement. In conclusion, QCG is an effective hemostatic agent for use in civilian and military trauma management.

Introduction

Trauma represents one of the leading causes of morbidity and mortality in both the civilian and military populations with uncontrolled hemorrhage as the major cause of complications and death.1–6 Historically, 20% of combat casualties were killed in action and 90% of those casualties never reached a field hospital.5 The major cause of death in this group was hemorrhage.5 In Vietnam, almost 40% of soldiers who died of exsanguination had a source of hemorrhage that may have been controlled by hemostatic measures.6 In the recent conflicts of Iraq and Afghanistan, uncontrolled hemorrhage accounted for almost 50% of the battlefield deaths before evacuation.3

Hemorrhage remains the leading cause of death even when the individual survives long enough to be transported to a medical treatment facility.1,2,7–9 If trauma patients survive the initial injury and hemorrhage is controlled, a large blood loss predisposes them to hypothermia, coagulopathy, infection, acidosis, and multiple organ failure.1,2,8,9 Hypotension secondary to hemorrhage usually follows with deleterious consequences. Specifically, trauma patients with isolated systolic hypotension (<90 mm Hg) have up to 54 % mortality.9 Therefore, rapid hemostasis is essential as a strategy not only for initial survival but also for optimal recovery. It is of paramount importance for health care professionals to find and implement the most effective methods of treating and managing hemorrhage. Moreover, the use of hemostatic agents may be one of the easiest and most effective methods of treating hemorrhage, preventing complications and death. They were specifically developed for first responders to control noncompressible hemorrhage in the military and prehospital setting.

Hemostatic agents have been investigated in multiple animal studies to include liver and complex groin injuries. These studies have produced inconsistent and mixed results regarding the effectiveness of hemostatic agents in controlling hemorrhage indicating the need for additional investigation.7,10–26 Furthermore, movement of the patient may exacerbate bleeding because of the fragile, newly formed clot. No studies have examined the effects of movement on bleeding when hemostatic agents are used.

Two agents that were widely used by the military, QuikClot (Z-Medica, Wallingford, Connecticut) and WoundStat (TraumaCure, Bethesda, Maryland), have been removed from the U.S. military inventory because of potential complications, specifically thermal tissue injury to patient and provider and microemboli formation.10,27 Other hemostatic agents in current use do not report these complications. Hemostatic agents have evolved from first generation granular or fine powders to second generation wafers and sponges. The newest agents are gauze dressings impregnated with a hemostatic agent designed to simplify application and decrease complications.

QuikClot Combat Gauze (QCG) is a rayon/polyester gauze impregnated with kaolin, a white aluminosilicate inert mineral. Kaolin promotes clotting by activation of Factor XII, which in turn initiates the intrinsic clotting pathway via the activation of Factor XI that ends with the formation of a fibrin clot. In addition, Kaolin promotes the activation of platelet-associated Factor XI, which initiates the intrinsic clotting pathway in normal and Factor XII deficient patients.28 There are limited data demonstrating the effectiveness of the QCG and Kaolin. The purpose of this study was twofold: (1) to examine the effectiveness of QCG compared to a control group and (2) investigate the effect of movement on hemorrhage control when QCG is employed. The following research question guided the study:

Are there statistically and clinically significant differences between QCG and control groups relative to hemostasis and movement causing rebleeding?

Methods

This study was a prospective, between subjects, experimental design using a porcine model. The protocol was approved by the Institutional Animal Care and Use Committee and the animals received care in compliance with the Animal Welfare Act, the Guide for the Use of Laboratory Animals. Twenty-two Yorkshire swine weighing between 60 and 90 kg (mean = 70.2 ± 7.6) were randomly assigned (n = 11 per group) to one of two groups: QCG and a control group. The rationale for using this weight range was that it represents the average of the U.S. Army soldier.29 This study was conducted in four phases: induction/stabilization, hemorrhage, blood loss, and movement.

Induction/Stabilization Phase

The induction phase was initiated with an intramuscular injection of ketamine (20 mg/kg) and atropine (0.04 mg/kg). Subjects were placed supine on a litter and administered inhaled isoflurane (4% to 5%). After placement of an endotracheal tube, a peripheral IV catheter was inserted and the isoflurane concentration was reduced to 1% to 2% for the remainder of the experiment. The swine were ventilated with a standard Narkomed anesthesia machine (Dräger, Telford, Pennsylvania). Heart rate, electrocardiography, blood pressure, oxygen saturation, end-tidal carbon dioxide, and rectal temperatures were continuously monitored for the remainder of the experiment.

The left carotid artery was cannulated with a 20G angio-catheter using a cut-down technique. It was attached to a hemodynamic monitoring system (Hewlett Packard, Palo Alto, California) for continuous monitoring of the arterial blood pressures. A central venous catheter was inserted into the right subclavian vein using a modified Seldinger technique for fluid volume management and blood sampling. Following line placement, the NPO fluid deficit was replaced with 0.9% normal saline, per the Holliday–Segar formula. The investigators used an activated clotting time (ACT) test to screen all subjects for coagulopathy before procedures. Subjects were further monitored for 30 minutes to ensure hemodynamic stability before intervention. Body temperature was monitored via a rectal probe and maintained at greater than 36.0°C using a forced air-warming blanket. A complex groin injury as described by Alam et al12,13 was generated to simulate a penetrating combat injury. All swine were hemodynamically stable before intervention.

Hemorrhage Phase

Following the 30-minute stabilization period, the exposed femoral artery and vein were transected with a scalpel blade. The swine were allowed to hemorrhage for 1 minute simulating the response time of a battlefield health care provider. Blood was collected by gauze, absorbent pads underneath the animals, and in a suction canister using a suction tip catheter placed in the distal portion of the wound. After 1 minute of hemorrhage, proximal pressure was applied to the transected femoral vessels, and 4″ × 4″ gauze was used to blot the blood from the wound per the hemostatic agent manufacturer's guidelines. At this time, the QCG was packed into the wound followed by standard wound packing consisting of a single layer of petroleum dressing and roller gauze (Kerlix, Covidien, Mansfield, Massachusetts). The control group received proximal pressure and standard wound packing.

Firm manual pressure of 25 lbs per square inch was applied for 5 minutes to the injury site as measured by an electronic TIF scale (Thermal Industries of Florida, Miami, Florida). The TIF scale is precise within 0.5 ounces and accurate within 0.5%.30 It was placed between the litter and operating room table and zeroed per manufacturer's instructions. Five hundred milliliter of 6% hetastarch in lactated ringer's solution (Hospira, Lake Forest, Illinois) was administered to all subjects in accordance with current battlefield resuscitation protocol recommended by the Committee on Tactical Combat Casualty Care. After 5 minutes of direct manual pressure, a 10-pound sandbag was applied to the wound for an additional 30 minutes.

Blood Loss Phase

After 35 minutes of pressure on the wound (5 minutes manual pressure plus 30 minutes with the sandbag), the standard pressure dressing was removed being careful not to disrupt the newly formed clot. The rationale for using the petroleum gauze was that it allowed removal of the pressure dressing with minimal clot disruption. For the purposes of this study, hemostasis was defined as a clot formation with oozing of no more than 2% of the swine's total blood volume over a 5 minute period (approximately 100 mL in a 70 kg pig). Blood loss was measured over two time periods: the initial injury to intervention and postintervention to the completion of the study. Blood loss was calculated by weighing the dressings, absorbent pads underneath the animals, and blood suctioned from the distal portion of the wound before and after transection of the femoral vessels.

Movement Phase

For swine achieving hemostasis, the investigators systematically moved the leg on the side of the complex groin injury. In a real battlefield or trauma scenario, personnel would take significant precautions when moving combat casualties. However, there may be instances when the injured extremity may be inadvertently moved by the patient or others, especially during medical evacuation. For purposes of this study, movement consisted of the following: flexion, extension, abduction, and adduction 10 times sequentially or until rebleeding occurred. Flexion consisted of movement of the leg until it touched the abdomen, whereas the extension consisted of movement of leg until it touched the litter. The abduction and adduction consisted of lateral and medial movement of the leg until no additional motion could be accomplished. Each flexion was followed by an extension, and each abduction was followed by an adduction. The number of movements were counted up to 40 (10 of each movement) or until there was bleeding (2% of blood volume).

Results

The minimum number of animals was used to obtain a statistically valid result. The determination of effect size for this experiment was based upon previous work by Alam and Pusateri.7,13,19,31 Using the data reported in those studies, the investigators calculated a large effect size of 0.6. Using G-Power 3.00, an effect size of 0.6, a power of 0.80, and an α of 0.05, it was determined that a sample size of 11 swine per group (22 total) was needed for this study.

There were no statistically significant differences between the groups in reference to the amount of initial 1 minute hemorrhage ($p = 0.544$): QCG group ranged from 149 to 1004 mL (mean = 654, SD ± 283 mL) and control group ranged from100 to 992 mL (mean = 582, SD ± 259 mL). The ACT, the body weights, core body temperatures, amount of 1 minute hemorrhage, arterial blood pressures, amount of blood volume, and the amount and percentage of total blood volume of the initial hemorrhage were analyzed using a multivariate analysis of variance (MANOVA). There were no statistically significant differences between the groups ($p > 0.05$) indicating that the groups were equivalent on these parameters. The ACT was within normal limits for all subjects.

A MANOVA was used to determine if there were significant differences in the groups relative to the amount of hemorrhage over a 5 minute period and the number of movements before hemorrhage. The MANOVA was significant: Wilk's $\lambda = 0.152$, $F(2, 19) = 52.8$, $p < 0.05$, $\eta 2 = 0.848$. There was a significant difference between the QCG and control groups relative to the amount of hemorrhage: $F(1, 20) = 6.66$, $p = 0.018$, $\eta 2 = 0.25$. The amount of bleeding QCG group ranged from 0 to 514 mL (mean = 50, SD ± 154 mL) and control group ranged from 0 to 1002 mL (mean = 351, SD ± 354 mL). There was a significant difference between the QCG and control groups relative to the number of movements before rebleeding: $F(1, 20) = 106.58$, $p = 0.000$, $\eta 2 = 0.842$. The number of movements for the OCG group ranged from 3 to 40 (mean = 36.6 ± 11) and for control group ranged from 0 to 9 (mean = 0.9 ± 2.7).

Discussion

Currently QCG is used by the U.S. military for management of combat casualties. Furthermore, the U.S. military's Committee on Tactical Combat Casualty Care is responsible for developing guidelines for the management of wounded military personnel. It recommends QCG as the first-line hemostatic agent for use in treatment of severe hemorrhage.32 There are limited data and quality evidence demonstrating the effectiveness of QCG, especially in humans. There are no randomized controlled trials investigating QCG in the control of hemorrhage in humans; all involve animal models. The only human study investigating QCG was a case series. Ran et al reported 14 uses of QCG with a 79% (11/14) success rate and a 93% survival rate. He concluded QCG is effective in controlling hemorrhage.33 These articles provide low-level and quality evidence. Lastly, there is limited anecdotal evidence of the effectiveness of QCG. The U.S. Army's goal is that each soldier carries a hemostatic agent but continued research needs to be conducted to determine the most efficacious and cost-effective agent.10

Pusateri outlined ideal qualities of hemostatic agents for civilian and military use. These include (1) being able to rapidly stop large vessel arterial and venous bleeding within 2 minutes of application when applied to an actively bleeding wound through a pool of blood; (2) no requirement for mixing or preapplication preparation; (3) simplicity of application by wounded victim, buddy, or medic; (4) light weight and durable; (5) long shelf life in extreme environments; (6) safe to use with no risk of injury to tissues or transmission of infection; and (7) inexpensive.10 The QCG meets each of these criteria. The QCG waterproof package was easy to open and pack into the wound with its accordion fold. Vacuum packaging allows it to be carried easily in pockets, backpacks, or medic rolls. Furthermore, QCG could be easily used by physicians, nurses, medics, and ordinary citizens in providing emergency care. In addition, QCG has a shelf life of 3 years, approved by the FDA, and currently fielded by all branches of the U.S. military.28 Anecdotally, investigators noted that QCG with the active ingredient Kaolin did not produce an exothermic reaction and there

were no obvious signs of tissue damage. First generation QuikClot employed granular zeolite to control hemorrhage and was noted to initiate a significant exothermic reaction causing tissue injury.10

Conclusion

The purpose of this study was twofold: (1) to examine the effectiveness of QCG compared to a control group and (2) investigate the effect of movement on hemorrhage control when QCG is employed. QCG is statistically and clinically superior at controlling hemorrhage compared to the standard pressure dressing control group. Furthermore, it produces a more robust clot that can withstand significant movement. These movements were severe and should be avoided in patients with an inguinal injury. However, the investigators wanted reproducible movements that would test the robustness of a newly formed clot. Based on this study and the requirements outlined by Pusateri, QCG is an effective hemostatic agent for use in civilian and military trauma management.

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BACK TO TOP

Outbreak of Gastrointestinal Illness During Operation *New Horizons* in Pisco, Peru

Medical Surveillance

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7 Dec 2012

In July 2012, the U.S. Naval Medical Research Unit No. 6 investigated an outbreak of gastrointestinal illness characterized by diarrhea among U.S. service members participating in Operation *New Horizons* in Pisco, Peru. Overall, there were 25 cases of self-reported diarrheal illness among 101 respondents to a questionnaire (attack rate: 24.8%). Personnel who consumed food that was prepared at the two hotels where they were lodged were more likely to report diarrhea than those who did not eat at the hotels (40.9% [9/22] versus 20.3% [16/79]; RR=2.1; p=.047). The difference in diarrhea attack rates between lodgers at the two hotels was not statistically significant. Known or putative pathogens were identified in 72.7 percent (8/11) of samples tested: *Blastocystis hominis, Shigella sonnei*, diffusely adherent *Escherichia coli*, and norovirus genotypes I and II. The investigation's findings suggested a food-borne etiology from hotel kitchens. Among all personnel, hand-washing hygiene was reinforced; however, food sources were not restricted.

Stool samples preserved in Cary-Blair medium were cultured for bacterial enteropathogens. Isolates of *E. coli* were tested by conventional real-time multiplex PCR for ETEC, enteropathogenic *E. coli*, and diffusely adherent *E. coli* as previously described. Real-time reverse transcription PCR for norovirus genotypes I and II was also performed using primers and probes targeting the polymerase gene. Investigators performed an environmental assessment, which included a physical inspection of hotel living quarters, hygiene facilities, kitchens, worksite latrines, and food vendors. Environmental sampling of food and water sources was not performed.

RESULTS

An epidemiological survey was distributed to 103 ONH engineering personnel who were present in Pisco at the time of the investigation. One hundred one (98.1%) surveys were completed, and 25 respondents met the case definition for a “suspected case of diarrheal illness” (attack rate: 24.8%). Thirteen (52%) suspected cases had sought care at the medical aid station and were prescribed treatment by the medical officer; five (20%) other suspected cases had self-medicated with antibiotics.

In addition to diarrhea, the 25 suspected cases reported headache (56%), abdominal cramping (52%), nausea (48%), fever (32%), and dehydration (20%). The median duration of illness was 2 days (interquartile range [IQR] 1–3 days). Twelve (48%) of the suspected cases reported stopping or significantly reducing work for at least one day. Eleven cases (44%) provided stool samples; known or putative pathogens were identified in 8 (72.7%): *Blastocystis hominis* (n=4), *S. sonnei* (n=3), diff usely adherent *E.coli* (n=2), and norovirus genotypes I (n=2) and II (n=2). One of the *S. sonnei* isolates was not susceptible to azithromycin.

Among the engineering groups lodged at Hotels A and B, 22 personnel reported eating at least one time in their respective hotels; the other 79 individuals reported not eating at either Hotel A or B during the period. Diarrheal illness was reported by 9 of the 22 (40.9%) persons who had eaten at either Hotel A or B and by 16 of the 79 (20.3%) persons who had not eaten at the respective hotels (RR=2.1; p=0.047).

There was no statistically significant difference in the proportions of diarrheal illness between those who were lodged in Hotels A or B (18.9% [10/53] versus 31.3% [15/48]; p=0.15). Seventeen of the 78 service members who responded (21.8%) reported eating food from local vendors at the ONH construction job sites. Of those, 17.6 percent (3/17) reported diarrhea.

Forty-fi ve (44.6%) of the affected engineer group reported receiving pre-deployment preventive medicine information; 31 (30.7%) and 28 (27.7%) of the engineers recalled receipt of pre-deployment information regarding personal hygiene and diarrheal illness, respectively.

There were no statistically significant differences in suspected diarrheal illness rates in relation to demographic characteristics, hotel of residence, duration of deployment, or preventive medicine training prior to deployment.

COUNTERMEASURES

Case management and antimicrobial prophylactic measures were conducted by the ONH medical technician in consultation with the ONH senior medical officer. Following the increase in diarrheal cases noted on 16 July, the investigative team reiterated the importance of personal hygiene

measures among ONH personnel through an evening briefing at Hotels A and B. Additional hand sanitizer was provided at latrine stations on construction worksites. Immediately following stool collections on 17 July, all 48 personnel lodged at Hotel B were given an oral dose (500 mg) of ciprofloxacin (per the ONH medical officer). Restrictions on food sources were not implemented.

EDITORIAL COMMENT

This report summarizes epidemiologic and clinical characteristics of an outbreak of diarrheal illnesses that affected 25 percent of U.S. service members who were conducting engineering projects in Pisco in July 2012 and resulted in at least one missed workday for nearly half of those affected. The impact of diarrheal outbreaks on lost productivity, particularly among military reservists conducting two-week annual training during missions such as ONH, could delay project completion and mission readiness.

The investigation identified an increased risk of diarrheal illness among engineering personnel who ate at the hotels used for lodging during ONH; however, a single microbial etiology or specific type of food or meal causing the diarrheal outbreak could not be identified. The absence of a single etiologic organism suggests that infections may have been acquired from several, and perhaps even all, of the sources from which food was procured.

This is not particularly surprising, since the U.S. personnel involved were likely immunologically naïve to many of the potential pathogens in the locally prepared food. This is the second reported outbreak of diarrheal illness affecting U.S. forces deployed for U.S. Southern Command engagement missions. The first outbreak occurred during Operation *Beyond the Horizon* in El Salvador in 2011. In both instances, the suspected cause of the outbreak was non-U.S. military approved food sources. In the case of ONH 2012, some U.S. personnel frequently ate food prepared in the hotel kitchens even though the kitchens had been inspected and determined to be unsanitary during pre-deployment site assessments.

Service members' knowledge about the risks of disease during deployment may have been low; among those who completed questionnaires less than half reported having received pre-deployment preventive medicine information and less than a third specified information on diarrheal illness and personal hygiene. Nevertheless, risk for food-borne illness cannot always be easily avoided; in some deployment settings it may be that there is simply no "safe" place to eat unless MREs or other safe dining options are provided and operated by the sponsoring mission. However, even in such controlled settings, outbreaks of diarrheal illness have been reported. Preventive medicine education regarding food and water use and reinforcement of principles of hand washing and good personal hygiene should be mandatory for all deployed personnel. It must be noted, however, that such measures are difficult to implement uniformly and, as a result, they have not consistently been shown to reduce the incidence of diarrheal illness.

Antibiotic prophylaxis, with or without the use of an anti-motility agent, may be another option to protect deployed personnel from diarrheal illness. Indeed, the outbreak in Pisco prompted a decision to administer mass prophylaxis with a onetime oral dose of ciprofl oxacin 500mg.

However, this and other uniform antibiotic regimens may cover only a portion of the range of common etiologic organisms of traveler's diarrhea. In the case of the Pisco outbreak, only 5 of the 11 putative pathogens would have been covered by ciprofloxacin. Broader spectrum antimicrobial regimens could be considered, but likely at an increased risk of adverse events. Diarrheal illness remains a common and challenging problem for

U.S. military forces. Solutions will likely require a combination of preventive and curative options tailored to each individual setting. Thorough education of service members in general and of healthcare providers about disease prevention measures will be key to countering this disease threat to mission success. Surveillance during U.S. military field operations such as that conducted by NAMRU-6 and GEIS in Peru for ONH 2012 can be important to unraveling the complex epidemiology of diarrheal illness in deployment settings. These settings also provide excellent opportunities for future evaluation of preventive and curative strategies.

BACK TO TOP

Invasive Mold Infections Following Combat-related Injuries

Clinical Infectious Diseases

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Abstract

Background. Major advances in combat casualty care have led to increased survival of patients with complex extremity trauma. Invasive fungal wound infections (IFIs) are an uncommon, but increasingly recognized, complication following trauma that require greater understanding of risk factors and clinical findings to reduce morbidity.

Methods. The patient population includes US military personnel injured during combat from June 2009 through December 2010. Case definition required wound necrosis on successive debridements with IFI evidence by histopathology and/or microbiology (*Candida* spp excluded). Case finding and data collected through the Trauma Infectious Disease Outcomes Study utilized trauma registry, hospital records or operative reports, and pathologist review of histopathology specimens.

Results. A total of 37 cases were identified: proven (angioinvasion, n = 20), probable (nonvascular tissue invasion, n = 4), and possible (positive fungal culture without histopathological evidence, n = 13). In the last quarter surveyed, rates reached 3.5% of trauma admissions. Common findings include blast injury (100%) during foot patrol (92%) occurring in southern Afghanistan (94%) with lower extremity amputation (80%) and

large volume blood transfusion (97.2%). Mold isolates were recovered in 83% of cases (order Mucorales, n = 16; *Aspergillus* spp, n = 16; *Fusarium* spp, n = 9), commonly with multiple mold species among infected wounds (28%). Clinical outcomes included 3 related deaths (8.1%), frequent debridements (median, 11 cases), and amputation revisions (58%).

Conclusions. IFIs are an emerging trauma-related infection leading to significant morbidity. Early identification, using common characteristics of patient injury profile and tissue-based diagnosis, should be accompanied by aggressive surgical and antifungal therapy (liposomal amphotericin B and a broad-spectrum triazole pending mycology results) among patients with suspicious wounds.

Invasive fungal wound infections (IFIs) of skin and soft tissue occur in both immunocompromised and immunocompetent hosts. Among immunocompetent individuals, traumatic injury is the most common risk factor for IFI, occurring in settings such as agricultural, motor vehicle, and blunt crush injuries, as well as during natural disasters as recently reported among tornado victims. Local invasive infection often requires repeated and extensive surgical debridement and systemic antifungal therapy complicated by amputations (31%) and mortality (as high as 25%).

Major advances in combat casualty care have led to increased survival of patients with complex extremity trauma. Blast traumas, secondary to those caused by improvised explosive devices, are among the most severe injuries. Gross contamination of these wounds with organic material may introduce environmental filamentous fungi (molds), among other pathogens. This report describes IFI epidemiology, clinical findings, and laboratory findings among American combat casualties in Afghanistan from June 2009 through December 2010.

MATERIALS AND METHODS

Study Population

The population includes US military personnel who were injured in combat in Afghanistan, then medically evacuated through Landstuhl Regional Medical Center (LRMC) in Germany and admitted to 1 of 3 US military hospitals: Walter Reed Army Medical Center (WRAMC) in Washington, DC; National Naval Medical Center (NNMC) in Bethesda, Maryland; and Brooke Army Medical Center in San Antonio, Texas.

IFI Case Definitions

Case definitions were adapted from the Mycosis Study Group. Diagnostic criteria were as follows: (1) traumatic wounds, (2) after ≥1 irrigation and debridement, (3) tissue necrosis on ≥2 consecutive debridements, and (4) IFI evidence. Cases were classified as either proven IFI (fungal hyphae angioinvasion of viable tissue), probable IFI (viable tissue invasion, but no angioinvasion), or possible IFI (mold grown in culture but either histology not performed or no fungal elements seen). *Candida* spp were specifically excluded because their role in pathogenesis in wound infections is unclear.

Case Investigation

The investigation was undertaken through the Trauma Infectious Disease Outcomes Study (TIDOS). Trauma history, *International Classification of Diseases (Ninth Revision)* injury codes, and surgical management history were obtained through the US Department of Defense Joint Theater Trauma Registry (JTTR). IFI-specific data were collected through a supplemental JTTR infectious disease module. All histopathology specimens were reviewed by 2 surgical pathologists. The study was approved by the institutional review board of the Uniformed Services University of the Health Sciences.

Case Identification

Cases were identified through review of the TIDOS database for all positive fungal wound cultures and histology during the investigation period. To assure complete case capture, histopathology and clinical microbiology reports were reviewed, as were case records from infectious disease and trauma surgery services.

Clinical Outcomes and Statistical Analysis

IFI diagnosis date was the earliest specimen collection yielding a positive result from either culture or pathology. Time to clean wound was defined as the number of days from IFI diagnosis to first documented clean wound (operative report with no evidence of infection and no subsequent histopathology or culture evidence). High-level amputations were defined as hip disarticulation or hemipelvectomy.

Fisher exact and χ^2 tests were used to test the association of levels of categorical variables with IFI classes and clinical mycology groups. The Kruskal-Wallis test was implemented to compare medians among these groupings.

RESULTS

Demographics and Injury Patterns

The investigation included the period from 1 June 2009 (TIDOS start date) through 31 December 2010. Trauma-patient evacuations to LRMC from Afghanistan (n = 2413) are displayed in Figure 1 by calendar quarter against patients diagnosed with IFI (n = 37; proven, 20 patients [54.1%]; probable, 4 patients [10.8%]; possible, 13 patients [35.1%]). No IFI cases were identified from Iraq during the study period. The IFI rate gradually increased to the highest level of 3.5% in the fourth quarter of 2010. The progressive increase was also observed among trauma patient admissions (not restricted to Afghanistan evacuations) to the LRMC intensive care unit (ICU), reaching a high of 8% in the fourth quarter of 2010.

Number and percentage of patients with diagnoses of invasive fungal wound infections based on dates of admission to Landstuhl Regional Medical Center (LRMC), from June 2009 through December 2010. An average of 324 patients (range, 95–509 patients) per quarter admitted to LRMC with an average of 5 patients (range, 0–12 patients) with invasive fungal infection per quarter. Abbreviation: IFI, invasive fungal infection.

All cases were male enlisted personnel (25 Marines and 12 Army) with median age 23 years (interquartile range [IQR], 21–27). All injuries were secondary to explosive blasts, 34 (91.9%) were dismounted (ie, on foot patrol) at the time of injury (more common in proven and probable groups),

and 35 (94.6%) received initial care in a military facility in southern Afghanistan (Helmand or Kandahar provinces). All had extremity injuries with 29 (78.4%) sustaining an amputation at time of injury or first surgery as exemplified in one patient's infected wound. Multiple limb amputations were common with 25 (67.6%) bilateral and 6 (16.2%) involving three limbs. Other common findings included perineal and genital wounds (67.6%), vascular repair (51.4%), and penetrating abdominal trauma (32.4%).Explosive blast injury subsequently infected with invasive mold (*A*) and after successful surgical and medical therapy (*B*). High-level lower extremity amputation with necrotic fibrinous material documented on histopathology with aseptate mold angioinvasion (initial presentation). Wound appearance after serial debridements, hemipelvectomy, and antifungal therapy (8 days later).

Clinical Findings and Trauma Care

Characteristics of patients' clinical findings and early trauma care are detailed by IFI classification. Overall, most patients presented with borderline hypotension and tachycardia, with significant base deficit and required massive blood transfusion, approximately 30 units on average of both packed red blood cells and fresh frozen plasma, in the first 24 hours (proven and probable cases had higher transfusion requirement than did possible cases). The majority of patients were febrile (temperature, >38°C) with leukocytosis (white blood cell count, $>10 \times 10^9$ cells/L) within 1 week of IFI diagnosis irrespective of IFI classification.

IFI Wound Characteristics and Microbiology

Among the 37 patients, a total of 54 distinct wounds with IFI were identified, 27 (50.0%) classified as proven, 8 (14.8%) as probable, and 19 as (35.2%) possible (12 of which did not have specimens sent for histopathology).These wounds were characterized by myonecrosis (81%), liponecrosis (52%), eschar (14%), purulence (43%), and fibrinous exudates (18%) observed on surgical examination.

Among the wounds with pathological examination (n = 41), hyphae were seen, from any staining technique, in 34 (82.9%) wounds. Hyphal element staining was more commonly observed with Gomori methenamine silver staining (72.4%) than with periodic acid Schiff (PAS) staining (51.4%). Of critical importance in specimens with aseptate hyphae, visualization with routine hematoxylin-eosin (H&E) staining was occasionally the only method of identification (19.5%). Although an intra-operative frozen section was not commonly obtained, among the 15 wounds for which frozen sections were evaluated, there were 6 positive frozen sections (all also found positive for hyphae on standard histopathology) and 9 negative frozen sections (6 later found to be positive on definitive staining).

A total of 31 (83.8%) patients had at least 1 mold isolated. In 16 patients, a mold from the order Mucorales was identified (multiple species isolated in some cases). Pathogens from the order Mucorales were isolated from 62.5%, 100%, and 38.5% of proven, probable, and possible cases, respectively. Evidence of order Mucorales, from culture and/or aseptate hyphae on histopathology, was observed in 25 (47.2%) infected wounds: 10 (40%) from culture and aseptate morphology, 6 (24%) from culture only, and 9 (36%) from pathology only. In addition, there were 16 patients with *Aspergillus* spp and 9 with *Fusarium* spp. Two or more mold isolates, with one from Mucorales and another from a non-Mucorales species, were recovered in 28.3% of infected wounds. There were no statistically significant clinical differences based on fungal pathogen isolation. No mold isolates were recovered from sites distant from the affected extremity or blood with the exception of abdominal cavity involvement contiguous

with extensive perineal and hip invasive disease in 2 of the fatal cases as well as respiratory secretion cultures (commonly sputum and tracheal aspirates) which were not felt to represent invasive pulmonary disease.

All 54 wounds were also either colonized or infected with a bacteria or yeast by the date of IFI diagnosis, with the most commonly identified organisms being *Enterococcus faecium* (n = 11; 20.4%) and *Acinetobacter calcoaceticus-baumannii* complex (n = 9; 17%). *Candida albicans* grew in cultures from 5 wounds (9.3%).

IFI-specific Management and Outcomes

The overall median duration from the time of injury to IFI diagnosis was 10 days (IQR, 7–14 days). The time from IFI diagnosis to discharge from the US facility was 57.5 days (IQR, 35–68 days). The median number of surgeries at the IFI wound site after medical evacuation from the operational theater was 11 surgeries (IQR, 7–16 surgeries) consisting of frequent debridements and amputation revisions. Time from IFI diagnosis to clean wounds, documented in 20 cases, was a median of 21 days (IQR, 18–35 days). Ten patients (27%) ultimately required a high-level lower extremity amputation.

Thirty-three patients (89.2%) received antifungal therapy, most commonly lipid formulations of amphotericin B (LFAB) in 91% of patients, voriconazole in 85% of patients, and posaconazole in 49% of patients. Eight (21.6%) patients received monotherapy, whereas the most common combination therapy (≥3 days of overlap) was LFAB plus a triazole (voriconazole or posaconazole) in 65% of patients. Overall, patients with possible cases received less total antifungal therapy than did patients with proven or probable cases as reflected by overall receipt (69% vs 100%), shorter treatment duration, and less common combination therapy (46% vs 79%). The 4 patients who did not receive antifungal therapy were all classified as having possible IFI, with 1 diagnosis of IFI on the day of death. The other 3 patients underwent frequent debridements (range, 8–11 debridements) leading to infection resolution. Several topical agents were used, including 0.025% sodium hypochlorite solution (modified Dakin solution) applied through a negative pressure therapy device in 12 (32.4%) patients, amphotericin B beads in 3 (8.1%) patients, and amphotericin peritoneal irrigation in 1 patient. The median time between the IFI diagnosis date (when specimen yielding first positive result was collected) and antifungal therapy initiation was 4 days (IQR, 1.5–7 days). The median duration of antifungal therapy was 26.5 days (IQR, 14.5–42.5 days).

There were no significant differences for duration of hospitalization, ICU stay, new amputations, or revised amputations by IFI classification. Five patients with IFI died. IFI contributed to death in 3 (8.1%) of these cases. In each of these 3 cases, new-onset necrotic wounds presented 8–12 days after injury with widespread progression of necrosis despite intensified debridements over a period of 2–7 days. In each of these fatal cases the necrosis extended beyond affected extremities into truncal areas as well as through the abdominal wall with involvement of intra-abdominal tissues. All fatal cases were in the proven group except 1 possible case (no tissue specimen sent for histopathology). Three patients who died with positive cultures near time of death were all from the group with Mucorales infection. One patient tested positive for an *Alternaria* species at the infected wound site 1 week prior to patient death; however, wound culture was negative with documented angioinvasion the day prior to death (primarily attributed to severe head injury and not IFI). The fifth patient had aseptate angioinvasive fungal elements observed but no culture obtained.

DISCUSSION

To our knowledge, this is the largest case series of trauma-related IFI described to date. Invasive fungal infections have emerged as an important cause of morbidity and mortality among US military personnel who have suffered combat-related traumatic injuries. The most common features among these patients are lower extremity amputation with perineal or pelvic injury and receipt of massive blood transfusions following blast injuries incurred while on foot patrol in southern Afghanistan. This profile is consistent with a previous British military report in the “green zone” of Helmand province in Afghanistan. This region, with large agricultural areas, may have a more dense concentration of environmental molds than more arid regions of Afghanistan or in Iraq; however, the primary risk may be more related to the mechanism of injury in an individual on foot patrol than to a regional endemic threat given the ubiquitous nature of these molds. The increasing number of IFI cases follows the upward trend in lower extremity amputations among injured personnel returning from Afghanistan.

Previous case reports of US combat-related IFI describe wound infections with rare mold species, one of which was a fatal case included in this investigation. Cases have also been reported from a military burn center noting higher numbers of attributable deaths related to invasive mold infection in combat-related compared with civilian burn patients at the center. In addition, there were 6 patients with IFI, all injured in Iraq, from March 2002 through July 2008 among US military personnel sustaining traumatic war wounds who wer hospitalized at WRAMC, yielding estimates of 0.4 cases per 1000 admissions, much lower than observed during this investigation.

Blast extremity wounds typically undergo meticulous low-pressure irrigation and debridement within 1–2 hours of injury and are commonly dressed using vacuum-assisted wound closure. Serial debridement occurs approximately every 48 hours with wound closure often first considered after injury day 8 if evidence of wound contraction and healthy noninfected-appearing granulation tissue. Techniques of wound closure are as follows, in order of preference: delayed primary closure, split thickness skin graft, rotational flap, and free flap. The average injury severity score (ISS) from one case series of mucormycosis after traumatic injury was 24 (range, 9–41), similar to the average ISS observed in this series. The high fatality rate exceeds observed mortality among wound infections secondary to bacterial infections, although causes of death in this series were multifactorial in nature and 2 deaths were not related to IFI diagnosis. IFI case fatality is lowest among trauma-associated etiologies that typically occur in previously immunocompetent individuals; however, mortality of 25% exceeded our observed rate despite the more extensive trauma in our series. A recent large series of cutaneous mucormycosis among persons injured in the tornado that struck Joplin, Missouri, in 2011 reported an even higher fatality rate of 38.5%. The 13 confirmed case patients in the Joplin series had a higher median age with a wide range (as high as 76 years) and diabetes in 2 cases but none were immunocompromised.

All but 1 patient in this series were transfused with ≥10 units of blood in theater (a commonly used threshold delineating massive transfusion requirement) with an initial 24-hour requirement almost 3 times this threshold. The receipt of blood products can have immunosuppressive effects and thereby increase the risk for infection. An additional consideration pertaining to IFI is the iron burden that is received with blood transfusions, given that these molds are known to utilize iron as a nutrition source, which may be further exacerbated with acidosis during the immediate posttrauma period. Iron burden was not assessed in these patients.

In recent years, rates of IFI have increased, most commonly among immunocompromised patients with mucormycosis. *Mucor* spp, *Saksenaea vasiformis,* and *Apophysomyces elegans* were the most common species isolated from the order Mucorales in this case series. The invasive potential of *S. vasiformis* and *A. elegans* observed in this series is consistent with previous reports and a recent review. Of note, there were no isolates of *Rhizopus* spp*,* the most common identified mucormycosis etiology; although this is primarily due to the predominance of immunocompromised hosts among cases. Other environmental molds such as *Aspergillus* spp, *Fusarium* spp, and *Scedosporium* spp have been reported to cause wound infections and were isolated in this series. Only the Mucorales group and *Aspergillus* spp were observed in proven cases as solitary pathogens. It is likely that many of the diverse mold species isolated, particularly given the common finding of multiple isolates per wound, represent wound contamination.

A favorable prognosis is dependent upon early identification and aggressive surgical debridement combined with antifungal treatment. IFI diagnosis relies on histopathological confirmation of tissue invasion, with fungal culture providing species identification. Mold cultures often require several days to grow and may be insensitive (20% of wounds in this series had negative cultures); therefore, surgical tissue samples for histopathology are essential for accurate diagnosis particularly since fungal colonization alone is not indicative of an invasive infection. Standard H&E staining is reported to be insensitive, prompting recommendations for special staining; however, in this series more wounds with hyphae were identified with H&E staining than with PAS staining, particularly aseptate hyphae. Real-time frozen sections demonstrated poor negative predictive value, limiting clinical utility, although the number of cases examined was small and no prospective evaluation was undertaken. Calcofluor white, a fluorescent stain used for rapid detection of fungal elements in the microbiology laboratory, was positive in only 49% of 33 mold culture positive specimens at one of the hospitals. The 4-day average “delay” between IFI diagnosis and start of antifungal therapy reflects the time required for tissue specimen collection, laboratory work-up, reporting results, and starting therapy. This delay was most evident among cases reliant upon microbiological findings to fulfill IFI criteria, highlighting the need for improved rapid and sensitive diagnostic methods, as well as use of empiric antifungal therapy pending laboratory results. Encouraging reports applying rapid diagnostic molecular methods warrant further investigation.

Debridement of necrotic material is paramount, as the thrombosed blood vessels from the IFI results in poor tissue penetration of antifungal agents. Frequent debridement is necessary (potentially daily); one series had an average of 10 surgeries, comparable with the average number in this series. The majority (89%) of the patients in this series received antifungal therapy, with those managed with surgery alone classified as possible IFI. No well-controlled studies are available on which to base antifungal therapy in trauma-associated IFI. A lipid polyene, amphotericin B (LFAB), at a dose of 5 mg/kg per day, is the preferred agent for mucormycosis without controlled trial evidence for added benefit when combined with other antifungal agents. Voriconazole is not active against mucormycosis, but it is primary therapy for invasive aspergillosis including molds such as *Aspergillus terreus* which are resistant to amphotericin B. Empiric regimens should include LFAB and voriconazole pending results of serial wound cultures and histopathology findings to better target treatment on probable pathogens rather than transient colonizing species.

Topical therapy was commonly used, including specific antifungal agents or, more commonly, the disinfectant sodium hypochlorite (0.025% Dakin solution instilled in wound vacuum device). Anecdotally, Dakin solution was felt to be effective, leading to common use in the latter half of the investigation period; however, no outcome difference was apparent. Potential adjunctive therapy options for invasive mucormycosis have been

reported including hyperbaric oxygen, with encouraging results from case series but no controlled studies, and deferasirox iron chelation, recently reported to have higher mortality among patients receiving adjunctive treatment in a small randomized placebo-controlled trial.

In summary, IFI is an increasingly important cause of morbidity and mortality among US military personnel who suffer combat-related traumatic injury. Awareness of the common features (blast injury while on foot patrol, extensive lower extremity traumatic amputations with associated perineal injury, and massive blood transfusion) in the setting of necrotic wounds requires aggressive and extensive surgical debridement and empiric systemic antifungal therapy. In addition, clinicians should also recognize that the median time from injury to diagnosis is 10 days (IQR, 7–14 days). Increased awareness and early diagnostic efforts utilizing tissue histopathology and clinical mycology may shorten this interval, lessening the requirement for extensive debridement and ultimately minimizing long-term disability due to high-level amputations. Future strategies for IFI prevention, diagnosis, and treatment require preclinical and clinical research efforts to support ongoing refinement of clinical practice guidance.

BACK TO TOP

Residual limb wounds or ulcers heal in transtibial amputees using an active suction socket system. A randomized controlled study

European Journal of Physical and Rehabilitation Medicine
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December 2012

BACKGROUND:

The factors that determine successful rehabilitation after lower limb amputation have been widely investigated in the literature, but little attention has been paid to the type of prosthesis and clinical state of the residual limb, particularly the presence of open ulcers.

AIM:

The aim of this study was to investigate the effects of a vacuum-assisted socket system (VASS) in a sample of trans-tibial amputees with wounds or ulcers on the stump and to evaluate prosthesis use as a primary outcome. Secondary outcome measures were mobility with the prosthesis, pain associated with prosthesis use, and wound/ulcer healing.

STUDY DESIGN:

Randomized controlled study.

SETTING:

Inpatient.

POPULATION:

Twenty dysvascular transtibial amputees suffering from ulcers due to prosthesis use or delayed wound healing post-amputation were enrolled.

METHODS:

Participants were separated into two groups: the experimental group was trained to use a VASS prosthesis in the presence of open ulcers/wounds on the stump; and the control group was trained to use a standard suction socket system prosthesis following ulcers/wounds healing.

RESULTS:

At the end of the 12-week rehabilitation program, all VASS users were able to walk independently with their prosthesis as reflected by a median Locomotor Capability Index (LCI) value of 42, whereas only five participants in the control group were able to walk independently with a median LCI value of 21. At the two-month follow-up, the participants used their VASS prostheses for 62 hours a week (median; range: 0-91), which was significantly longer than the control group using the standard prosthesis for 5 hours per week (range: 0-56, p=0.003). At the six-month follow-up, the difference between VASS-users (80, range: 0-112 hours a weeks) and control-users (59, range: 0-91) was no longer significant (p=0.191). Despite more intense use of the prosthesis, pain and wound healing did not significantly differ between the two groups.

CONCLUSION:

These results showed that the VASS prosthesis allowed early fitting with prompt ambulation recovery without inhibiting wound healing or increasing pain.

BACK TO TOP

TBI

Heterotopic ossification following traumatic brain injury and spinal cord injury: insight into the etiology and pathophysiology

J. Musculoskelet Neuronal Interact
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Abstract

Neurogenic heterotopic ossification (HO) is the ectopic formation of lamellar bone in non-osseous tissues following traumatic brain or spinal cord injury. The associated complications affect greatly their quality of life. This fact has shifted the focus of scientific effort towards the investigation and understanding of related risk factors and the pathophysiological mechanisms. Recent advancements include the investigation for genetic predisposition and association various biomarkers. In the present article we will analyze the current concepts on this topic, based on clinical and physiological evidence and we will discuss the potential areas for future research on this field.

Introduction

HO is defined as the formation of mature, lamellar bone in non-osseous tissue, usually between the muscle and the joint capsule. Histologically and radiographically, heterotopic bone resembles normal mature bone but it can be easily distinguished from simple calcifications by the nature of its osteoblastic capacity. Although there are rare hereditary disorders associated with HO, it is well established that HO is usually acquired following soft-tissue trauma, fractures (commonly in acetabular and elbow fractures followed by internal fixations), dislocations, elective orthopedic surgeries (e.g. hip surgery), electrocution and burn injuries and neurological damage.

Specifically, for neurogenic HO following TBI and SCI (Figures 1 & 2), the incidence of ectopic bone formation has been reported to be between 10% and 23%35 and 4050%68 respectively. Other neurologic conditions associated with neurogenic HO such as Guillain-Barré syndrome (GBS), tumors and infections of the Central Nervous System (CNS), although reported, are not well documented and related data are scarce.

To date, multiple studies strongly suggest that the bone remodeling pathways leading to HO are more complex than previously thought, however the exact pathophysiological mechanism is not fully understood. It has been suggested that there are pathways of the immune system, the central nervous system and the indigenous inflammatory response that lead to the release of osteoinductive factors resulting in HO7. As, firstly, suggested by Chalmers et al.9, HO is the result of the interaction of 3 conditions, which should necessarily be met. The presence of (a) an osteoinductive factor, (b) osteoprogenitor cells, and (c) an environment which is permissive to osteogenesis. This has been furthered investigated and nowadays is commonly accepted that HO requires stimulation of mesenchymal cell recruitment, proliferation and differentiation, followed by osteoprogenitor maturation and osteoblast activation10. Several groups of investigators have established a clear connection between the humoral factors released by the injured CNS and the following events (i.e. oxidative stress, effects of mechanical ventilation, free radical formation etc) leading to the development of neurogenic HO1116.

Etiology and risk factors of NHO

Although there are a few risk factors especially investigated only for neurogenic HO, which they will be discussed at the end of this chapter, the general risk factors of HO still apply to neurogenic HO and must be mentioned here.

The generally established risk factors for HO are shown in Table 1.

Of these factors only a few have been investigated in patients with TBI and SCI with the last four presenting a special interest for neurological patients:

•Demographic factors (Sex, Age, Race): Male sex17,18 and young age (2030 years old)19 have been suggested to be a risk factor for neurogenic HO formation but it has not been established yet. Race, however, it is not significantly correlated with the development of neurogenic HO.
•Genetics: As previously mentioned, the fact that not all patients with similar patterns and demographics develop neurogenic HO, has evoked the theory that certain individuals are genetically predisposed to neurogenic HO and generally HO formation, which may be triggered by environmental influences.

i. HLAType Antigens

First, in 1981 Larson et al.22 in a study of 43 patients with SCI, found that not only the HLAB27 antigen was expressed in 5 of the 21 patients with HO, but also that none of the 22 patients without HO expressed it.

In the following years, the literature data are more differing yielding some or no association with HLA type antigens. Although some other HLA antigens have been suggested (HLA B18, HLAB27 and DW7), subsequent publications associated only HLAB18 with NHO. However, it is still observed that up to 75% of patients with neurologic injury that develop HO are HLAB18 negative6,2225.

ii. Hereditary Disorders

It is a fact that a genetic predisposition of neurogenic HO has not yet directly been established and for this reason the research community has shifted interest into genetic disorders that may shed light into the genetic causes of neurogenic HO.

Fibrodysplasia ossificans progressiva (FOP) is an autosomal dominant disorder leading to ossification in the same locations as does HO secondary to TBI and SCI, with congenital malformation of the big toes, with valgus hallux deformities and tumor like swelling on the head, neck, shoulders and back. In FOP has been observed an overexpression of bone morphogenetic proteins (BMP4)26 and an underexpression of its antagonists (noggin, gremlin, follistatin and chordin) resulting to a subsequent increased differentiation of osteogenic cells.

Later, Shore et al.29 identified a specific mutation that existed in all known cases (hereditary and sporadic) of FOP. In other words, he found a highly specific codon for the particular disease, which can lead to new insights into the treatment of HO26.

Progressive osseous heteroplasia is also another autosomal dominant disorder under research for its association with the genetic predisposition of HO but no significant result is published up to date.

Finally, the possible genetic predisposition of HO, and consequently neurogenic HO, is also supported from the fact that patients with ankylosing spondylitis, heterotrophic osteoarthrosis and diffuse idiopathic skeletal hyperostosis have a higher risk of HO.

a. Single Nucleotide Polymorphisms (SNPs)

As stated before, although it is extremely unlikely that a single “HO gene” exists, the investigation of the genetic predisposition of HO formation will help us immensely not only in the treatment but also, and more importantly, in the prophylaxis oh HO by helping us identify the “at-risk” patient earlier.

Mitchell et al.16 in a recent study investigated and presented three possible genetic associations with the development of HO. Three single nucleotide polymorphisms (SNPs) from the adrenergic, the immune and the alternative complement systems each, showing a clear representation of the interplay of multiple pathways that affect bone remodeling. However, we must underline that, although 61 SNPs from six different metabolic systems were investigated, only those 3 systems yielded significant results. The less common polymorphism of the β2adrenergic receptor (ADRB2) gene was associated with increased risk of HO and the toll-like receptor 4 (TLR4) and the complement factor H (CFH) were associated with a decreased risk of HO formation. Interestingly enough there has already been an association between bone remodeling and those three metabolic systems (inflammatory, immune and the central and sympathetic nervous system.

iii. Trauma

Trauma as a risk factor of HO, and neurogenic HO in the case of TBI and SCI, is one of the most investigated factor associated with HO formation. There is a wide range of situations from a direct injury (e.g. combat-related trauma) to the result of a aggressive passive joint manipulation as trigger of heterotopic bone formation. Especially for neurologically impaired patients, several studies have suggested an increased incidence of HO after TBI and SCI with an associated trauma.

Finally, the association of trauma to HO formation has also been tested in rabbit studies3638 where the forcible passive movement of previously immobilized legs resulted in ectopic bone formation. Adapting the previous scenario in clinical medicine, this issue is present in critical ill patients in the Intensive Care Unit setting with burns, multiple injuries and paraplegia, which are also “high-risk” groups for HO formation. However, Casavant et al.39 and Linan et al.53 concluded that passive range of motion (PROM) and early mobilization of patients with TBI and HO is safe, which is nowadays the consensus of the clinical world in terms of not only treatment but also prevention of HO6.

Studies have proposed that artificial ventilation may be a risk factor for neurogenic HO formation. A decrease in oxygen supply has been shown to affect osteogenesis: bone cell proliferation is increased by low oxygen concentrations and macromolecular synthesis is favored by high oxygen concentrations40. The proposed mechanism behind the association of artificial ventilation and HO formation is that an increased duration of artificial ventilation (extremely common in patients with TBI and SCI) may alter the homeostasis of the patient, especially in terms of electrolytes (calcium and phosphorus) and acid-base balance (oxygen tension and pH changes). However, no study has yet to establish a clear connection between those two, or even investigate the differences in local oxygen tension, local pH differences and local electrolyte disturbances at the site of HO.

Finally, another theory of the association of artificial ventilation and HO formation suggests that the attempted iatrogenic hyperventilation on the acute phase of traumatic brain injured patients, in order to lower intracranial pressure by reducing pCO2, may result in systemic alterations. The

blood pH becomes more alkaline resulting in increased risk of salt precipitation, specifically of calcium precipitation41, which may promote a more rapid formation of callus and accelerated fracture healing42.

2. Plegia and muscular spasticity or hypertonia

Marked muscle spasticity or hypertonia is extremely common symptom of CNS injured patients and has been suggested as a risk factor in numerous studies as a cause of muscle hypoxia and increased risk of muscle tears from active or passive mobilization.

Pathophysiology of neurogenic HO

The exact pathophysiology of neurogenic HO is not clear yet. Initially, HO presents histologically as local microvascular alterations, vascular stasis with circumscribed edema and swelling. Following, it is observed a fibroblast and osteoblast proliferation, osteoid formation and finally ectopic bone deposition45. Several studies, with most representative that of Bidner et al. and Kurer et al., provided a clear evidence for the hypothesis of a humoral mechanism for accelerated fracture healing with increased bone formation after TBI and SCI. Gautschi et al.15 even suggested an osteoinductive effect of the cerebrospinal fluid (CSF) from patients with severe TBI. Most recent studies support this by examining the proliferation rates of hFOB cells or primary human osteoblasts.

As a result of the aforementioned specifics-facts in combination with the clinical presentation of neurogenic HO and the theory of Chalmens9, the postulate theory for neurogenic HO formation is that it occurs from the induction of muscle progenitor cells from the mitogenic and osteogenic effects of the serum of CNS injured patients. In detail, the induction is believed to be the result of an imbalance of local and/or systemic factors in soft tissue following traumatic injury (Figure 3). In other words, it is believed that it is not so much the proinflammatory and osteoinductive biochemical factors that give rise to neurogenic HO, but the balance-ratio of proosteoinductive and antiosteoinductive mediators located on the soft tissues. Furthermore, the current trending theory of neurogenic HO formation also supports the interactions of “signaling molecules” secreted from the injured tissue (such as the spinal cord) with not only local but also circulating progenitor cells in the immediate period after trauma. As a consequence we have the aberrant commitment, growth and differentiation of these cells into osteoblasts and finally ectopic bone formation48. This is substantiated by the fact that muscle-derived mesenchymal stem cells (MSCs) have been shown to be inherently plastic, enabling them to differentiate along multiple lineages (osteo, chondro and fibroblast, adipocytes, smooth muscle cells and also have the ability of stimulation, proliferation and differentiation of resident progenitor cells). However, very little is known to the involvement of MPC differentiation and the signaling pathways between them and the osteoinductive-released biochemical factors. Many humoral factors have been tested in numerous studies (e.g. alkaline phosphatase (ALP), creatine kinase (CK), prostaglandins (PGs)) but there is no conclusive evidence of a direct association between any of them and neurogenic HO formation.

Hereby, we will provide a concise review of the consensus of recent studies on the nature of those humoral factors and the suggested mechanisms involved based on Chalmers9 prevalent theory:

1. Presence of Osteoprogenitor Cells

There is strong evidence of the presence of these potential osteogenic cells in most adult connective tissues (e.g. muscle and fascia) and organs9,49. In more detail it is observed that the mineralized nodules, which later lead to bone formation, arise from vimentin positive spindle-shaped cells47. Some of these spindle-shaped cells, present in skeletal muscle, have been associated to mesenchymal stem cells, bonemarrow

stromal cells and pericytes because of their similar morphological, im munohistochemical and mRNA profiles and their capacity for multilineage differentiation as mentioned before47,4951.

Concluding, the well-established presence of mesenchymal stem cells within muscle tissue is believed to be the site of action of the osteoinductive factors released in the systemic circulation by the injured CNS.

2. Osteoinductive Factors

a) Autonomic Dysregulation

Major et al.52 concluded that local microvascular alterations, edema and prolonged swelling (similar histological characteristics as the initial phase of heterotopic bone formation) can appear in the involved tissues as a result of sympathetic activity. Campos da Paz et al.43 speculated that an interruption in neural pathways, from a TBI or a SCI, would result in a chaotic regulation of bone growth. Specifically it was hypothesized that a dysfunction of proprioception, from the CNS injury, would make the ligaments to react to stimulus (e.g. forceful manipulation from intensive physical therapy) in an independent, isolated way resulting to a chaotic differentiation of mesenchymal osteoprogenitor cells into heterotopic bone. Contrary to this, the consensus of the rehabilitation world and of recent studies is that active or passive exercising of joint within the pain free range has a favorable effect in the maintenance of a good physical condition, diminishing the need for additional treatment6,53.

Relevant to the nervous dysregulation secondary to CNS trauma, are the previously established role of the hypopituitary humoral axis after head trauma2,54,55 and the production of growth factors from the brain and pituitary glands5,56. It has been suggested that those sites secrete systemic growth factors that may lead to heterotopic bone formation, however, it is also suggested that the activity of those systemic growth factors can be blocked by being bound to plasma proteins57,58.

b) Altered immunity and abnormal inflammatory response to neurological damage

The examination of the serum from TBI patients has shown an increase in various humoral factors especially of inflammatory nature. There is a consensus among researchers that the serum from CNS injured patients, even in the very first hours post-trauma, shows increased levels of several biochemical markers, including Creactive protein (CRP), Erythrocyte Sedimentation Rate (ESR), Interleukin6 (IL6), Parathyroid Hormone (PTH), Alkaline Phosphatase (ALP), some of which we will discuss in more detail. However, we must underline that those laboratory findings, although useful, have a disputable specifity especially in critically ill patients with concurrent infections, tracheostomies and recent surgeries. The following biomarkers have been suggested in relation to neurogenic HO formation:

Inflammatory markers:

Serum CRP has been shown to increase in patients with a severe TBI when compared to patients without TBI13,59, indicating a strong acute phase inflammatory response.

Although high levels of interleukin6 (IL6) characterize the inflammatory phase of bone healing60 and IL6 has been established as a powerful predictor of early neurological deterioration61, there is no direct association of their effect on NHO formation.

Also, tumor necrosis factoralpha (TNFa), another cytokine of inflammatory nature, due to its dependence to interleukins, is being investigated as a potential biomarker of HO formation. Especially interesting is the fact that TNFa is released from astrocytes and microglia achieving high concentrations soon after TBI62,63.

Leptin has been shown to promote local activation of bone progenitor cells and osteoblasts but also to decrease osteoblastic activity by binding to hypothalamic neurons. Serum leptin levels were found low in patients with neurogenic HO64,65 but no casual relation was established between the low leptin levels and neurogenic HO. Furthermore, the fact that no differences were found across the groups of the studies in terms of renal function, food intake or body fat arose the question of possible connection between leptin levels and hypothalamic damage contributing to neurogenic HO formation.

Osteoblastic markers:

PTH was also significantly increased in TBI patients as early as 6hours post trauma according to Gautschi et al.13 and Trentz et al.66. PTH as a regulator of homeostasis of calcium and phosphate is considered to play a significant role in the enhanced bone formation observed in TBI patients. Contrary, a recent study47 showed no significant differences in serum PTH between the different groups of the study at any tested time post trauma.

For ALP the data are disputable since in recent studies, despite the observed increase throughout the examined period post trauma, there has not been shown any statistically significant different ALP levels between patients with head trauma and patients without head trauma (fracture group or control group)35,47.

Respectively for serum calcium, the data are also controversial with studies showing no significant change between all groups35,66 and studies showing significantly lower serum calcium levels in patients with a TBI than in the other groups47.

Another protein associated with neurogenic HO is osteocalcin. It is an important marker for bone remodeling67. In experimental level has been suggested to induce matrix secretion and recruitment of bone resorbing cells. Trentz et al.66 found osteocalcin to be significantly lower in patients with combined or isolated TBI, suggesting the possible predictive role of osteocalcin levels in future ectopic bone formation.

Finally, an increased expression of marker genes of osteoblastic differentiation RUNX2, SP7 and CATK has been observed in the serum of TBI patients13. RUNX2 and SP7 are transcription factors for osteoblastic differentiation and CATK is a marker of osteoblastic activity13.

Bone turnover markers:

Trentz et al.66 in a study of 80 patients with TBI supported the previously expressed theory of imbalance between proosteoinductive and antiosteoinductive factors in the TBI patients by investigating Carboxyl Terminal Propeptide of Type 1 Pro collagen (PICP) and Carboxyl Terminal Pyridinoline CrossLinked Telopeptide of Type 1 Collagen (ICTP) levels. Specifically, not only PICP levels were above the normal range and higher than in other groups in patients with TBI (showing an enhanced osteoblastic activity70,71) but also ICTP levels were lower in patients with isolated or combined TBI (showing a decreased osteoclastic activity72,73).

From the two IGFs, IGFII has been suggested to play a role in HO formation as it is known to stimulate type 1 collagen production and cartilage matrix synthesis but the data are inconclusive.

Osteogenic differentiation and other markers:

Bone morphogenic proteins (BMPs), which belong to the TGFbeta superfamily, specifically BMP9 and BMP2, have been investigated on recent studies for their osteoinductive influence and involvement in HO pathophysiology. They are known to induce not only mesenchymal and osteoprogenitor cells, but also osteoinducing factors such as insulin-like growth factor (IGF) and vascular endothelial growth factor (VEGF) leading to the regulation of osteoblast differentiation and bone formation74,75. However, a recent study of Gautchi et al. concluded that BMPs in CSF from TBI patients are not present in high enough concentrations to be responsible for the osteogenic cell response that triggers HO15.

Basic fibroblast growth factors (FGFs), another member of the TGFbeta superfamily, known to undergo a rise after a fracture as they stimulate fibroblast activity76, were shown to increase up to seven times than normal in head injured patients with a concurrent local injury77.

Matrix Metalloproteinases (MMPs), involved in numerous remodeling processes, including bone remodeling phase and angiogenesis through their degrading capabilities, are involved in NHO research because of their potential of biomarkers of brain tissue damage and, consequently, neurological outcome78. Specifically, MMP9 is found in high levels in acute TBI patients, and in correlation with high levels of IL6 after TBI, it is believed to play a crucial role in the post-TBI inflammatory events.

The WNT signaling pathway is a class of signaling factors (proteins) required for the development of several types of tissues including musculoskeletal. There has been an increased interest for the WNT genes because it has recently been shown that mutations of those pathways result in disorders of deficient or excess bone formation80. In the future we hope to manipulate pharmacologically those pathways, for orthopedic applications including HO.

Lastly, 24hour urinary hydroxyproline has also been observed in spinal cord injured patients with HO formation but there has not been further investigation of its clinical diagnostic importance81.

We should also mention various factors that have been investigated in a more experimental level, with scarce though research data. Lately there has been an increased interest of the research community towards prostaglandins (PGs). It is being investigated not only their role as biochemical inflammatory factors on heterotopic bone formation38 but also how their inducing factors (e.g. BMP2 and PTH) result in different actions of PGs on bone homeostasis82. However the research of these factors is still evolving with no direct clinical correlation yet.

3. Permissive Environment

Despite the aforementioned osteoinductive capacity of the humoral factors secreted systemically by the injured tissue and acting locally on the site of HO formation, it is also investigated the osteoinductive capacity of the local changes occurring right after soft tissue trauma. The hypothesis is that there is interplay between the release of local osteoinductive factors and the local environmental changes.

Locally observed contributing factors include salt precipitation and electrolyte disturbances, tissue hypoxia, pH changes, changes in local sympathetic nerve activity, immobilization or forcible mobilization after prolonged immobilization, local disequilibrium between parathyroid hormone

and calcitonin83. It is known84 that even in the normal process of fracture healing there are occurring changes in local blood flow, associated with pH changes and changes in serum calcium levels, but also significant alteration of local pO2 in the fracture callus40,85.

However, many clinical studies8688 have described HO in critically ill internal medicine patients and in patients with complicated organ transplantation, meaning in patients without local injury on the site of developing HO. This contrasts the importance of a permissive local environment but supports the theory of systemic factors inducing HO. Nonetheless, it is also conceivable that localized pressure caused by supine positioning of these patients may play a role but it is not investigated yet.

Management and Prognosis

1. Pharmacological Interventions

The role of indomethacin and other NSAIDs in prevention of HO is extensively reported89,90. They have been shown to inhibit cyclooxygenase, which is needed for the production of prostaglandin E2 that is thought to be a mediator in heterotopic bone formation. Banovac et al. highlighted the prophylactic effect of indomethacin or rofecoxib compared placebo treatment in patients with spinal cord injuries. They found a significantly lower incidence of HO in the treatment group (25.0%) compared to the placebo group (64.7%) ($p<0.001$). Additionally, HO symptoms presented significantly later than those in the placebo group (31.7 days vs. 19.2 days; $p<0.048$).

The use of bisphosphonates, and specifically etidronate, in patients with HO due to TBI patients is generally limited91. The theoretical effect thereof is associated with a potential delay in mineralization of the osteoid. Etidronate that is administered prophylactically within a week of injury for 6 months was associated with decreased radiographically and clinically evidenced development of HO when compared to those without treatment ($p<0.025$). Study results indicate that there is Level 2 evidence that etridonate reduces the development of heterotopic ossification in severe head injury patients. In a prospective controlled trial Banovac et al. compared the intravenous etidronate (given for 35 days) followed by oral etidronate treatment for 6 months with the oral only editronate treatment for 6 months. The authors showed that there is no significant difference between the two groups in the development of HO. However, intravenous etidronate treatment significantly reduced swelling from baseline ($p<0.01$). In another study, Banovac et al. reported that treatment with intravenous etidronate treatment followed by oral etidronate treatment for 6 months can halt post-SCI HO progression if initiated before radiographic evidence is present. However, there is no substantial evidence of improvement in SCI patients with clinical signs of HO following long term (2 years) etidronate treatment. Garland et al.. Overall, results of these studies indicate there is Level 4 evidence that etidronate is not effective in treating HO post SCI once there is radiographic or clinical evidence of HO. Recent experimental data indicate that nuclear retinoic acid receptorγ agonists are potent inhibitors of heterotopic ossification in mouse models and, thus, may also be effective against injury induced and congenital heterotopic ossification in humans.

2. NonPharmacological Interventions

Several nonpharmacological interventions, including both operative and nonoperative treatment modalities, have been tested for the prevention and/or treatment of HO after traumatic brain injury during the recent years. There is Level 4 evidence that surgical excision alone does not significantly improve HO post SCI95. This specific study found profound functional improvement directly following surgical excision that did not remain throughout a mean period of 6 years. Specifically, 12.5% of the individuals returned to preoperative levels or worse and total recurrence rate for HO in the hip joint was 92%.

The use of radiotherapy postsurgical excision of HO was studied in two case series in patients with SCI96,97. The studies indicated that progression or recurrence of the excised bone is prevented in 71%96 and 90.9%97 of the cases. Furthermore, combined surgical treatment and irradiation is associated with significant improvement in ROM for 82% of patients, 64% of whom maintain their ROM or gain further range through rehabilitation.

Prophylactic pulse low intensity electromagnetic field therapy with range of motion and exercise therapy has been found to be effective in progression of the disease94.

3. Multimodal approach

The use of pharmacological treatment in combination with surgical excision, irradiation, physiotherapy has been introduced as a superior holistic approach of patients with HO post traumatic brain injury during the latest decade. Fuller et al.98 reported on a case series of 17 brain injury patients who underwent surgical excision of knee HO followed by etidronate treatment. A significant increase in range of motion (average 65°) was documented without clinical or radiographic recurrence of HO. Moore99 presented similar results in 17 cases after surgical excision of HO at hips and elbows due to traumatic brain injury that was combined with etidronate treatment for the prevention of secondary HO. Twenty-three months post surgery, the immediate postoperative range of motion was maintained after an average 23 months period. De Palma et al.100 found that the benefit of multimodal approach in range of motion is greatest in patients with the largest restriction preoperatively.

The importance of continuous passive motion (CPM) in addition to surgical excision and indomethacin administration was highlighted by Lazarus et al.101, who presented a series of 24 patients with traumatic brain injury and elbow HO. The maximum flexion and extension increased significantly at 2 years postoperatively ($p=0.0003$, 0.0005 respectively) with the patients that received CPM demonstrating higher gain in range of motion than those that did not receive CPM ($p=0.04$)

Conclusion

In conclusion, neurogenic heterotopic ossification is a complex and common clinical oddity that provokes difficult problems to patients and physicians. The research community has already identified numerous clinical factors and biochemical markers that are predictive of eventual neurogenic HO and has explained various pathways involved in the pathophysiology of neurogenic HO. However, to date, the entity of neurogenic HO is not clear leading to diagnostic and, mainly, therapeutic anomalies. We believe that future research should investigate in more detail the genetic and biomolecular element of neurogenic HO, as still, very little is known on this level. Finally, it is crucial to emphasize that a better understanding of neurogenic HO will not only help us immensely in the prophylaxis and treatment of Heterotopic Ossification but will also broaden our knowledge in other common orthopedic problems such as fracture nonunion.

BACK TO TOP

White Matter Abnormalities in Veterans With Mild Traumatic Brain Injury

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Abstract

Objective

It has been estimated that 10%–20% of U.S. veterans of the wars in Iraq and Afghanistan experienced mild traumatic brain injury (TBI), mostly secondary to blast exposure. Diffusion tensor imaging (DTI) may detect subtle white matter changes in both the acute and chronic stages of mild TBI and thus has the potential to detect white matter damage in patients with TBI. The authors used DTI to examine white matter integrity in a relatively large group of veterans with a history of mild TBI.

Method

DTI images from 72 veterans of the wars in Iraq and Afghanistan who had mild TBI were compared with DTI images from 21 veterans with no exposure to TBI during deployment. Conventional voxel-based analysis as well as a method of identifying spatially heterogeneous areas of decreased fractional anisotropy (“potholes”) were used. Veterans also underwent psychiatric and neuropsychological assessments.

Results

Voxel-based analysis did not reveal differences in DTI parameters between the veterans with mild TBI and those with no TBI. However, the veterans with mild TBI had a significantly higher number of potholes than those without TBI. The difference in the number of potholes was not influenced by age, time since trauma, a history of mild TBI unrelated to deployment, or coexisting psychopathology. The number of potholes was correlated with the severity of TBI and with performance in executive functioning tasks.

Conclusions

Veterans who had blast-related mild TBI showed evidence of multifocal white matter abnormalities that were associated with severity of the injury and with relevant functional measures. Overall, white matter potholes may constitute a sensitive biomarker of axonal injury that can be identified in mild TBI at acute and chronic stages of its clinical course.

BACK TO TOP

Blast-related mild traumatic brain injury is associated with a decline in self-rated health amongst US military personnel

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Mild traumatic brain injury (MTBI) has emerged as the preeminent injury of combat from the recent conflicts in Iraq and Afghanistan. Very little is known about short- and long-term outcomes after combat-related MTBI. As a measure of outcome after injury, self-rated health is a reliable, widely used measure that assesses perceived health. The primary aim of this study was to determine the effect of combat-related MTBI on self-reported health status after return from deployment. The secondary objective was to examine predictors of a decline in self-reported health status amongst US service members with MTBI, as compared to those service members with other minor non-TBI injuries.

PATIENTS AND METHODS:

MTBI cases and an injured comparison group were identified from the Expeditionary Medical Encounter Database records of 1129 male, US service members who experienced blast-related injuries in Iraq from March 2004 to March 2008. Self-rated health was assessed from the routinely administered pre- and post-deployment health assessment questionnaires by the following question, "Overall, how would you rate your health during the past month?" Possible responses were "poor", "fair", "good", "very good", or "excellent." A distinction was made between minor and major negative changes in health (i.e., very good to fair) based on these self-rated health outcomes captured post-injury.

RESULTS:

For all personnel, post-injury levels of self-rated health were statistically significantly worse than pre-injury health rating. At 6months post-injury, service members with MTBI were 5 times more likely to report a major negative change in health as compared to members with other mild injuries. This association was independent of age, rank, branch of service, Injury Severity Score, mental health diagnosis prior to injury, and having been referred to a health care professional.

DISCUSSION:

Blast-related injuries, specifically MTBI, during deployment have negative consequences on service members' perception of health. Future research is needed to improve our understanding of the overall effects of MTBI on health and quality of life.

BACK TO TOP

A Trial of Intracranial-Pressure Monitoring in Traumatic Brain Injury

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Although the monitoring of intracranial pressure is widely recognized as standard care for patients with severe traumatic brain injury, its use in guiding therapy has incomplete acceptance, even in high-income countries. Successive editions of the guidelines for the management of severe traumatic brain injury have documented the inadequate evidence of efficacy, calling for randomized, controlled trials while also noting the ethical issues that would be posed if the control group consisted of patients who did not undergo monitoring. The identification of a group of intensivists in Latin America who routinely managed severe traumatic brain injury without using available monitors and for whom there was equipoise regarding its efficacy eliminated that ethical constraint and led to the implementation of the randomized, controlled trial described here.

Data from rigorous randomized, controlled trials of intracranial-pressure monitoring in the management of traumatic brain injury are lacking, and few high-quality, prospective case–control or cohort studies have been conducted. Historically, the use of monitoring-based management has been confounded by several factors. These include the involvement of intensivists and the development of the subspecialty of neurocritical care; the vast improvements in the resuscitation of patients with trauma (and those with brain injury, in particular); myriad developments in the management of traumatic brain injury during prehospital emergency care, emergency department care, and rehabilitation; and marked improvements in monitoring and management techniques in the intensive care unit (ICU). Such confounding can be rigorously addressed only in a randomized, controlled trial. Here we report the results of such a trial.

The primary objective of the Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure (BEST:TRIP) trial was to determine whether the information derived from the monitoring of intracranial pressure in patients with severe traumatic brain injury improves medical practice and patient outcomes. Our primary hypothesis was that a management protocol based on the use of intracranial-pressure monitoring would result in reduced mortality and improved neuropsychological and functional recovery at 6 months. Our secondary hypothesis was that incorporating intracranial-pressure monitoring into the management of severe traumatic brain injury would have benefits for the health care system, including a reduced risk of complications and a shorter ICU stay.

Methods

Study Design

The study was a multicenter, parallel-group trial, with randomized assignment to intracranial-pressure monitoring (the pressure-monitoring group) or imaging and clinical examination (the imaging–clinical examination group). Randomization was stratified according to study site, severity of injury, and age. The study was started at three Bolivian hospitals; an additional Bolivian hospital and two Ecuadorian hospitals were subsequently

recruited to increase enrollment. All six sites had ICUs staffed with intensivists, 24-hour computed tomographic (CT) services and neurosurgery coverage, and high volumes of patients with trauma.

Eligibility

All patients presenting with traumatic brain injury were screened for eligibility on admission at the study hospitals. To be included in the study, patients had to be 13 years of age or older and have a score on the Glasgow Coma Scale (GCS) of 3 to 8 (with a score on the GCS motor component of 1 to 5 if the patient was intubated) or a higher score on admission that dropped to the specified range within 48 hours after injury. (The GCS ranges from 3 to 15, with higher scores indicating higher levels of consciousness; the motor score ranges from 1 to 6.) Patients with a GCS score of 3 and bilateral fixed and dilated pupils and those with an injury believed to be unsurvivable were excluded.

Group Assignments and Interventions

Randomization sequences were computer-generated by a data-center biostatistician and were stratified according to site, severity of injury (GCS score of 3 to 5, or GCS motor score of 1 to 2 if the patient was intubated, vs. GCS score of 6 to 8, or GCS motor score of 3 to 5 if the patient was intubated), and age (<40 years vs. ≥40 years), with a block size of 2 or 4.

The study was conducted in accordance with the protocol (available at NEJM.org), which specified that three CT scans be obtained (at baseline, 48 hours, and 5 to 7 days) and standard supportive care provided for each patient, with care to include mechanical ventilation, sedation, and analgesia. Non-neurologic problems were managed aggressively in both groups.

Patients randomly assigned to the pressure-monitoring group had an intraparenchymal monitor placed as soon as possible and were treated to maintain an intracranial pressure of less than 20 mm Hg, in accordance with the guidelines for the management of severe traumatic brain injury. Drainage of cerebrospinal fluid required ventriculostomy placement. The care for patients randomly assigned to the imaging–clinical examination group was provided in accordance with a protocol based on the pretrial standard for care at the three original participating hospitals. In the absence of intracranial mass lesions requiring surgery, signs of intracranial hypertension on imaging or clinical examination were treated first with hyperosmolar therapies with the use of protocol-specified doses on a fixed schedule of administration, optional mild hyperventilation (at a partial pressure of arterial carbon dioxide of 30 to 35 mm Hg), and optional ventricular drainage. Continuing edema prompted consideration of the administration of high-dose barbiturates. Additional treatments were required for patients with “neuroworsening,” persistent edema, or clinical signs of intracranial hypertension.

Outcomes

The primary outcome, assessed within 6 months after the study onset, was a composite of 21 components: measures of survival (survival time, counted as 1 component), duration and level of impaired consciousness (time to follow commands, sum of errors on the orientation questions from the Galveston Orientation and Amnesia Test [GOAT] on discharge from the hospital — 2 components), functional status and orientation 3 months after injury (assessed with the use of the Extended Glasgow Outcome Scale [GOS-E], the Disability Rating Scale, and GOAT — 3 components),

and functional and neuropsychological status 6 months after injury (15 components). The battery of tests included measures of mental status, working memory, information-processing speed, episodic memory and learning, verbal fluency, executive function, and motor dexterity. Trained examiners who were unaware of the group assignments administered the tests at 3 and 6 months.

For the primary outcome, each participant's percentile was determined separately for each of the 21 measures; the overall outcome was the average of the 21 percentiles (on a scale from 0 to 100, with lower percentiles representing worse outcomes). Protocol-specified secondary outcomes were the length of stay in the ICU (measured as the total number of days in the ICU and the number of days in the ICU on which the patient received at least one brain-specific treatment) and systemic complications. Brain-specific treatments were those directed at intracranial hypertension and included the administration of hyperosmolar agents and pressors and the use of hyperventilation but excluded ventilation, sedation, and analgesia. Additional, post hoc secondary outcomes were the hospital length of stay, the number of days of mechanical ventilation, treatment with high-dose barbiturates or decompressive craniectomy, and therapeutic intensity. For some analyses focused specifically on interventions for intracranial hypertension, we defined the duration of therapy as the number of days from injury until the last brain-specific treatment. Data for patients who survived for more than 1 day after the last brain-specific treatment (collectively referred to as the brain-treatment survivors subgroup) were also analyzed. We integrated brain-specific treatments by summing the number of treatments delivered per hour over the course of the treatment interval.

Study Oversight

The study was approved by the institutional review board at the University of Washington and the ethics committees at all study centers. All authors vouch for the accuracy and completeness of the data and data analyses and for the fidelity of this report to the study protocol. Integra Life Sciences donated the catheters used in monitoring intracranial pressure and provided additional unrestricted support for this project. Integra had no role in the design or conduct of the study, the data analysis, or the writing of the manuscript.

Statistical Analysis

The planned sample size of 324 was determined by means of simulation to provide 80% power to detect an increase of 10 percentage points in the percentage of patients with a good outcome or with moderate disability according to the GOS-E (odds ratio with imaging and clinical examination vs. pressure monitoring, 1.5), and a corresponding improvement on other measures. One planned interim efficacy analysis was conducted when half the participants had undergone the 6-month assessment.

The primary hypothesis was tested with the use of the blocked Wilcoxon test, with blocking on stratification factors, and a two-sided significance level of 0.05. We obtained odds ratios and confidence intervals from a logistic proportional-odds model, accounting for the same factors. This analysis was supplemented by similar analyses of individual measures and composite analyses of subgroup measures. Cox models were used to analyze survival. A significance level of 0.01 was used to test secondary hypotheses. The main analyses included data on all participants randomly assigned to a treatment group (intention-to-treat population). Sensitivity analyses included analyses restricted to patients who survived, those who received the assigned treatment, and those who survived for at least 24 hours after receiving brain-specific treatments.

Results

Study Participants

Patients were recruited between September 2008 and October 2011, with the last follow-up visit occurring in May 2012.. The trial ended when the planned sample size was attained. Of 528 eligible patients, 204 (39%) were excluded before randomization. Of the patients who underwent randomization, 92% were followed for 6 months or until death. Protocol violations were few. The two treatment groups were similar at baseline with regard to all baseline characteristics.

Traffic incidents were the primary cause of injury. Only 45% of participants were transported to the first hospital by ambulance. Most were transferred to study hospitals from another center; the median time to arrival at the first hospital was 1.0 hour for direct admissions and 2.7 hours for transfers. The median time from injury to arrival at study centers for all patients was 3.1 hours. We were unable to acquire accurate information on prehospital interventions or early secondary insults (i.e., hypoxemia or hypotension) because they were not uniformly assessed and recorded.

Initial Injury

Of the study participants who underwent randomization, 24% had a GCS score that was higher on admission but subsequently dropped to the specified range for enrollment. The median GCS motor score at randomization was 4.0; 49% of participants had localizing brain injuries, with none of the participants following commands. One or both pupils were nonreactive in 44% of participants. On the Abbreviated Injury Scale (ranging from 0 to 6, with higher scores indicating more severe injury), the median score for head injury was 5; 82% of participants had a score of 4 or higher. Initial CT revealed a high severity of injury overall, with grade III diffuse injury (swelling of the brain causing compression of the basal cisterns, without a mass lesion or a midline shift of >5 mm) in 43% of the participants and mass lesions requiring surgical treatment in 33%. Mesencephalic cisterns were compressed or absent in 85% of the participants, and the midline was shifted by more than 5 mm in 36%.

Processes of Care

The hospital length of stay was marginally shorter in the imaging–clinical examination group than in the pressure-monitoring group only when all participants who underwent randomization were included in the analysis. There were no significant differences between groups with respect to the ICU length of stay, in either the intention-to-treat population or the brain-treatment survivors subgroup. For this subgroup, the median length of stay was 13 days in the ICU and 26 days in the hospital. There were no significant between-group differences in the number of days of mechanical ventilation. The evaluation of non-neurologic complications also revealed no significant differences between treatment groups, except that patients in the pressure-monitoring group had a significantly higher rate of decubitus ulcers (12%, vs. 5% in the imaging–clinical examination group; P=0.03).

The median time during which intracranial pressure was monitored was 3.6 days in the entire pressure-monitoring group and 4.0 days in the brain-treatment survivors subgroup. The median and mean percentages of readings that were 20 mm Hg or higher were 7 and 20%, respectively, in the entire study population and 5 and 13%, respectively, in the brain-treatment survivors subgroup. For these respective groups, the intracranial

pressure was 20 mm Hg or higher initially in 37% and 29% of patients and at any time during monitoring in 79% and 76% of patients. The incidence of neuroworsening after randomization was 25% for the entire study population and did not differ significantly between the two treatment groups.

The median interval during which patients received brain-specific treatment was significantly longer in the imaging–clinical examination group than in the pressure-monitoring group. In addition, post hoc analyses of integrated treatment intensity revealed that the total number of treatments was significantly greater for the imaging–clinical examination group as a whole and for the brain-treatment survivors subgroup than for the pressure-monitoring group. The use of high-dose barbiturates was greater in the pressure-monitoring group than in the imaging–clinical examination group (24% vs. 13%). There was no significant between-group difference in the number of patients who underwent craniectomy. The proportion of patients treated with hypertonic saline and the proportion treated with hyperventilation were significantly higher in the imaging–clinical examination group than in the pressure-monitoring group (72% vs. 58% and 73% vs. 60%, respectively). Among patients who received treatment with mannitol or hypertonic saline, the duration of treatment was longer in the imaging–clinical evaluation group than in the pressure-monitoring group (21 hours vs. 13 hours for mannitol and 21 hours vs. 10 hours for hypertonic saline)..

Discussion

Our results do not support the hypothesized superiority of management guided by intracranial-pressure monitoring over management guided by neurologic examination and serial CT imaging in patients with severe traumatic brain injury. Intracranial-pressure monitoring is the cornerstone of treatment for severe traumatic brain injury. The principle guiding additional interventions, such as the monitoring of cerebral perfusion pressure or tissue-perfusion modification, is the maintenance of intracranial pressure below 20 mm Hg.

Most of the data from nonrandomized, controlled trials support the association of treatment based on monitored intracranial pressure with improved recovery, which has led to the recommendation of this approach in successive editions of published guidelines for the management of severe traumatic brain injury (although there have been calls for a randomized, controlled trial). Dissenting literature does exist. In two retrospective studies, there was no association or a negative association between monitoring-based treatment and outcome, and in an older, small, low-quality study of the usefulness of monitoring in guiding mannitol dosing, monitoring was not found to be useful.

Since our study was conducted in Bolivia and Ecuador, the extent to which the findings can be generalized to other patient populations warrants discussion. Our data suggest that the care provided in the study hospitals adhered to the fundamentals of ICU care and was consistent with the study design. Prehospital resuscitation is less developed in Bolivia and Ecuador than in higher-income countries, and the more severely injured patients in those two countries may not survive long enough to reach the hospital. Thus, the study population may have had less severe brain injury than comparable ICU populations in higher-income countries. On the other hand, less advanced prehospital resuscitation may result in secondary insults (e.g., hypoxemia and hypotension), which would serve to increase the severity of the injury. In our study, the initial and subsequent readings of intracranial pressure, findings on CT, and pupillary responses were all consistent with very severe injury. The early outcome curves in our study appear to be consistent with what would be expected for young adults with severe brain injury whose care was being well managed in ICUs in wealthier countries. The results we report on early mortality were also similar to those reported in higher-income

countries. Survival at 6 months is confounded by high mortality (35% of the deaths) after the first 14 days, which is probably related to the limited resources available after discharge from the ICU. None of the study participants received rehabilitation or extensive medical care after hospital discharge. The elderly population with traumatic brain injury, which is prominent in high-income countries, was not represented in this study.

Between-group differences in the individual treatments delivered (with greater use of hypertonic saline, mannitol, and hyperventilation in the imaging–clinical examination group than in the pressure-monitoring group) reflect differences in approaches to treatment: scheduled treatment in the imaging–clinical examination protocol and treatment as indicated in the pressure-monitoring protocol. The quantitative measurement of intracranial pressure and the consequent fixed treatment threshold probably explains the more frequent administration of high-dose barbiturates and high-dose hypertonic saline in the pressure-monitoring group.

There was a need to standardize the type of monitoring used. Intraparenchymal monitoring was chosen for its accuracy, ease of insertion, safety profile, and low maintenance requirements. The alternative — a transduced ventricular catheter, which is accepted worldwide and was available but rarely used at the study sites before the start of the study — was not believed to be as compatible with our study setting, even though it offers the inherently useful therapeutic option of draining cerebrospinal fluid. Cerebrospinal-fluid drainage was a treatment option that would have required separate ventriculostomy placement — an approach to monitoring that is similar to that specified in the protocol for the ongoing Brain Tissue Oxygen Monitoring in Traumatic Brain Injury (BOOST 2) trial (ClinicalTrials.gov number, NCT00974259). Drainage of cerebrospinal fluid is consistent with guidelines-based management. Although it is effective as a means of lowering elevated intracranial pressure temporarily, drainage has not been shown to improve the outcome of severe traumatic brain injury.

At issue here is not the question of whether intracranial pressure is important — both groups were treated for intracranial hypertension. We investigated whether the guidelines-based protocol used in this study significantly improved the outcome. Our results do not support the superiority of treatment based on intracranial-pressure monitoring over treatment guided by neurologic testing and serial CT imaging in improving short-term or long-term recovery in the general population of patients with severe traumatic brain injury. This finding does not argue against the use of intracranial–pressure monitoring. Only the monitoring-based interventional algorithm was tested here. It is possible that the imaging–clinical examination protocol provided superior control of intracranial pressure. Alternatively, the lack of efficacy may be attributable to other factors, such as the use of a universal threshold for intracranial pressure or the efficacies and toxic effects of the therapeutic agents used, individually or in combination. Additional reasons for the lack of efficacy may include the interpretation of the data on intracranial pressure (a focus on instantaneous values rather than trends or on intracranial pressure rather than cerebral compliance), the lack of identification of subtypes of traumatic brain injury requiring different approaches to management (subtype identification may evolve over the course of treatment), the universal primacy of manipulation of intracranial pressure as opposed to consideration of other physiological interventions (e.g., management of cerebral perfusion pressure), or even the consideration of intracranial pressure as a treatment variable rather than merely an indication of disease severity.

The value of knowing the precise intracranial pressure is not being challenged here, nor is the value of aggressively treating severe traumatic brain injury being questioned. Rather our data suggest that a reassessment of the role of manipulating monitored intracranial pressure as part of multimodality monitoring and targeted treatment of severe traumatic brain injury is in order.

BACK TO TOP

PTSD

Cognitive behavioural therapy as an adjunct to pharmacotherapy for primary care based patients with treatment resistant depression: results of the CoBalT randomised controlled trial

The Lancet
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Summary

Background

Only a third of patients with depression respond fully to antidepressant medication but little evidence exists regarding the best next step treatment for those whose symptoms are treatment resistant. The CoBalT trial aimed to examine the effectiveness of cognitive behavioural therapy (CBT) as an adjunct to usual care (including pharmacotherapy) for primary care patients with treatment resistant depression compared with usual care alone.

Methods

This two parallel-group multicentre randomised controlled trial recruited 469 patients aged 18—75 years with treatment resistant depression (on antidepressants for ≥6 weeks, Beck depression inventory [BDI] score ≥14 and international classification of diseases [ICD]10 criteria for depression) from 73 UK general practices. Participants were randomised, with a computer generated code (stratified by centre and minimised according to baseline BDI score, whether the general practice had a counsellor, previous treatment with antidepressants, and duration of present episode of depression) to one of two groups: usual care or CBT in addition to usual care, and were followed up for 12 months. Because of the nature of the intervention it was not possible to mask participants, general practitioners, CBT therapists, or researchers to the treatment allocation.

Analyses were by intention to treat. The primary outcome was response, defined as at least 50% reduction in depressive symptoms (BDI score) at 6 months compared with baseline. This trial is registered, ISRCTN38231611.

Findings

Between Nov 4, 2008, and Sept 30, 2010, we assigned 235 patients to usual care and 234 to CBT plus usual care. 422 participants (90%) were followed up at 6 months and 396 (84%) at 12 months, finishing on Oct 31, 2011. 95 participants (46%) in the intervention group met criteria for response at 6 months compared with 46 (22%) in the usual care group (odds ratio 3·26, 95% CI 2·10—5·06, p<0·001).

Interpretation

Before this study, no evidence from large-scale randomised controlled trials was available for the effectiveness of augmentation of antidepressant medication with CBT as a next-step for patients whose depression has not responded to pharmacotherapy. Our study has provided robust evidence that CBT as an adjunct to usual care that includes antidepressants is an effective treatment, reducing depressive symptoms in this population.

Funding

National Institute for Health Research Health Technology Assessment.

Introduction

Depression is a major public health problem. It is predicted to be the leading cause of disability in high-income countries by 2030, with only HIV/AIDS and perinatal disorders ranking higher for low-income and middle-income countries.1 Antidepressants are often the first-line treatment for depression and prescriptions for such drugs have increased substantially in the past 20 years.2, 3 However, only a third of patients respond fully to pharmacotherapy and half do not have at least a 50% reduction in depressive symptoms after 12—14 weeks of medication.4 When an adequate dose and duration of treatment has been given, such nonresponse can be termed treatment resistance. No agreed definition of treatment resistance exists5 but, in view of the extent of nonresponse, treatment-resistant depression clearly has a substantial effect on individuals, health services, and society.

No standard approach to the management of treatment-resistant depression exists. Options include increasing the dose of pharmacotherapy, switching to a different antidepressant, or augmentation with another pharmacological or psychological treatment. However, evidence that these approaches improve outcome is scarce.6, 7

Evidence shows that cognitive behavioural therapy (CBT), the most widely available structured psychotherapy for depression, is effective for previously untreated episodes of depression. CBT and its variants have been investigated for treatment of chronic and treatment-resistant depression but previous trials have not included a comparison group of patients who continued with their existing medication, meaning that the

effectiveness of augmentation of antidepressant medication with CBT has not been assessed as a next-step treatment option. Some researchers have investigated a variant of CBT—cognitive behavioural analysis system of psychotherapy (CBASP)—which puts more emphasis on behavioural and interpersonal factors than does standard CBT. However, these trials in patients with chronic depression have provided inconsistent results as to the effectiveness of CBASP combined with medication compared with medication alone.9, 10

Scarce access to psychological treatment in the UK and elsewhere has meant that, in clinical practice, CBT has often been reserved for individuals who have not responded to antidepressants. No large-scale randomised controlled trials6, 7 have assessed the effectiveness of CBT after nonresponse to pharmacotherapy compared with continuing pharmacotherapy as part of usual care for patients with treatment-resistant depression. We chose to investigate CBT rather than CBASP because some evidence suggests that CBT might reduce rates of relapse, including among individuals with residual depressive symptoms.12 Furthermore, some models of more persistent depression put emphasis on cognitive rather than behavioural aspects of treatment.13

The aim of the CoBalT trial was to examine the effectiveness of CBT as an adjunct to usual care including pharmacotherapy for primary care patients with treatment resistant depression compared with usual care alone. The economic evaluation will be reported separately.

Methods

Study design and participants

CoBalT was a multicentre pragmatic randomised controlled trial with two parallel groups. We recruited participants from 73 general practices in urban and rural settings in three UK centres: Bristol, Exeter, and Glasgow. Most participants were identified through a search of practice computerised medical records, although general practitioners (family doctors) were able to refer patients directly to the research team.

Eligible patients were those aged 18—75 years who had adhered15, 16 to an adequate dose of antidepressant medication (based on the British National Formulary and advice from psychopharmacology experts, appendix p 1) for at least 6 weeks and had a Beck depression inventory (BDIII)17 score of 14 or more. They also met international classification of disease (ICD) criteria for a depressive episode assessed with the revised clinical interview schedule.18, 19 General practitioners were asked to exclude patients who had bipolar disorder, psychotic disorder, or major alcohol or substance abuse problems; were unable to complete the questionnaires; or were pregnant. Individuals who were currently receiving CBT or other psychotherapy (including counselling) or secondary care for their depression, or who received CBT in the past 3 years, or who were taking part in another intervention study were also excluded.

We used a three-stage recruitment process.14 The record search identified patients who had received repeated prescriptions for antidepressants. Those who agreed to be contacted by the research team were mailed a short questionnaire that included questions about their depression and adherence to antidepressants. Those who met the definition of treatment-resistant depression (BDI score ≥14 and adhered to antidepressants at an adequate dose for at least 6 weeks) were contacted by telephone by a researcher to ascertain their eligibility with respect to present and past psychological treatment and present secondary care for depression. Potentially eligible patients were invited to attend a face-to-face appointment

with a researcher to discuss participating in the trial and to confirm their eligibility. Ineligible patients (and those who declined participation) were referred back to their general practitioner.

The West Midlands Research Ethics Committee (NRES/07/H1208/60) gave ethics approval and we obtained research governance approval from the local primary care trusts or health boards.

Randomisation and masking

After baseline data and written informed consent for trial participation were obtained, eligible patients were randomised to one of two groups: usual care or CBT in addition to usual care. Randomisation was by means of a computer-generated code from a remote automated telephone randomisation service, which thus ensured that the treatment allocation was concealed from the recruiting researcher. Allocation was stratified by centre and minimised (with a probability weighting of 0·820) according to baseline BDI score (14—19, 20—28, ≥29); whether the general practice had a counsellor (yes or no); previous treatment with antidepressants (yes or no); and duration of present episode of depression (<1 year, 1—2 years, ≥2 years).

Participants were taking antidepressants at the time of randomisation and were expected to continue with these drugs as part of their usual care from their general practitioner. Because of the nature of the intervention it was not possible to mask participants, general practitioners, CBT therapists, or researchers to the treatment allocation.

Procedures

We placed no restrictions on the treatment options for patients randomised to be managed as usual by their general practitioner. Participants could be referred for counselling, CBT, or to secondary care, when such treatment was clinically appropriate.

Participants in the intervention group received 12 sessions of individual CBT (each lasting 50—60 min), with (up to) a further six sessions when judged to be clinically appropriate by the therapist (maximum of 18 sessions) in addition to usual care from their general practitioner. Therapy took place in the patient's general practice surgery or at nearby National Health Service (NHS) or university premises. Therapists used the CBT for depression treatment manuals21, 22 and, where appropriate, elaborations designed to address treatment resistance.13 Therapists received at least 1 day of training specific to the trial from an experienced CBT therapist and trainer (AG) and weekly supervision from skilled CBT supervisors at each centre (GL, WK, and CK). Therapists were flexible in responding to problems raised by the patient (eg, by targeting symptoms of anxiety with appropriate cognitive behavioural models, when these were deemed important). Emphasis was also given to formulating the psychopathology in terms of conditional beliefs. Beck's theory suggests that conditional beliefs (eg, “If I am not perfect then others will reject me”) increase vulnerability to depression and delay recovery.

The intervention was delivered by 11 part-time therapists in the three sites who were representative of those working within NHS psychological services.14 Ten of the 11 therapists were female, their mean age was 39·2 years (SD 8.1), and they had practised as a therapist for a mean of 9·7 years (8·1). With written consent from patients, therapy sessions were audio-recorded. Fidelity of the intervention to the CBT model was

assessed14 for a random sample of recordings by three independent raters from the Oxford Cognitive Therapy Centre with the Cognitive Therapy Rating scale, which is a valid and reliable CBT rating scale.

Participants were followed up 3, 6, 9, and 12 months after randomisation.14 Wherever possible, to maximise retention, researchers met with the participant face-to-face at 6 months and 12 months. Follow-ups at 3 and 9 months were done by telephone.

The primary outcome was BDI score at 6 months, specifically a binary variable representing response, defined as a reduction in depressive symptoms of at least 50% compared with baseline. Secondary outcomes were the BDI score as a continuous variable, remission of symptoms (BDI score of less than 10), and quality of life (assessed with the short form [SF] health survey 12)24 at 6 and 12 months.14 Other secondary outcomes at 6 and 12 months were panic,25 and measures of depression (patient health questionnaire 926), and anxiety (generalised anxiety disorder assessment 727) used in psychological services.28 Data for use of, and adherence to, antidepressant medication were also collected. Additionally, data for healthcare use in primary and secondary care, private treatments, and complementary and alternative treatments were collected at 6 and 12 months, and patients were also asked to the complete the EQ5D29 at both time points. These data will inform the economic evaluation (to be reported separately)

Statistical analysis

The original sample size calculation (with nQuery 5.0) showed that 472 participants would provide 90% power to detect a difference of 16 percentage points in response between the two groups based on a two-sided 5% significance level and 15% loss to follow-up at 6 months. This corresponds to an odds ratio (OR) of 2, deemed clinically important and smaller than that derived from a systematic review of CBT.30 However, a slightly lower recruitment rate in one centre and difficulty matching recruitment rates to therapist capacity in two centres resulted in a revised sample size target of 432, which had 90% power to detect a 17 percentage point difference (30% vs 47%) in the binary response outcome and 87% power to detect the original difference.14 Analysis and reporting of this trial was in accordance with Consolidated Standards of Reporting Trials guidelines.31 We did all analyses in Stata 11.2, following a predefined analysis plan agreed with the Trial Steering Committee.

We compared characteristics of patients at various stages of study recruitment, including using descriptive statistics to assess baseline comparability of randomised groups. We did primary comparative analyses between the randomised groups by intention-to-treat, without imputation of missing data. We used logistic regression to compare the binary primary outcome at 6 months between the groups as randomised, adjusting for study centre, baseline BDI score, and the other three minimisation variables. We used similar regression models for secondary analyses with additional adjustment for any variables that showed marked imbalance at baseline and any differences in the actual time to follow-up. We used linear or logistic regression as appropriate for analysis of other secondary outcomes, and we adjusted for any baseline imbalances. We used repeated measures logistic and linear regression models to summarise the effect of the intervention on outcomes over 12 months. We report ORs or differences in means, 95% CIs, and p values.

We used generalised latent and linear mixed models for secondary analyses to obtain a fully specified heteroscedastic model32 to examine the effect of clustering by therapist. Additionally, we used sensitivity analyses to examine the effect of missing data with the method of multiple

imputation by chained equation (ice procedure version 1.9.5, April 15, 2011; 25 datasets; ten switching procedures). The imputation model included the variables in the primary intention-to-treat model, together with variables associated with missing BDI data at 6 or 12 months and other measures of depression and anxiety. We used instrumental variable regression methods to estimate the Complier-Average Causal Effect (CACE)33 for individuals who were viewed as on track to receive the full course of therapy at the time of the 6 month follow-up (defined as having received nine or more sessions of CBT) and the longer-term 12 month outcome (participants who had received at least 12 sessions of CBT) for the binary response (probit regression) and continuous (linear regression) BDI outcomes (the original definition14 of a complier included individuals whose therapy goals were achieved but this definition was made stricter because it included those who had received fewer than eight sessions.) Finally, we did two preplanned subgroup analyses by including an interaction between treatment allocation and patient expectation of outcome or degree of treatment resistance (on the basis of duration of present symptoms and past treatment with antidepressant drugs). This trial is registered, ISRCTN38231611.

Role of the funding source

The funding source had no role in study design, data collection, data analysis, interpretation of data, 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

We did the first record search for eligible patients on Nov 4, 2008, and randomised the last patient on Sept 30, 2010 (appendix pp 2—3). We obtained follow-up data between March 16, 2009, and Oct 31, 2011. We identified 912 patients as having treatment-resistant depression and invited them to attend a baseline appointment, but 163 (18%) declined (figure). We identified no age or gender differences between individuals who declined and those who agreed to attend such an appointment (data not shown), although those who agreed were more highly educated ($p=0·009$). At baseline, men were more likely to be ineligible ($p=0·02$) but we noted no differences in age or educational background between those who were or were not eligible to participate in the trial (data not shown). Of the 749 who attended a baseline appointment, 63% (469) were eligible to participate and gave written informed consent.

Of the randomised individuals, 234 were allocated to receive the intervention and 235 to continue with usual care from their general practitioner. 422 (90%) participants were followed up at 6 months and 396 (84%) at 12 months (figure). Older individuals, women, those from higher socioeconomic backgrounds, those with more social support, and those with better physical function were less likely to have missing BDI outcome data (data not shown). We identified some evidence that individuals who were single, those with more severe depression at baseline, and those who scored more highly on measures of panic were more likely to have missing outcome data (data not shown).

72% (339 of 469) of participants were women, mean age was 49·6 years (SD 11·7), and 44% (206) were in paid employment (full or part-time). Mean BDI score at baseline was 31·8 (10·7). 28% (129) of participants fulfilled ICD10 criteria for a severe depressive episode and 88% (415) had had depression in the past. Duration of present episode of depression was 2 years or longer for 59% (276) of participants and 70% (327) had

been prescribed their present antidepressants for more than 12 months. Selective serotonin reuptake inhibitors (SSRIs) were the most common antidepressant taken at baseline (334 individuals, appendix p 4).

347 [75%] of 463 participants who had a secondary psychiatric diagnosis had a secondary diagnosis of an anxiety disorder according to the revised Clinical Interview Schedule (245 generalised anxiety, 67 panic disorder, 35 phobias). 43% (202) of participants reported another longstanding illness or disability (diabetes, asthma, arthritis, heart disease, high blood pressure, or lung disease).

Among randomised individuals, the intervention group included more men, more individuals in paid employment and more who reported financial difficulty, fewer individuals with caring responsibilities or longstanding illness or disability, and better physical function (measured by SF12, table 1) than did the usual care group. Compared with participants in the usual care group, a smaller proportion of individuals in the intervention group had taken their current antidepressants for more than 12 months and participants in this group were less likely to have had five or more previous episodes of depression, although a greater proportion had a family history of depression.

Nine of the 11 therapists delivered 97% of the intervention and, for these nine, the number of patients per therapist ranged from 13 (6%) to 41 (18%). Mean Cognitive Therapy Rating scale rating (adjusted for caseload) on the basis of a random sample of 54 sessions was 38·8 (95% CI 36·7—40·8), which is greater than the threshold of competence expected in UK CBT training programmes.34

Mean duration of intervention (from randomisation) was 6·3 months (SD 3·0). 20 participants in the intervention group (9%) did not attend any therapy sessions. 74 participants (32%) either withdrew from therapy (47) or were discharged having repeatedly not attended appointments (27); patients in both categories were followed up by the research team unless they withdrew from the study. The number withdrawing increased to 70 when we included participants who reached an agreed end in fewer than 12 sessions. By 6 months, individuals randomised to the intervention had received a median of 11 sessions of CBT (IQR 5—13) and 62% (144) had received at least nine sessions. By 12 months, median number of sessions was 12 (6—17) and 141 participants had received at least 12 sessions.

Individuals in the intervention group had threefold increased odds of response at 6 months compared with those in the usual care group (table 2). Adjustment for imbalances at baseline had little effect, and adjustment for actual time to follow-up did not affect the findings (data not shown). The difference in proportions responding equated to a number needed to treat of four (95% CI three to six) for each additional responding patient.

The beneficial effect of the intervention was confirmed for the secondary outcomes at 6 months (table 2). Participants in the intervention group had a BDI score that was, on average, 5·7 points lower (less depressed) than those in the usual care group, which equated to an effect size of 0·53, using baseline SD for BDI (pooled). Compared with participants assigned usual care, individuals in the intervention group were also more likely to experience remission (BDI score <10) at 6 months (number needed to treat eight, 95% CI five to 20), to have fewer symptoms of anxiety (according to Generalised Anxiety Disorder Assessment 7) and panic at 6 months, and had greater improvements in the SF12 mental health subscale (table 2). Compared with the usual care group, we identified weak evidence that participants in the intervention group fared worse on the SF12 physical subscale, but the difference was not significant (table 2). Adjustment for baseline imbalances did not affect any of these findings (data not shown).

We noted little evidence of clustering of outcomes by therapist (intra-cluster correlation coefficient for continuous BDI score, after adjustment for baseline imbalances, 0·0027). In a fully heteroscedastic model that accounted for clustering by therapist, the results obtained for the primary response outcome were identical to those obtained from the primary intention-to-treat analysis (data not shown). The results imputing missing data were consistent with the findings of the primary complete-case analysis (table 3). For apriori subgroup analyses, we identified no evidence that patient expectation of outcome (p for interaction=0·16) or degree of treatment resistance (p for interaction=0·88) had any effect on the difference between intervention and usual care groups. In a post-hoc subgroup analysis, we noted no evidence that study centre had any effect on the difference between the intervention and usual care groups (p for interaction between treatment allocation and centre=0·61).

In repeated measures analyses with data from 6 and 12 months, individuals in the intervention group had about threefold increased odds of response and remission over 12 months (table 4). We identified little evidence that the effect of the intervention varied over time (p value for interactions >0·10), with the exception of the outcomes on the Patient Health Questionnaire 9 (p=0·059) and SF12 physical subscale (p=0·047), for which we identified weak evidence for an interaction.

Compared with the intention-to-treat models in table 2, the estimates of treatment efficacy obtained from CACE analyses showed that the effect of the intervention was larger among individuals who were on track at 6 months to complete the intervention, and likewise among those who received at least 12 sessions by 12 months. At 6 months the CACE estimate for the continuous BDI outcome was −8·2 (95% CI −11·4 to −5·0, effect size 0·77, p<0·001), and at 12 months −7·1 (—10·4 to −3·8, 0.66, p<0·001). We recorded larger effects for the CACE analyses for the binary outcomes using probit regression compared with findings of intention-to-treat analyses using similar models (data not shown).

Of 388 participants with data at 6 and 12 months, 66 participants (17%) had at least one session of counselling or talking therapy outside the trial during the 12 months (41 [21%] of 195 given usual care; 25 [13%] of 193 given intervention). Only five participants (three usual care; two intervention) had received at least 12 sessions of CBT outside the trial by 12 months. Estimates of treatment efficacy accounting for contamination by the receipt of such CBT were identical to the primary analyses (data not shown).

At 6 months, 93% of both groups (194 of 209 given intervention; 199 of 213 given usual care) were taking antidepressant medication (difference −0·6%, 95% CI −5·4 to 4·2). At 12 months, 88% (174 of 198) of those in the intervention group were taking antidepressants compared with 92% (183 of 198) of those randomised to usual care (—4·5%, −10·4 to 1·3). Of the 354 participants with self-report data for type and dose of antidepressant medication taken at 12 months, 154 (44%) reported taking a different type or dose of medication from that at baseline (76 [44%] of 172 in intervention group; 78 [43%] of 182 in usual care group). Of individuals taking antidepressants at 6 months, 92% (178 of 193) of the intervention group and 88% (174 of 198) of those in usual care had adhered to their medication during the previous 6 weeks. Adherence during the past 6 weeks at 12 months was 93% for both groups (160 of 173 in intervention group; 168 of 180 in usual care group).

Discussion

CBT as an adjunct to usual care that included pharmacotherapy was effective in reducing depressive symptoms and improving quality of life in primary care patients with treatment-resistant depression. The beneficial effect of the intervention was also identified for the more stringent criteria of remission and improvements were maintained over 12 months.

No one definition of treatment-resistant depression is accepted, hence we used an inclusive and pragmatic definition that would be generalisable to primary care.35 Participants had not responded to at least 6 weeks of treatment with an antidepressant; however, this was a heterogeneous group with many individuals reporting severe and chronic depression often associated with psychological or physical comorbidities, or both. Hence, we believe that the results can be generalised to a wide range of patients who have not responded to antidepressants.

As far as we are aware, before this study, no evidence was available from large-scale randomised controlled trials of the effectiveness of CBT as an adjunct to pharmacotherapy as a next-step treatment option for primary care patients who had not responded to antidepressants.6, 7 Other trials (including our pilot36) were small (n<50, panel).37, 38 In the STAR*D study,8 which assessed several alternative treatment strategies after nonresponse to antidepressant medication, only 26% of participants were willing to be randomised to CBT as a second-step option and individuals who could not tolerate citalopram were included, making extrapolation difficult because clinically such individuals would usually be managed by a change of antidepressant. Like CoBalT, many participants in the CBT augmentation group of STAR*D (n=65) had a history of depression (86%), with an average of seven previous episodes.8 35% of STAR*D participants whose medication was augmented by CBT fulfilled criteria for response on the basis of self-rated depressive symptoms, slightly lower than our findings with the BDI (46%), although occurrence of remission was much the same. However, STAR*D8 and other studies37, 38 answered a different question than that posed in CoBalT. They provide evidence for alternative treatment approaches to the management of individuals who do not respond to antidepressants, rather than examining the effectiveness of augmenting antidepressant medication with CBT as a next-step option.

The effects we recorded are much the same as the findings of an earlier randomised controlled trial9 of combined psychological (CBASP) and pharmacological treatment (with nefazodone, now withdrawn) for chronic depression. However, results of the REVAMP trial10 of a population with chronic depression who had not responded to antidepressant medication showed no difference in response after 12 weeks between those who received combined treatment compared with medication alone. In REVAMP, participants attended fewer sessions of CBASP than for the earlier chronic depression trial9 (mean 12·5 vs 16), which might partly explain the differing findings. CBASP and the more traditional CBT delivered in CoBalT differ in terms of emphasis. The CBT approach developed by Aaron T Beck21 and adapted by Moore and Garland13 that therapists used in CoBalT emphasises the cognitive elements of treatment and is effective in people with residual depression.12

In the REVAMP trial, investigators used a treatment algorithm and pharmacotherapy changed to the next-step after randomisation. However, use of a medication algorithm is not a pragmatic approach towards pharmacotherapy. Occurrence of remission among participants receiving pharmacotherapy alone in REVAMP (39·5% of 76 at 12 weeks) was higher than for CoBalT (15% for the usual care group at 6 months), but this finding might relate to differences in the patients recruited; only 33% of REVAMP participants had previously had an adequate trial of pharmacotherapy, whereas 80% of CoBalT participants had previously been prescribed antidepressants and most (70%) had been on their present medication for more than 12 months.

This was a large study with high follow-up at 6 and 12 months. We identified no evidence that missing data had biased findings. Though some baseline characteristics were imbalanced between groups, adjustment for these differences tended to increase the size of the treatment effect for the primary outcome. Only a few participants received CBT outside the trial so such contamination had little effect on the findings.

We did not compare CBT with an attention control because we wanted to ask a pragmatic question about the value of addition of CBT to antidepressants in this population. This decision meant we could not mask patients or researchers to treatment allocation but we avoided observer bias by using self-report questionnaires to measure outcome.

Our primary outcome was depressive symptoms on the BDIII. This instrument was also used by the therapists within CBT sessions; hence, for participants in the intervention group, the responses on this specific measure might have been affected by the process of therapy. However, results were consistent for the other mental health outcomes (that were not used in therapy), including for Patient Health Questionnaire 9, which is part of the core outcome dataset within UK psychological services.28

An independent assessment confirmed that the therapy was delivered at a competent23 standard. The therapists were broadly representative of those working in NHS psychological services with a range of experience and backgrounds, and the results should therefore be generalisable. We identified no evidence of any clustering of outcomes by therapist.

We relied on a self-report measure of adherence to medication15 that had been validated against electronic monitoring bottles16 to define our population with treatment-resistant depression. Although some of the people recruited might not have adhered to their medication (false positives), most had, at baseline, been on their present antidepressant for more than 12 months, which is likely to minimise the effect of occasional non-adherence.

A substantial proportion of people do not respond to antidepressants and our results have provided robust evidence that CBT given as an adjunct to usual care that includes antidepressant medication is an effective treatment in reducing depressive symptoms and improving quality of life in this population. The size of the treatment response was substantial and of clinical importance and was maintained at the 12 month follow-up after the CBT treatment had ended. In view of the chronic relapsing nature of depression, examination of the long-term outcome of this intervention will be important.

Though we did not test different approaches towards delivery of CBT, we think that the complex mental health needs of this population require therapists who are able to tailor the treatment approach to the individual and formulate conditional beliefs that, according to cognitive theory, 21 underpin the longer term risk of depression. This kind of therapy would be delivered by so-called high-intensity services in England28 and requires both training and regular supervision.

In many countries, access to psychological treatment is limited to people who can afford to pay, or those with health insurance, for whom, cost sharing through copayment is common. Increasing the availability of CBT is more difficult than provision of an intervention such as pharmacotherapy. England28 and Australia have introduced initiatives to increase access to psychological therapies. England's Improving Access to Psychological Therapies scheme, for example, has provided training and set minimum standards of competencies and supervision to provide a

consistent standard of care. Worldwide, such initiatives are rare and more investment is needed. In the USA, less than a quarter of people with depression have seen a psychologist or counsellor in the previous 12 months,39 and half receive less than the recommended number of therapy sessions.40 Even people who attend therapy often receive an “eclectic mix of psychotherapy techniques”41 rather than CBT. Only through greater investment in psychological services that deliver evidence-based therapies will it be possible to reduce the great burden to patients, healthcare systems, and society that is associated with nonresponse to the most common first-line treatment for depression in primary care.

BACK TO TOP

The relationship between Hippocampal asymmetry and working memory processing in combat-related PTSD -- a monozygotic twin study

Biology of Mood & Anxiety Disorders
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Abstract

Background

PTSD is associated with reduction in hippocampal volume and abnormalities in hippocampal function. Hippocampal asymmetry has received less attention, but potentially could indicate lateralised differences in vulnerability to trauma. The P300 event-related potential component reflects the immediate processing of significant environmental stimuli and has generators in several brain regions including the hippocampus. P300 amplitude is generally reduced in people with PTSD.

Methods

Our study examined hippocampal volume asymmetry and the relationship between hippocampal asymmetry and P300 amplitude in male monozygotic twins discordant for Vietnam combat exposure. Lateralised hippocampal volume and P300 data were obtained from 70 male participants, of whom 12 had PTSD. We were able to compare (1) combat veterans with current PTSD; (2) their non-combat-exposed co-twins; (3) combat veterans without current PTSD and (4) their non-combat-exposed co-twins.

Results

There were no significant differences between groups in hippocampal asymmetry. There were no group differences in performance of an auditory oddball target detection task or in P300 amplitude. There was a significant positive correlation between P300 amplitude and the magnitude of hippocampal asymmetry in participants with PTSD.

Conclusions

These findings suggest that greater hippocampal asymmetry in PTSD is associated with a need to allocate more attentional resources when processing significant environmental stimuli.

Background

Post Traumatic Stress Disorder (PTSD) is characterised by recurrent and intrusive memories, avoidance, and hyperarousal. PTSD is also associated with impairment in attention, and some studies have shown deficits in learning and memory [1] It has been suggested that disturbed processing of new environmental information in PTSD is due to continuous background re-processing of traumatic events, resulting in modifications of neural circuits [2,3]. The resources required to maintain these autonomous loops may therefore not be available for general attention and memory function. The capacity of working memory has been shown to be directly related to the severity of intrusive memories [4], providing empirical support for this theory.

The hippocampus (HC), located within the ventral medial temporal lobe, is central to the encoding and reconstruction of episodic memories [5]. the hippocampus is part of a large extended network involving the learning of material available within working memory. Plasticity in the physical connections between the HC and the neocortex is crucial for integrating multi-modal sensory information and modifying memory dynamics over time [6]. In addition the HC has a significant role in executive processing systems [7,8]. The HC also contributes to regulation of the hypothalamic-pituitary-adrenocortical system, which is crucial in both acute and chronic responses to stress [9].

The hippocampus, located within the ventral medial temporal lobe, has long been known to be central to explicit long-term recognition memory. Olsen et al. (2012) [10], reviewed recent research showing that the hippocampus is also involved in short-delay recognition and perception. Olsen et al. (2012) [10] concluded that the hippocampus rapidly and continuously forms associations between disparate environmental inputs, including comparing current perceptual input with internal representations. The hippocampus is therefore part of a large extended network involving the recognition and learning of material available within working memory. This network incorporates multiple brain regions, including the prefrontal cortex. Failure in a significant part of this extended network will compromise the functioning of the network as a whole. The hippocampus also contributes to regulation of the hypothalamic-pituitary-adrenocortical system, which is crucial in both acute and chronic responses to stress [9].

Psychological trauma has been found to have damaging effects on the HC [11-14], and animal studies have shown that stress induces changes in hippocampal morphology and function [15,16]. In normal subjects the volume of the right hippocampus is larger than the left hippocampus [17,18]. Numerous studies have shown that hippocampal volume (HCV) is smaller in people with PTSD compared to controls [19-21]. A recent meta-analysis of 39 studies reporting hippocampal volume in PTSD [22] found that people with PTSD and trauma-exposed people without PTSD had smaller left, right and total hippocampal volumes than people never exposed to trauma. This suggests that trauma has an impact on the

hippocampus bilaterally. In addition, people with PTSD had smaller volumes of the right, but not the left, hippocampus compared to people who had been exposed to trauma but did not have PTSD. The reduction in right hippocampal volume in PTSD reported by Woon et al. is consistent with an MRI study showing reduced neuronal density in the right medial temporal cortex in people with PTSD, compared to trauma-exposed people without PTSD [23]. These findings suggest that the right hippocampus is differentially reduced in volume in people who develop PTSD.

Disruption of the normal pattern of hippocampal asymmetry has been found in people with schizophrenia [24,25] and in young people meeting criteria for an at-risk mental state for psychosis [26]. Studies in mild cognitive impairment and dementia suggest that there may be changes in hippocampal asymmetry as memory deteriorates [27]. Taken together, these findings demonstrate that abnormal hippocampal asymmetry is found in people subject to pathological processes that affect brain function and manifest as disorders affecting mental state and cognitive function.

Our participants consisted of male Vietnam combat veterans with and without PTSD, and their non-combat exposed monozygotic twins. The contributions of familial vulnerability and trauma exposure to biological abnormalities in this study population have been investigated by Pitman and colleagues [28]. Gilbertson et al. [29] demonstrated that total hippocampal volumes were about 10% smaller in men with severe PTSD, compared to men who did not have PTSD. Consistent with this finding, there was a significant correlation between total hippocampal volume and PTSD symptom severity in the PTSD group. However, these investigators also found that there was no difference in hippocampal volume between participants with severe PTSD, and their combat-unexposed identical twins, suggesting that smaller hippocampal volume might be a biological risk factor, rather than a consequence of trauma exposure and the pathophysiological processes associated with PTSD.

In the present study, we investigated the relationship between hippocampal asymmetry and the capacity to process information about the immediate environment in a sample of identical twins discordant for Vietnam combat exposure. We utilised the amplitude of the event related potential (ERP) P300 component as a measure of the controlled allocation of attentional resources to an anticipated stimulus. The P300 reflects processing of information about a significant stimulus, including context updating, context disclosure, event-categorisation and memory updating [30,31]. The P300 is most commonly elicited by asking participants to identify target tones in an auditory oddball task. The P300 has generators in a number of brain regions, including the temporo-parietal cortex, the cingulate cortex, the thalamus and the inferior and middle frontal cortex [32]. There are two separate generators in the hippocampus, located in the anterior subiculum and the posterior hippocampal body.

Numerous studies [34-39] including a meta-analysis by Karl et al. [40] have indicated that the amplitude of the P300 at midline electrodes in relation to trauma-neutral target tones is generally reduced in patients with PTSD. In a study involving the same monozygotic twin population as the present study, Metzger et al. [41] found smaller P300 amplitude in non-medicated, non-smoking twins with PTSD, compared to their combat-unexposed co-twins. In the full sample, there was no difference in reaction time or P300 amplitude between any of the groups (combat veterans with and without PTSD, and their combat-unexposed co-twins respectively). A recent study [42] found that P300 current source density was significantly reduced in people with PTSD in the inferior frontal gyrus, insula, and anterior cingulate.

The aim of the present study was to investigate the relationship between P300 amplitude and hippocampal asymmetry in the twin sample described above. As noted above, it has been established that hippocampal volume has a role in predisposing to PTSD, and there may be further changes related to both trauma exposure and to the development of PTSD. The amplitude of the P300 to trauma-neutral stimuli is generally

reduced in PTSD, indicating that the information processing abnormalities characteristic of PTSD are reflected in changes in the P300. In addition, hippocampal generators contribute to P300 amplitude.

Given that both reduced P300 amplitude and greater hippocampal asymmetry (with relatively great volume reduction of the right hippocampus) are likely to reflect pathological changes related to PTSD, we hypothesised that there would be a negative correlation between P300 amplitude to trauma-neutral target tones and the magnitude of hippocampal asymmetry in people with combat-related PTSD (such that smaller P300 amplitude would be found in participants with greater hippocampal asymmetry).

Methods

Participants

Participant recruitment, informed consent, and data collection procedures have been described in previous publications [29,43]. Participants completed the 18-item Combat Severity Scale [44], employed in Vietnam Era Twin Registry research and previously validated against combat related medals, which yielded a measure of the severity of their combat exposure; and the Mississippi Scale for Combat-Related PTSD [45], a 35-item instrument for quantifying PTSD and related symptoms. The presence of PTSD in participants was determined by The Clinician-Administered PTSD Scale (CAPS): Current and Lifetime Diagnosis Version [46,47]. All subjects with PTSD included in this study had CAPS scores greater than 65 indicating severe PTSD. In addition, a Structured Clinical Interview for DSM-IV [48] was used to screen for the presence of Axis 1 mental disorders.

Sixty-four male subjects, comprising 32 monozygotic twin pairs where one twin had experienced combat in Vietnam while the other had not, participated in the present study. The mean age of the twin pairs in which the combat-exposed member had PTSD was 53.1 years (SD = 3.3) and the mean age of twin pairs in which the combat-exposed member did not have PTSD was 51.8 years (SD = 2.3) ($F(1,76) = 3.8$, $p = .050$). The mean years of education was 13.5 (SD = 2.6) for combat-exposed subjects with PTSD, 14.3 (SD = 2.8) for their non-combat exposed co-twins, 14.7 (SD = 2.4) for combat-exposed subjects without PTSD, and 14.7 (SD = 2.6) for their non-combat exposed co-twins (NS). Combat-exposed subjects with PTSD had higher combat severity scores (Mean = 7.9, SD = 1.9) than combat-exposed subjects without PTSD (Mean = 3.5, SD = 2.6) and this difference was significant ($F(1,76) = 67.4$, $p < .001$). The participants have been described in more detail by Gilbertson et al. [29].

Oddball paradigm

Participants were seated upright in a sound-attenuated room. E-A-RTONE (Aearo Company, Santa Barbara, California, USA) earphones were used to present tones binaurally. A five dB descending and ascending staircase method was used to gauge the hearing threshold for a 1,000 Hz test-tone in each participant. All participants completed an auditory target detection task involving 285 tone-stimulus presentations. Three distinctly pitched tones were used: a target (2,000 Hz), a common (1,000 Hz) and infrequent distractor (500 Hz). The entire sequence included 40 target, 40 distracter and 205 common tones with a random inter-stimulus interval varying between 1,950 and 2,050 ms. The task was to identify the high pitched tones as quickly and accurately as possible, by pressing a button with the dominant hand. The presentation sequence was pseudo-

randomised to prevent the consecutive occurrence of two infrequent tones. Tones were generated by STIM software (Neuro Scan Inc, Herndon, Virginia, USA) and tone amplitude was verified using an Abbeon AB-85 sound meter (Abbeon, Indianapolis, Indiana, USA).

EEG measurement

EEG activity was recorded from parietal sites (Pz, P3, and P4) [49], using tin electrodes embedded in a nylon cap (Electro-Cap International, Eaton, UK). EEG was grounded from the forehead and referenced to linked ear lobes. Electrooculogram (EOG) activity was recorded at the outer canthus and infraorbitally to the left eye. Trials with excessive eye-movement artefact (EOG range ±85 μV) were excluded from the averaging process.

EEG impedances were approximately equal and kept below 5 k Ohms. Signals were amplified using Coulbourn High Gain Bioamplifiers (Coulbourn, Allentown, Pennsylvania, USA), band-pass filtered (0.1-150 Hz) and digitally sampled at 1,000 Hz, with a resultant signal sensitivity of .049 μV/bit. The EEG epoch extended from 100 ms pre-stimulus to 900 ms post-stimulus, and was averaged at each site according to stimulus type. It was digitally bandpass filtered between .1 and 14 Hz (12 dB/Oct). Peak measures for P300 were determined from each subject's averaged waveforms for each stimulus type, using a Neuro

Scan interactive scoring program. P300 was defined as the most positive peak between 300– 500 ms post-stimulus onset.

MRI

A 1.5 Tesla MRI scanner (General Electric Signa System, Milwaukee, Wisconsin, USA) was used to perform a whole-brain scan. Automated step algorithms were used to calculate whole brain volume. Subsequently, hippocampal volume was determined by a person blind to the individual's group characteristics, using a manual tracing procedure [50]. Although hippocampal volume was the focus of the present study, left and right amygdala volumes, and total brain volume, were also measured to provide control data [29]. The reliability of the volume measures was confirmed by a second 'blind' rater as previously described [29].

Statistical analysis

Participants were classified into four groups designated by PTSD diagnosis and combat exposure: (1) combat veterans with current PTSD and (2) their non-combat-exposed co-twins; (3) combat veterans without current PTSD and (4) their non-combat-exposed co-twins. An absolute magnitude HCV asymmetry (HCVA) measure was created for each participant according to the formula: | (right HCV – left HCV)/(right HCV + left HCV) |.

Hippocampal volumes and P300 amplitudes at all electrode sites were screened for outliers more than three standard deviations from the mean. Square root or logarithmic transformations were used as required to correct violations of homogeneity and the Greenhouse-Geisser epsilon correction was used for violations of sphericity. A one-way Analysis of Variance (ANOVA) was used to compare accuracy of target detection between groups, and a repeated measure ANOVA was used to compare P3 amplitude across the three electrodes.

One-way ANOVA was used to compare the total hippocampal volume, and the volumes of the left and right hippocampus, between the four groups. A one-way ANOVA was also performed to compare the asymmetry measures across groups. As EEG scalp potentials are not independent, a principal components analysis was performed across the P300 amplitude data to quantify the number of independent dimensions accounting for 95% of the data variance. A Pearson product–moment correlation coefficient was used to investigate the relationship between the magnitude of asymmetry and P300 amplitude at the three parietal sites (Pz, P3 and P4) in all four diagnosis and exposure groups separately. Finally, separate correlations were performed to evaluate whether significant correlations could be accounted for either 'right side greater than left' (R > L) or 'left side greater than right' (L > R) hippocampal volume changes. The Pearson product–moment correlation coefficient was also used to investigate the relationships between HC volume and HC asymmetry, total CAPS scores, and scores on individual CAPS dimensions.

Results

HC asymmetry

Hippocampal volumes are presented in Table 1. There was a significant main effect for diagnosis for right hippocampal volume ($F(1,66) = 9.63$, $p = .003$) and total hippocampal volume ($F(1,66) = 8.73$, $p = .004$). The mean volume of the left hippocampus was also smaller in the PTSD group but this difference did not reach significance ($F(1,66) = 3.35$, $p = .070$). We found that seven subjects with PTSD had a reversal of normal asymmetry with a larger left than right hippocampus, and five had a normal asymmetry with a larger right hippocampus. However, when one-way ANOVAs were performed to investigate between group differences in absolute asymmetry, no significant differences were found between any of the four diagnosis/exposure groups. There was no significant difference between groups in the volumes of the left or right amygdala or in total brain volume.

Correlations between HC asymmetry and P300 amplitude

There was no significant difference between the four groups in performance of the target detection task or in P3 amplitude. A principal components analysis of the P300 data across the three electrodes demonstrated that two components accounted for >97% of the total variance, so a Bonferroni corrected p value of ≤ .025 was taken as significant.

We found positive correlations between hippocampal volume asymmetry and P300 amplitude in participants with PTSD at sites Pz ($r = .69$, $n = 12$, $p \leq .025$) and P3 ($r = .64$, $n = 12$, $p \leq .025$), with higher magnitudes of hippocampal volume asymmetry associated with larger P300 values (Table 2). Neither of the two non-combat exposed co-twin groups, nor the non-PTSD combat-exposed group demonstrated significant correlations between these two variables. The inclusion or exclusion of outliers did not significantly affect the results.

Comparing those with normal HC asymmetry and those with abnormal HC asymmetry, there was no significant difference in P300 amplitude at any electrode, and no group difference in asymmetry of amplitude at the individual electrodes.

HC asymmetry and symptom measures

In the PTSD group, there was no difference in CAPS scores between those with normal vs abnormal HC asymmetry. There was a negative correlation between total HC volume and re-experiencing symptoms ((r = −.56, n = 13, p ≤ .043), and between left HC volume and re-experiencing symptoms ((r = −.71, n = 13, p ≤ .006).

Discussion

Based on the results of their meta-analysis, Woon et al. [22] conclude that there may be a differential sensitivity to the effects of trauma, with the right hippocampus being more vulnerable than the left hippocampus. It should be noted however that the subjects from the present study were included in this meta-analysis, contributing about 3% of the PTSD subjects and 11% of the non-PTSD subjects. Our findings were consistent with the findings of this meta-analysis in that the PTSD group had a reversal of normal asymmetry; on average the left hippocampus was slightly larger than the right hippocampus. However their co-twins, and the trauma-unexposed subjects, similarly had slightly larger mean left than right hippocampal volumes. These differences were small and none of these comparisons reached significance. Our results do not support previous findings that the right HC is more sensitive to the effects of trauma than the left HC [22]. In our data, the mean volume of the right HC in trauma-exposed co-twins, both with and without PTSD, was larger than the mean right HC volume of the non-trauma exposed co-twins.

Our results did not support the hypothesis that there would be a negative correlation between P300 amplitude and hippocampal asymmetry. We expected that greater asymmetry, taken to indicate greater pathology, would correlate with a smaller allocation of attentional resources to the working memory task. Instead, we found that although there was no significant asymmetry difference between the four groups, there were significant positive correlations between hippocampal asymmetry and P300 amplitude to target tones in participants with PTSD, at midline (Pz) and left (P3) parietal sites.

The lack of correlation between hippocampal asymmetry and P300 amplitude in the monozygotic co-twins of the PTSD participants, and in the other two groups (including participants with combat exposure) suggests that the correlations are associated with PTSD itself, rather than being genetically determined or related to combat exposure. It has previously been suggested [51] that the presence of such correlations in subjects with psychiatric illness, but not in normal subjects, may reflect disease-associated pathology. This conclusion might be strengthened if there was a correlation between P300 amplitude or the magnitude of hippocampal asymmetry, and symptom severity. Bae et al. (2011) [42] have demonstrated associations between P300 current source density (CSD) in regions in the frontal, parietal and temporal cortices, and various PTSD symptoms including re-experiencing and increased arousal (positively correlated with P300 CSD) and avoidance and numbing (negatively correlated with P300 CSD). Investigation of the associations between hippocampal volume asymmetry, P300 amplitude, and symptom severity, was beyond the scope of the present study. However, further research is required looking at the links between brain structure, brain function, and measures of disease severity. In addition, we did not have information about handedness, although co-twins would be expected to be matched for handedness. The proportion of people with mixed or right hemisphere dominance in the general population is small so it is unlikely that the presence of such subjects would have affected the overall conclusions.

Whilst most ERP studies of subjects with PTSD have found P300 amplitude reduction, an increase in P300 amplitude to trauma-neutral stimuli has been reported in a population of nurses who developed PTSD following exposure to wounded combatants in Vietnam [52]. P300 amplitude has

been shown to be increased to trauma-relevant stimuli in people with PTSD, indicating an increase in allocation of attention resources towards elements in the environment that may be immediately threatening [43].

It is possible that the larger P300 in our subjects with greater hippocampal asymmetry might reflect a greater allocation of attention, in an effort to overcome difficulties performing the task. Amman et al. [53] report that in multiple sclerosis, a disease that is associated with neuropsychological impairment, patients showed stronger fMRI activation change in the right parahippocampal cortex and in the middle and medial frontal regions during the performance of simple tasks involving attention and working memory, compared to normal controls. There was a linear increase in activation with increasing task complexity, until the task load became excessive. Similarly, Fabiani and Friedman [54] found increased P300 amplitude was associated with poorer performance on the Wisconsin Card Sorting Test.

Our results might therefore indicate that the subjects with PTSD needed to give greater attention to the task in order to achieve normal results. Both auditory and visual stimulus processing in working memory are associated with hippocampal activation [55], and the hippocampus is involved in the processing mechanisms that determine attentional allocation and P300 amplitude [56]. A large asymmetry of hippocampal structures may necessitate a change in the neurophysiology of non-traumatic stimulus encoding, reflected in the enlarged P300 components.

Working memory capability has been shown to be decreased in those individuals who experience intrusive memories, indicating that a proportion of finite working memory resources is required during re-experiencing of traumatic memories, leaving fewer resources available for updating online content [57]. Nadel et al. [5] have shown that the hippocampus is intimately related to the processing and retrieval of spatial and episodic memories, long after they have been established, supporting the role of the hippocampus in the re-experiencing of intrusive memories. Our PTSD subjects may therefore have less capacity to process non-trauma related stimuli, because of the ongoing processing of intrusive trauma-related material. As noted above, this could result in a greater allocation of effort, to overcome these difficulties. Our results are consistent with the proposition that the increased allocation of attention was maximal in those with greatest hippocampal pathology, reflected in greater hippocampal asymmetry. In PTSD, the availability of hippocampal neurons required for encoding the stimuli in the oddball task may act as a rate-limiting step in non-trauma related information processing. In addition, the correlation between smaller HC volume and re-experiencing symptoms could suggest that HC damage is associated with an inability to process and eventually recover from traumatic memories.

Whilst this study focused on hippocampal pathology, following on from previous research demonstrating hippocampal abnormalities associated both with trauma, and with PTSD, there is also evidence of volume reductions in other brain regions in PTSD. Araki et al. (2004) [58] investigated the relationship between lower P300 amplitude and anterior cingulate grey matter volume in people who developed PTSD as a result of the Tokyo subway sarin attack. The numbers were quite small (8 subjects with PTSD and 13 subjects without PTSD who had been exposed to the sarin attack). There was a trend-level correlation ($p = 0.077$) between P300 amplitude at Pz and left anterior cingulate grey matter volume. Further research into brain structure and function in PTSD should therefore extend to other brain regions beyond the hippocampus.

Conclusions

In conclusion, the hippocampus is clearly sensitive to the effects of trauma, with changes in both structure and function. Further, smaller hippocampal volume appears to be associated with vulnerability to developing PTSD when the person is exposed to trauma. Hippocampal volumes and hippocampal asymmetry have therefore been taken as reflecting both genetically determined vulnerability and trauma-related damage to the hippocampus. Our monozygotic twin sample enables us to control for genetic factors, so hippocampal volume differences are therefore related to trauma exposure, in some cases with the addition of the pathological processes associated with PTSD. The oddball P300 event related potential reflects the allocation of attentional resources during working memory processing, and hippocampal structures make a substantial contribution to P300 amplitude. Previous research has shown that the P300 is sensitive to the effects of PTSD [38]. Our results show that, in people with PTSD only, there is a positive correlation between hippocampal asymmetry and allocation of attentional resources. This could be because a proportion of finite processing capacity is being utilised by the constant re-experiencing of traumatic memories, leaving limited resources for non-trauma related cognitive tasks.

BACK TO TOP

Group Exposure Therapy Treatment for Post-Traumatic Stress Disorder in Female Veterans

Military Medicine
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ABSTRACT

Objectives: The purpose of this study was to examine the application of a group exposure therapy model, the content of which consisted solely of repeated imaginal exposure during sessions, in a clinical sample of female veterans with post-traumatic stress disorder (PTSD). Establishing group delivery of exposure therapy will expand options, increase efficiency, and introduce group curative factors. Methods: Eighty-eight female veterans with PTSD completed a six-session exposure group, three participants per group, as a component of a larger treatment program. The PTSD symptom checklist (PCL) was used as the outcome measure and administered in each session. Results: Pre/post-paired *t*-tests showed significant improvement in PTSD on the PCL, with 40% of completers showing at least a 10-point drop in the PCL scores. In addition, a repeated measures analysis of variance showed a significant main effect and a significant quadratic equation, with expected initial increases in the PCL followed by a decrease below baseline at session 6. Conclusions: The group exposure treatment protocol showed positive outcomes on PTSD symptoms in a real-world clinical sample of female veterans. The implications include an expansion of exposure treatment choices for veterans with PTSD and increased options for therapists.

INTRODUCTION

Exposure therapy, a treatment for post-traumatic stress disorder (PTSD), has consistently proven to be efficacious and effective in reducing PTSD symptoms and is one of the two therapies recommended as the first line of treatment by VA/DoD guidelines. Early research examining the utility of exposure therapy addressed PTSD among civilian rape victims and male combat veterans. Recently, effectiveness was established for exposure therapy over present-centered therapy in reducing PTSD symptoms in a sample of female veterans. The most developed model for the delivery of exposure therapy is prolonged exposure (PE), which consists primarily of in-session, repeated imaginal exposures to a traumatic memory and out-of-session in vivo exposures to avoided situations. Minor elements of PE are education about PTSD symptoms, rationale for treatment, and breathing retraining.

The PE model and the majority of exposure therapy clinical trials have examined exposure therapy delivered in an individual format—one therapist to one patient—for 10 to 12 sessions, with imaginal exposure conducted in 8 to 10 of these sessions. Although historically most veterans administration (VA) outpatient PTSD programs have offered therapies in a group format, research on group delivery of treatments for PTSD is sparse and methodologically weaker than the individual trials, with no differential effects found between treatment interventions and minimal examination of exposure therapy in a group format.

The primary challenge of providing exposure therapy in a group format comparable to the robust individual PE model is logistic. In a typical 8-member, 90-minute group, in-session imaginal exposures cannot be conducted for each member in every session. Two studies included two in-session imaginal exposures per participant among other treatments in a group format and found PTSD improvement after 30 to 36 sessions. The two in-session imaginal exposures were supplemented by daily listening to audio recordings of the trauma narrative between sessions to achieve desensitization. Problematic with this approach is controlling for dosage of exposure, as homework compliance is variable and expected to be high in early sessions. Another methodological limitation was determining the contribution of exposure compared to other treatments (cognitive, relapse prevention, relaxation training). The other therapies likely contributed to PTSD improvement, serving to confound conclusions on the effects of the exposure treatment. Despite these limitations, these two studies provided the necessary first steps in establishing the prospect of examining group exposure therapy as an expansion to the existing individual model.

The primary aim of this study is to examine the effects of group exposure therapy on PTSD with imaginal exposure separated from other interventions, with the expectation of improvement in PTSD. The model for the exposure intervention was developed as part of a larger protocol for PTSD treatment by the first author and is described in detail elsewhere. A second aim of the study is to describe the course of PTSD symptoms across sessions. It is expected that PTSD symptoms will increase slightly before decreasing at the termination of therapy. Ultimately, our goal is to expand options for exposure therapy utilization.

METHODS

Participants

The sample consisted of 88 female veterans with current and/or lifetime PTSD, treated in 33 groups in a southwest VA outpatient women's PTSD clinic between 1995 and 2011. Participants diagnosed with a comorbid psychotic disorder were excluded from the exposure group. Individuals with other acute comorbid psychiatric disorders (e.g., substance use disorder and depression) were stabilized before treatment.

Measures

The assessment consisted of a semistructured interview and interview administration of the clinician administered PTSD Scale (CAPS). The CAPS is a structured interview administered by a trained clinician to assess for PTSD and is considered the gold standard in diagnosing PTSD. Each of the 17 symptoms are assessed for frequency and intensity in the past month and lifetime. The CAPS has shown internal consistency for the three-symptom categories of PTSD—reexperiencing, avoidance/numbing, and hyperarousal—with alpha coefficients that have ranged from 0.73 to 0.85; convergent validity has been found between the CAPS and other measures of PTSD. Internal consistency using Cronbach's α was computed on the 17 CAPS symptom scores in the clinic sample and revealed an overall $\alpha = 0.85$ with item correlations >0.40 for all items (symptoms) except symptom 8 (psychogenic amnesia), which had a correlation of 0.12. The PTSD symptom checklist (PCL) was administered at each of the six-exposure treatment sessions to document changes in PTSD symptoms during treatment. The PCL is a 17-item, five-point Likert scale with each PTSD symptom anchored from 1 (not at all) to 5 (extremely). The PCL is frequently used in clinical settings and has a high correlation (0.93) with the CAPS, high internal consistency (Chronbach's $\alpha = 0.94$), with a sensitivity of 0.78, specificity of 0.86, and diagnostic efficiency of 0.83.

Procedure

Female veterans diagnosed with PTSD were offered a variety of group treatments developed by the first author including an unstructured psychoeducation group, followed by four possible structured, topic-specific groups, including cognitive restructuring, behavioral interventions (assertiveness and relaxation training, nightmare therapy), sexual functioning, and exposure therapy, the latter of which is presented in this article. Selection of groups was optional, most attended exposure after other treatments, and most with the same cohort. Some individuals subthreshold for PTSD elected to attend the exposure group.

The exposure therapy group consisted of 6 weekly sessions of 90-minutes each focusing exclusively on repeated imaginal exposure. Three members participated in each group with two therapists. The PCL was administered at the beginning of each session. The structure of the exposure group consisted of a combination/modification of exposure techniques by Keane et al, Foa et al, and Resick and Schnicke. The first session included an orientation to the group, rationale for exposure treatment, selection of an index trauma, and direction to write a detailed trauma description for the following session. In-session imaginal exposure was conducted in sessions 2 through 5, and was structured such that each participant first read aloud their trauma narrative, was guided through an imaginal exposure of the trauma memory, and then processed the experience. Approximately 30 of the 90 minutes were spent with each participant on imaginal exposure for a total of four in-session imaginal exposures. Participants were instructed to write and rewrite the trauma narrative each week following sessions 1, 2, and 3 to allow for developing a complete narrative. Participants were asked to read the completed narrative daily between sessions 4 and 6, for 2 weeks. Measurement of homework compliance was not conducted; however, participants were strongly encouraged to write the trauma narrative each week and were

required to verbally complete the imaginal exposure regardless of writing compliance. It was not unusual for participants to write sparse descriptions or not write at all in first exposure sessions, but compliance increased in subsequent sessions. Treatment was provided by licensed clinicians, including four staff psychologists, two social workers, and two clinical nurse specialists, all trained by the first author in the 6-session protocol. Psychology interns and postdoctoral fellows cofacilitated groups with a licensed clinician. Training consisted of didactics on theory and procedure followed by cofacilitation with the first author, before conducting the groups independently. Fidelity was not systematically checked; however, training tapes for the exposure groups developed by the first author were reviewed periodically by clinicians after the initial training. All data were collected through archival record review and approved by local VA and University of New Mexico Institutional Review Boards.

RESULTS

An intent-to-treat analysis was conducted with all 88 participants, imputing the last PCL value forward in a paired *t*-test and was found significant ($p < 0.03$). Eleven participants (12.5%) were defined noncompleters, as they attended less than 4 of the 6 sessions. The final completer sample consisted of 77 participants in 32 groups, with 59% ($n = 45$) attending all 6 sessions, 31% ($n = 24$) 5 sessions, and 10% ($n = 8$) 4 sessions. The characteristics of the 77 subjects reflected entry level PTSD scores on the CAPS similar to other clinical populations (current: mean (M) = 67.55; lifetime: $M = 104.50$; total: $M = 170.28$). Trauma characteristics of the sample were sexual trauma alone (57%), combat and other nonsexual traumas (4%), and multiple traumas including sexual trauma (39%). Eighty-eight percent reported more than one trauma, with 18% childhood only (under age 18), 34% adult only, and 48% both childhood and adulthood trauma. Medical record review showed 73% diagnosed with a psychiatric diagnosis in addition to PTSD. The average age was 46.1 (SD = 9.4) and ethnicity reflected a primarily non-Hispanic white (65%) and Hispanic (23%) sample.

The 77 participants completing the treatment were compared to the 11 noncompleters (*t*-tests for continuous and χ^2-tests for discrete variables) on the entry level CAPS scores and baseline demographics (age at time of trauma, number of traumas, type of trauma, combat exposure, and comorbid psychiatric diagnoses), as well as the exposure group entry PCL scores. None of the comparisons revealed significant differences between the noncompleter and completer participants.

The examination of PTSD improvement with group exposure treatment was addressed through paired *t*-test analysis of the pre/post-total PCL scores. Paired *t*-tests were also computed on the three pre/post-PTSD symptom categories within the PCL—reexperiencing, avoidance/numbing, and hyperarousal. There was a significant decrease in the total PCL ($p < 0.01$, effect size = 0.26) and avoidance/numbing symptom category scores ($p < 0.001$, effect size = 0.40), suggesting the group exposure treatment was effective in lowering PTSD and avoidance/numbing PTSD symptoms in the sample.

Follow-up analyses examined PTSD improvement in three additional ways: (1) the percentage/number of subjects no longer meeting criteria for the disorder, defined as the PCL scores 50 or below, (2) the percentage/number improving by 10 PCL points, and (3) the percentage/number in complete remission, defined as the PCL scores decreasing 20 or more points. Twenty-two of the total 77 participants, with baseline PCL scores below 50 were removed, as they were not clinically significant on treatment entry. In the remaining sample of 55 participants, 22% ($n = 12$) no

longer met clinical significance for PTSD (PCL < 50), 40% (n = 22) dropped 10 or more PCL points, and 13% (n = 7) were in complete remission with PCL scores dropping 20 points or more at the completion of the group exposure therapy.

To address possible correlations (clustering) among individuals within groups and impact on outcome results, an analysis of variance (ANOVA) was conducted on CAPS and baseline PCL scores with group defined as the unit of analysis (n = 32; group mean scores) rather than the individual subject (n = 77). Significant differences were found between groups on both the PCL and CAPS scores ($p < 0.001$). A repeated measures analysis of covariance using baseline PCL scores as a covariate was computed to control for variability in PTSD between groups and the pre/post-PCL scores remained significant ($p < 0.01$), suggesting the correlation within groups did not alter the original significant outcome results.

The examination of the course of PTSD symptom change across sessions in the group exposure was conducted by a repeated measures ANOVA (RM-ANOVA) for the total PCL scores across the six sessions. The RM-ANOVA resulted in a significant session main effect ($p < 0.001$), suggesting differences between sessions across time. To determine the exact type of changes occurring in PTSD across the six sessions, the total PCL data were used in an RM-ANOVA to compute a quadratic regression by including linear and quadratic terms as factors. This analysis was significant ($p = 0.003$; predicted total PCL = 63.08 + 0.064 sessions − 1.18 [session–3]^2). As expected, the significant quadratic effect showed the total PCL scores increase (PTSD symptoms worsened) before decreasing (PTSD symptoms improved) to a value lower than baseline.

CONCLUSION

This study examined exposure therapy in a group format, in an applied setting, with a structure that excluded other interventions. Overall, PTSD symptoms decreased from pre- to post-therapy using this group exposure format, consistent with established findings of exposure treatment in an individual format. The findings were particularly notable, as (1) the clinical sample had multiple traumas highly comorbid with other psychiatric diagnoses, and (2) the sample received other therapies, including an evidence-based cognitive therapy, before the exposure group therapy. Also notable was the low noncompleter/dropout rate of 12.5%, much lower than the dropout rates in other studies (19–27%). The changes on the total PTSD symptom severity appear to be driven by decreases in avoidance and numbing symptoms, which can be explained by current theory and empirical work that indicates emotional and behavioral avoidance are particularly responsive to exposure interventions. Thus, the significant reduction in avoidance/numbing PTSD symptoms further testifies to the utility of group exposure therapy. Finally, increases followed by decreases in PTSD symptoms also replicate finding in the use of PE where some participants experienced a temporary increase in PTSD symptoms before improvement. The elevations in the PCL scores in sessions 2 through 4 in our study may appear exaggerated because of the weekly PCL administration, rather than bimonthly, as in typical PE protocols. Although slight increase in symptoms during initial exposure sessions is not surprising, given avoidance characterizes the disorder, most important is the significant decrease in PTSD symptoms at the completion of treatment. The significant parabolic curve lends information for further examination of the process of desensitization during exposure therapy.

The structure of the exposure group in this study improves on two key methodological issues of past studies by expanding the two in-session imaginal exposures to four and isolating the exposure component from other interventions. Repeated imaginal exposure to a trauma memory is necessary to attain desensitization effects and is less likely to occur with only two in-session imaginal exposures. In fact, a more recent study

showed a correlation between PTSD improvement and homework compliance in listening to recordings of the trauma. Although this group protocol only provided 4 in-session imaginal exposures—compared to 8 in the individual PE protocol—improvement was shown, charted across time, and addressed the logistic problems by limiting inclusion to three participants per group. The protocol more closely approaches the individual PE protocol than previous group studies investigating exposure therapy and assured an adequate dose of the therapy with imaginal exposure for every participant during sessions when imaginal exposure was conducted. This study also addressed the methodological issue of isolating the exposure component from other interventions to show PTSD improvements were attributable to the intervention. Importantly, the individual PE protocol does not require the use of other therapeutic interventions to provide resolution of the PTSD symptoms. Although participants in this study did receive other treatments before the exposure in group, it is the first to separate and show the effectiveness of the exposure piece. The next step in research is to develop and compare a 10-session group exposure protocol that parallels the individual 10-session protocol in a randomized controlled trial.

Clinically, the findings are promising for the application of exposure therapy in an additional venue—the group setting. Unlike the findings from the individual literature, most group therapy interventions for PTSD—support, cognitive-behavioral, psychodynamic—have all shown general improvement in symptoms, with no differential improvement by therapy type. Improvements in PTSD and other psychiatric symptoms in unstructured support/process-type groups could potentially be attributed to the curative group factors delineated by Yalom (instillation of hope, universality, imparting information, altruism, corrective emotional experience, and catharsis). These curative factors are likely the nonspecific effects that occur in a therapy group setting that contribute to improvement in psychological well-being. The expansion to a 10-session exposure group model can be compared to a present-centered therapy control group to control for nonspecific group factors to capture the additive value of exposure in a group, as Schnurr et al did with the individual PE model.

Although no qualitative assessment was conducted on participant and therapist perceptions of the group treatment approach, some observations are worth noting. The most common therapist concern was participants discussing details of traumas in the presence of other veterans. This concern was allayed, as the sharing of trauma details resulted in habituation with others' traumas and empathy between group members, which may have led to increased cohesion.

It is important to note the methodological limitations, which consist of lack of randomization, reliance on a single self-report outcome measure, and lack of follow-up data. Generalization is impacted and may be limited to individuals responsive to treatment (completers) and pretreatment, as has been shown in other studies. As participants for this article were a nonrandom convenience sample of women veterans in treatment for PTSD, no follow-up data were collected. The lack of randomization and absence of follow-up data is a limitation. The long-term effects and relative benefits of the group exposure therapy compared to individual or other treatments remain unclear and conclusions must be made with caution. Therefore, future research would benefit from the inclusion of a control group, as well as the use of structured interviews, such as the gold standard CAPS, for outcome analyses. It would be clinically useful to examine the lasting effects of the treatment results over time, perhaps the standard 3 to 6 months after treatment. Finally, although the results were significant, the decrease in PTSD was clinically small (5 points), likely attributable to previous treatment as evidenced by lower PTSD scores on entering into the exposure group (mean PCL = 58). A randomized controlled trial could control for prior treatment and more adequately reflect the contribution of a group intervention on changes in PTSD scores based on the CAPS. Given the limitations, the results must be considered preliminary and caution should be used in generalization of results.

This study provides encouraging results for the feasibility and effectiveness of exposure delivered in a group format. In turn, these results set the stage for larger-scale, future studies that improve on the methodology of the current work. This line of future research will ultimately lead to bridging the gap between treatment need and therapist supply by allowing the delivery of effective and efficacious treatments to higher numbers of patients experiencing PTSD symptoms.

BACK TO TOP

How Disorder-Specific are Depressive Attributions? A Comparison of Individuals with Depression, Post-Traumatic Stress Disorder and Healthy Controls

Cognitive Therapy and Research
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Abstract

Depressed individuals tend to assign internal, stable, and global causes to negative events. The present study investigated the specificity of this effect to depression and compared depressive attributional styles of individuals with major depression (MD), post-traumatic stress disorder (PTSD), and healthy controls. We indexed attributional style using the depressive attributions questionnaire in 164 participants. Additionally, we assessed appraisals characteristic of PTSD using the post-traumatic cognitions inventory (PTCI), depressive rumination, trauma history, and depression and PTSD symptom severity. Individuals with MD endorsed a depressive attributional style to a greater extent than both individuals with PTSD, who were not depressed, and healthy controls. Depressive attributional style was associated with the severity of depressive and PTSD symptoms, number and distress of traumatic experiences, frequency of rumination, and post-traumatic cognitions. Depressive attributions and PTCI appraisals independently predicted MD and PTSD symptom severity. They may thus be useful in predicting MD and PTSD, and should be targeted in psychological treatments of these conditions.

Introduction

People respond differently to stressful or traumatic life events. Negative cognitions about the self, the world, and the future, are thought to play a crucial role in the development of depression (Beck 1967, 1976). There is evidence that depression is characterised by a certain attributional style, also known as depressive attributional style or pessimistic explanatory style (Sweeney et al. 1986; Zullow et al. 1988). According to the reformulated model of learned helplessness and depression (Abramson et al. 1978), depressed individuals tend to attribute negative events to internal (“it is due to me”), stable (“it is permanent”) and global (“it will affect other areas of my life”) causes, and positive events to external (“it is

not due to me"), unstable ("it is temporary"), and specific ("it will only affect this area of my life") causes (see Sweeney et al. 1986, for a review). There is empirical evidence that attributional style is an important factor in the development and maintenance of depression (e.g., Ball et al. 2008; Elwood et al. 2009a, b; Southall and Roberts 2002). The hopelessness theory of depression (Abramson et al. 1988; Alloy et al. 1988) further specifies that individuals who make stable and global attributions following a negative event may experience hopelessness and, in turn, develop depression. A relationship between attributional style, hopelessness and later depression has previously been found in various samples, such as undergraduate students, adolescent psychiatric inpatients, or healthy participants at high versus low cognitive risk for depression (e.g., Abramson et al. 1998; Alloy et al. 2006; Gibb et al. 2001; Hilsman and Garber 1995; Voelz et al. 2003). Thus, the meaning and interpretation given to negative experiences may influence whether an individual becomes depressed, whether they are vulnerable to recurrent episodes of depression and how long and severe these episodes will be (Alloy et al. 1999).

Individual differences in the interpretation and personal meanings of traumatic events, which can be understood as extremely negative events, have been the focus of theoretical models of posttraumatic stress disorder (PTSD) (e.g., Dollinger 1986; Ehlers and Clark 2000; Foa and Riggs 1993; Resick and Schnicke 1993; Taylor 1983). Trauma-related appraisals about the self (e.g., "I am weak"), the world (e.g. "I cannot trust anybody"), and self-blame (e.g., "It was my fault that the event happened") have been shown to predict PTSD after a range of traumatic events (e.g., Ehring et al. 2008; Foa et al. 1999; Halligan et al. 2003; Laposa and Alden 2003). In line with the findings on increased self-blame in PTSD, several studies have found that internal, global and stable attributions of traumatic events are associated with PTSD symptoms in war veterans and survivors of childhood sexual abuse or disaster (Frye and Stockton 1982; Ginzburg et al. 2003; Gray et al. 2003; Joseph et al. 1991; McCormick et al. 1989; Wenninger and Ehlers 1998). One interpretative problem in these studies is that PTSD is often comorbid with depression (e.g., Breslau et al. 1991; Kessler et al. 1995; Shalev et al. 1998) so that it remains unclear whether the associations between attributional style and trauma reactions are due to PTSD or due to depression. The present study was designed to address this question.

Overall, there is very limited research on the specificity of cognitive factors in response to negative events (for exceptions see Ehring et al. 2008; Kleim et al. in press; Mayou et al. 2001; O'Donnell et al. 2004). Some research has provided initial evidence for a specificity of certain cognitive styles, including depressive attributional styles, to depression. For instance, Hankin et al. (2004) found that the interaction between cognitive vulnerability for depression, including depressive attributions, and negative events, specifically predicted future depression. Studies by Ehring et al. (2008) and Kleim et al. (in press) demonstrated a relative specificity of theory-derived cognitive factors in the prediction of depression and PTSD.

Based on the above reviewed studies, it seems relevant to clarify the nature and extent of overlap and specificity of attributions in MD and PTSD, and index depressive attributions, as well as trauma-specific appraisals characteristic of PTSD in such samples. If a depressive attributional style and trauma-specific appraisals were disorder-specific, this could point to separate mechanisms of development and maintenance of the two disorders and a need to target these cognitions in treatment.

The aim of this study was to compare depressive attributions in individuals with depression only, PTSD only, and PTSD comorbid with depression. We aimed to investigate the specificity of depressive attributions, i.e., whether depressed individuals endorse depressive attributions to a greater extent than those with PTSD. Moreover, we wanted to test the relationship between depressive attributions and the severity of depression and

PTSD symptoms, the number and distress of traumatic experiences, trauma-related appraisals, and the frequency of rumination. The latter is thought to maintain both depression (Nolen-Hoeksema 1991; Nolen-Hoeksema et al. 2008) and PTSD (Ehlers and Clark 2000). According to the studies presented above, we hypothesised some overlap between depression and PTSD in terms of attributional style and expected that depressive attributions may predict the severity of both depression and PTSD. However, we also predicted that attributional style would be more closely related to major depression than to PTSD.

Methods

Participants

Four groups of adult participants (ages 18–65 years) were recruited for the study. Participants had to meet the criteria specified below and had to be sufficiently fluent in English to complete the questionnaires. Exclusion criteria were psychosis, clinically significant head injury, ongoing domestic violence, and no memory for the traumatic events that participants had experienced.

Patients with Major Depression (N = 20) were recruited from inpatient and outpatient clinics at the Maudsley Hospital, London, UK.

Trauma Survivors with PTSD. Participants with PTSD were recruited from trauma survivors who had attended King's College Hospital's A&E Department following an assault, from outpatient clinics at the Maudsley Hospital, and through flyers at local newsagents. Of the 43 trauma survivors with PTSD, 17 had PTSD without comorbid depression and 26 had PTSD with comorbid major depression.

Control Participants (N = 101) who did not suffer from depression or PTSD were recruited from trauma survivors who had attended King's College Hospital's A&E Department following an assault, through flyer and poster advertisement at local shops, through a database of volunteers, and through emails to staff.

Table 1 shows the differences between the groups in terms of level of symptoms and scores obtained from the measures described below, as well as demographic information. One-way ANOVAs revealed significant differences between the groups in depression ($F(3, 159) = 70.33$, $P < 0.001$) and PTSD symptom severity ($F(3, 158) = 55.96$, $P < 0.001$), number of traumatic events ($F(3, 160) = 4.06$, $P < 0.01$), and total distress scores resulting from past traumatic events ($F(3, 157) = 4.96$, $P < 0.01$). Posthoc comparisons showed that the MD + PTSD group scored higher than healthy controls on all measures. Additionally, the MD only and the PTSD only groups also differed from healthy controls in depression and PTSD symptom severity, but not in the number of traumatic events or distress scores.

Diagnostic Assessment

The Structured Clinical Interview for DSM-IV (SCID) (First et al. 1996) was used to assess the presence of PTSD and MD, as well as past MD. Inter-rater reliability was good in the present study, with $\kappa = .75$ for PTSD and $\kappa = .86$ for depression (n = 13 interviews, 2 raters, blind to each others' diagnoses).

Measures

General Information Questionnaire. This questionnaire was adapted from earlier studies (Ehring et al. 2008; Halligan et al. 2003) to assess socio-demographic characteristics (age, gender, ethnic background, marital status, income, and education), and drug and alcohol consumption. For each question, participants marked the most appropriate from a selection of answers or filled in answers to open questions.

Trauma History Interview.

This semi-structured interview was adapted from Kubany et al. (2000) to assess exposure to a broad range of potentially traumatic events. Sixteen event types (e.g., natural disaster, motor vehicle accidents, sudden, unexpected death of a close friend or loved one, childhood physical or sexual abuse, etc.) are contained in this interview. Participants were asked how old they were when the events happened and how distressing they thought the events were on a rating scale from 0 (not at all stressful) to 100 (extremely stressful). A final open-ended question assesses exposure to some other life-threatening or highly disturbing event(s). The number of past traumatic events and sum of distress scores were used for the analyses.

Depressive Attributions Questionnaire (DAQ).

The DAQ (Kleim et al. 2011) assesses depressive attributions. Items were derived from Beck's cognitive model of depression (e.g., Beck 1967) and the reformulated model of learned helplessness and depression (Abramson et al. 1978). A total of 16 items assessed negative stable attributions (e.g., "When bad things happen, I am sure it will happen again"), negative internal attributions (e.g., "When bad things happen, I think it is my fault"), negative global attributions (e.g., "Bad things happen in all areas of my life"), and helplessness (e.g., "When bad things happen, I rely on other people to sort things out") on a 5-point scale ('not at all', 'a little', 'somewhat', 'strongly', 'very strongly'). Items are combined to a sum score. Internal consistency was excellent in the present study, $\alpha = .96$ for the combined sample.

Post-Traumatic Cognitions Inventory (PTCI).

The PTCI (Foa et al. 1999) is a self-report instrument that measures trauma-related thoughts about the self, other people and self-blame (e.g., "My reactions since the event mean that I am going crazy", "The world is a dangerous place"). The 32-item version used in this study asked participants to rate each item on a scale from 1 (totally disagree) to 7 (totally agree). The final score was the sum of all items. The internal consistency in the present study was very good, $\alpha = .95$ for the combined sample.

Response Styles Questionnaire (RSQ).

The 10-item rumination scale of the RSQ (Nolen-Hoeksema 1991; Nolen-Hoeksema and Morrow 1991) was used to assess the frequency with which individuals thought about their symptoms of depression, i.e. when they feel sad or depressed, on a four point scale from 1 (never) to 4 (always). Previous studies have shown the RSQ rumination scale to be internally consistent and factor-analytically derivable. Higher scores are

related to more severe and longer episodes of depression (e.g., Nolen-Hoeksema et al. 1993) as well as to distorted interpretations of hypothetical life events (Lyubomirsky et al. 1998). The internal consistency in the present study was very good, α = .93 for the combined sample.

Post-Traumatic Stress Diagnostic Scale (PDS).

The PDS (Foa et al. 1997) is a standardised and validated self-report measure of PTSD symptom severity that has been widely used with clinical and non-clinical samples of traumatised individuals. The PDS asks participants to rate 17 items regarding how often they were bothered by each of the PTSD symptoms specified in the DSM-IV (APA 1994), ranging from 0 (never) to 3 (5 times per week or more/very severely) and how much these symptoms had interfered with 9 specific areas of their life. The total symptom severity can range from 0 to 51 (≤10 = mild; ≥11 and ≤20 = moderate; ≥21 and ≤35 = moderate to severe; ≥36 = severe). Internal consistency in the present study was very good, α = .95 for the combined sample.

Beck Depression Inventory (BDI).

The BDI (Beck and Steer 1987) is a widely used, standardised and normed measure of severity of depression. The BDI asks participants to decide between four different response choices reflecting different degrees of depressive symptom severity. Items are scored from 0 to 3. The total BDI score thus ranges between 0 and 63 (0–9 = subclinical; 10–18 = mild to moderate; 19–29 = moderate to severe; 30–63 = severe). Internal consistency in the present study was very good, α = .91 for the combined sample.

National Adult Reading Test (NART).

The NART (Nelson 1991) is a short measure of verbal intelligence, which consists of a reading test of 50 irregularly spelled words. According to standard instructions, participants read aloud a list of words printed in order of increasing difficulty. The number of words read correctly comprises the final score. A conversion table (from NART to IQ scores) was used to obtain a predicted full-scale IQ. The NART has excellent reliability and construct validity (Crawford et al. 1990).

Study Design and Procedure

The study was approved by the local ethics committees. Participants gave written consent, filled in questionnaires, and completed diagnostic interviews. They received a modest financial reimbursement for their time.

Statistical Analysis

We performed one-way ANOVAs and Tukey's honest significance posthoc tests to compare the level of DAQ and PTCI scores and the number of past traumatic events between four diagnostic groups (MD, PTSD, PTSD and MD, and healthy controls). We also calculated Pearson's correlations between DAQ scores and severity of depression symptoms, severity of PTSD symptoms, level of rumination, number of traumatic events, total distress experienced during those events, level of post-traumatic cognitions (PTCI), and NART-predicted full-scale IQ. Finally, we

performed standard multiple regressions to assess the ability of the DAQ and the PTCI to predict the severity of depression and PTSD symptoms. All significance tests were two-tailed and the significance level was set at $\alpha = .05$.

Results

Comparisons Between Diagnostic Groups: Depressive Attributions

Significant differences in DAQ scores were observed between diagnostic groups, $F(3, 160) = 28.01$, $P < 0.001$. Tukey's posthoc comparisons showed participants with MD only ($M_{MD\text{-}only} = 33.90$; $SD_{MD\text{-}only} = 16.06$) and those with MD and PTSD ($M_{PTSD+MD} = 37.58$; $SD_{PTSD+MD} = 16.11$), but not those with PTSD only ($M_{PTSD\text{-}only} = 22.12$; $SD_{PTSD\text{-}only} = 12.24$), scored higher on depressive attributions than healthy controls ($M_H = 15.54$; $SD_H = 10.79$). Additionally, the PTSD only group scored significantly lower on depressive attributions that those with MD only and those with MD and PTSD. Figure 1 illustrates these findings.

Comparisons Between Diagnostic Groups: Trauma-Related Appraisals

Significant differences in the endorsement of trauma-specific appraisals were observed between diagnostic groups, $F(3, 157) = 21.37$, $P < 0.001$. Posthoc comparisons showed that participants with PTSD only ($M_{PTSD\text{-}only} = 3.61$; $SD_{PTSD\text{-}only} = .86$), MD only ($M_{MD\text{-}only} = 3.26$; $SD_{MD\text{-}only} = 1.16$), and MD and PTSD ($M_{PTSD+MD} = 4.19$; $SD_{PTSD+MD} = 1.30$) endorsed negative trauma-related appraisals to a greater extent than healthy controls ($M_H = 2.44$; $SD_H = 1.01$). Additionally, those with MD only endorsed significantly fewer negative appraisals than those with MD and PTSD.

Correlations Between DAQ and Measures of Symptom Severity, Rumination, Number and Distress of Traumatic Events, and Full-Scale IQ

DAQ total scale scores correlated significantly with measures of severity of depression and PTSD symptoms. The correlation between DAQ total scores and the measure of depression severity ($r = .69$; $P < 0.001$) was higher than the correlation between DAQ total scores and the measure of PTSD severity ($r = .55$; $P < 0.001$). However, this difference did not reach significance ($z = 1.57$; $P = 0.120$).

DAQ total scores showed significant positive correlations with PTCI total scores ($r = .52$, $P < 0.001$), with a tendency to ruminate ($r = .65$, $P < 0.001$), a greater number of traumatic events ($r = .19$; $P < 0.050$), and greater distress experienced during these events ($r = .19$; $P < 0.050$). There was no correlation between DAQ scores and NART-predicted full-scale IQ ($r = -.07$; $P > 0.050$).

Prediction of Depression and PTSD Symptoms Severity by Depressive Attributions and Negative Trauma-Related Appraisals

Standard multiple regression was used to assess the ability of the DAQ and the PTCI to predict the severity of depression symptoms (BDI). The total variance of depression symptom severity explained by the two independent variables combined (DAQ and PTCI) was 62%, $R2 = .62$, $F(2, 158) = 127.3$; $P < 0.001$. PTCI alone accounted for 14% of the variance and DAQ alone for 16% of the variance. The remaining 32% corresponds to shared variance. Both the DAQ ($\beta = .47$, $P < 0.001$) and the PTCI ($\beta = .44$, $P = < 0.001$), made unique significant contributions.

In the prediction of PTSD, the total variance of PTSD symptom severity (PDS) explained by the DAQ and PTCI total scores was 41%, $R2 = .41$ $F(2, 157) = 54.78$; $P < 0.001$. PTCI alone accounted for 11% of the variance and DAQ for 9% of the variance. The remaining 21% corresponds to shared variance. Both the PTCI ($\beta = .39$, $P < 0.001$) and the DAQ ($\beta = .35$, $P \leq 0.001$) made unique significant contributions.

Discussion

In accordance with previous findings on the role of attributional style in depression (Abramson et al. 1978; Försterling and Bühner 2003), individuals with major depression endorsed more internal, stable, and global attributions of negative events than participants without depression. This finding provides further support for cognitive theories of depression (Abramson et al. 1978; Abramson et al. 1989; Beck 1967).

The present results extend these previous findings, as this study compared participants with MD only (and no PTSD) with those who only had PTSD (and no depression). We found a significantly higher degree of depressive attributions in those with MD only than in those with PTSD only, who did not differ from healthy controls. Thus, the study provided evidence for some specificity of depressive attributions to depression. Individuals with major depression and comorbid PTSD endorsed depressive attributions to a greater extent than those with PTSD only, but did not differ significantly from those with major depression only. This pattern of results suggests that major depression may be the crucial factor in the endorsement of depressive attributions.

However, in the correlational analyses, depressive attributions correlated with both the severity of depression and PTSD symptoms. This probably reflects the overlap of symptoms of both disorders (e.g., diminished interest in activities, sleep disturbance, difficulty concentrating) and the high comorbidity rates. It may also indicate that depressive attributions are a common transdiagnostic process. Finally, it may also reflect the fact that symptom severity was assessed by self-report and thus shares method variance with the DAQ scores, whereas diagnoses are based on clinicians' judgements.

DAQ scores correlated with PTCI scores, indicating that causal attributions of negative events in general and negative interpretations about the implications of traumatic events for the self and the world may overlap to some extent (e.g., see DAQ item: "When something I do goes wrong, I think it is because I am incapable"; PTCI item: "I am inadequate"). The multiple regression analyses further showed that depressive attributions and trauma-related negative beliefs were independent predictors of both depressive and PTSD symptoms. This indicates that although they show some overlap, there are also important differences. Whereas the DAQ focuses on the process of assigning a cause to rather generic events (e.g., "When things go well, I think it is just due to good luck"), the PTCI addresses a wider range of cognitions about the meaning of the trauma (e.g., "My life has been destroyed by the event," "I have to be on guard all the time"), and thus possibly explains a wider range of post-trauma symptoms, including those not found in depression, such as hypervigilance.

Individuals who reported more pronounced depressive attributions also reported a higher degree of rumination. Due to the cross-sectional nature of our data, we cannot make inferences about the temporal and potentially causal patterns of these processes. However, one possibility could be that rumination may maintain depressive symptoms as it involves repetitively and passively focusing on the possible causes of symptoms, which may include and enhance depressive cognitions (e.g., Nolen-Hoeksema et al. 2008). Existing research in this area has shown that rumination

indeed interacts with depressive symptoms to predict negative attributional style (Lo et al. 2010) and that the interaction between negative cognitive style and stress-reactive rumination predicts the onset, number, and duration of prospective depressive episodes (Robinson and Alloy 2003).

Depressive attributions were also associated with greater and more severe exposure to trauma. Again, the cross-sectional nature of the data precludes causal interpretations. One could hypothesise a dose–response relationship in that re-exposure to trauma is more likely to result in more pronounced depressive attributions and learned helplessness than one single event. There is evidence that multiple trauma is associated with higher levels of PTSD symptoms (Follette et al. 1996; Green et al. 2000), as well as substance abuse, suicide attempts (McCauley et al. 1997), and mood disorder (Miranda et al. 1997) than single trauma.

It is also relevant to highlight how the DAQ compares with other measures of attributional style, which have been most widely used until now, such as the Attributional Style Questionnaire (ASQ; Peterson et al. 1982) and its expanded and modified version, the Cognitive Style Questionnaire (CSQ; Haeffel et al. 2008). Both these questionnaires require participants to generate one major cause to positive and negative hypothetical situations from the achievement and affiliation domains (e.g., “You have been looking for a job unsuccessfully for some time”, or “You meet a friend who acts hostilely towards you”). In contrast, the DAQ offers short statements containing negative attributions (e.g., “When something I do goes wrong, I think it is because I am incapable”) and requires participants to answer on a 0–4 scale how much each statement applies to them. Thus, the DAQ aims to take up less mental processing time and effort, which is crucial during clinical assessment. For instance, depressed individuals often have cognitive deficits in concentration, executive function and over-general memory (Williams et al. 2000) and individuals with PTSD often also present with over-general memory (Schönfeld and Ehlers 2006). In terms of length, the ASQ contains 12 hypothetical events with a total of 60 questions and the CSQ contains 24 hypothetical events, making both these measures much lengthier and more mentally demanding than the DAQ, which contains only 16 brief statements. During the validation process of the DAQ, the ASQ was also administered and several aspects of both questionnaires compared. Mean completion times for the DAQ (M = 2.36 min, SD = 1.15) and the ASQ (M = 17.32 min, SD = 7.73) were found to be significantly different for both depressed and non-depressed participants (Kleim et al. 2011). This validation study also showed that both depressed and non-depressed participants found the DAQ significantly easier to fill in than the ASQ. The same study showed that the mean number of ASQ situations for which participants were able to retrieve personal memories was 7.36, SD = 2.30 (61%) and they also specified some difficulties completing the ASQ but not the DAQ. In addition, both the ASQ and the CSQ were validated in samples of college students, whereas the DAQ was validated in participants from various diagnostic groups and healthy controls, making the latter a more appropriate tool for clinical use. Finally, the ASQ’s low reliability has been criticised in some studies (e.g., Sweeney et al. 1986) and there are sparse data on its validity. In contrast the DAQ has been shown to have high internal reliability, test–retest reliability, and convergent, discriminant and construct validity. Thus, although the differences between the DAQ and other measures might make it difficult to compare results across studies, it is important to introduce a measure of attributional style, which addresses the shortcomings of previous ones, i.e. (1) ease of use, (2) applicability to different participant groups, and (3) validity and reliability in clinical and research settings.

This study is not without limitations. First, we used the DAQ to index core aspects of depressive attributions, namely internal, stable and global attributions of negative events. It might also be useful to investigate other attributional dimensions reported in the literature, such as controllability, expectedness, and importance of events. Second, our study is cross-sectional. It would be clinically relevant to test the predictive power of

depressive attributions in the development of depression and PTSD symptoms in prospective studies. If these yielded positive results, a measure of depressive attributions could be used as a screening tool to detect individuals at high risk of developing MD or PTSD. Finally, our results would be strengthened by replication in further samples. Our analysis into the specificity of depressive attributions is limited to the comparison between MD and PTSD. It would be interesting to include further groups into the comparison, such as individuals with substance abuse or bipolar disorder.

The present results have implications for theory, as well as practical clinical implications. Some effective empirically-based therapies, for instance cognitive-behavioural therapies, address patients' maladaptive beliefs, and attempt to modify them by developing alternative explanations for events and gathering evidence for various explanations to create more evidence-based adaptive beliefs (Beck 1976; Ehlers et al. 2005; Ingram 2007; Kuyken et al. 2007; Markowitz 2008). According to current cognitive behavioural models, thoughts, including depressive attributions and negative trauma-related beliefs, influence behaviour, and may lead to the development and maintenance of clinical disorders, such as MD or PTSD. Attributional retraining has been described as an empirically based cognitive-behavioural technique, for instance in the treatment of child victims of sexual abuse, which involved decreasing abuse-related self-blame and encouraging the child to attribute responsibility for the abuse to the perpetrator (Celano et al. 2002). Dieser and Ruddell (2002) examined the effects of attributional retraining on attributions and explanatory style in depressed adolescent inpatients and reported that the training led to higher endorsement of personal control and stability attributions. Moreover, a recent experimental study by Peters, Constans, and Mathews (2011) showed that attributional style can be manipulated by use of computer-based cognitive bias modification (CBM). This training resulted in a decreased tendency to engage in negative causal attributions for poor performance and in less depressed mood. Identifying and modifying disorder-specific attributions and appraisals and their identification may thus be an important target of disorder-specific psychological therapies (e.g. Miller et al. 1975).

BACK TO TOP

Preclinical evaluation of reconsolidation blockade by clonidine as a potential novel treatment for posttraumatic stress disorder

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Abstract

Exposure to traumatic events can lead to posttraumatic stress disorder (PTSD). Current PTSD treatments typically only produce partial improvement. Hence, there is a need for preclinical research to identify new candidate drugs and to develop novel therapeutic approaches. Animal studies have indicated that fear memories can be weakened by blocking restabilization after retrieval, a process known as reconsolidation.

Furthermore, evidence suggests that there are important alterations of the noradrenergic system in PTSD, and hence it may be of interest to study drugs that target this pathway. Here, we investigated the efficacy of clonidine, an α2-adrenoreceptor agonist, to block reconsolidation in an animal model of persistent traumatic memories. Using an auditory fear conditioning paradigm in rats, we tested the efficacy of clonidine to weaken fear memory retention when administered systemically after retrieval. We evaluated dosage, number of treatments, and specificity in reconsolidation blockade. We found that postretrieval administration of clonidine disrupts fear-related memories in a dose-dependent manner and that two treatments are sufficient for maximal memory impairment. Furthermore, we determined that this effect is long lasting and specific to reconsolidation processes as shown by the selectivity to affect reactivated memories and the absence of spontaneous recovery and of postreactivation short-term memory impairment. Our results demonstrate the efficacy of systemic administration of clonidine following retrieval to persistently disrupt fear memory retention through reconsolidation blockade. This study provides important preclinical parameters for future therapeutic strategies involving clonidine to block reconsolidation as a novel treatment for PTSD symptoms.

Introduction

In a substantial minority of individuals, experiencing a traumatic event can lead to posttraumatic stress disorder (PTSD). This condition is characterized by several symptoms including irritability, hypervigilance, avoidance behaviors, intrusive memories, and frequent re-experiencing of the traumatic event through nightmares and flashbacks. PTSD affects 10–20% of people who have experienced a traumatic event. It has a lifetime prevalence of 6.8% in the United States (Kessler et al, 2005). Current therapeutic strategies include psychotherapy and pharmacological treatments; however, only 60% of patients will be responsive to these treatments (Davidson et al, 2006; Onder et al, 2006) and only 20–30% will achieve full remission (Berger et al, 2009). Consequently, there is a significant need to develop novel pharmacological approaches to reduce symptoms of PTSD.

A proposed therapeutic strategy involves the modification of memory reconsolidation processes. In order for a new memory to be retained, it has to be stabilized through a mechanism referred to as consolidation. When such a memory is retrieved (recalled), it becomes unstable again for a short period of time, at which point it is susceptible to modifications (Nader and Hardt, 2009). The memory is then restabilized (reconsolidated) in its modified state. In PTSD, flashbacks, nightmares, and recollection of intrusive memories allow the traumatic memory trace to be retrieved and then reconsolidated (Charney, 2004). Impairing reconsolidation of such memories may lead to their weakening and may consequently diminish PTSD symptoms.

In animal models, pharmacological interventions exploit the vulnerable state of a memory after recall in order to impair reconsolidation. Even though there is no animal model that recreates PTSD entirely, fear conditioning is known to model the fear that accompanies reminders of the traumatic event (Pitman et al, 1999; Siegmund and Wotjak, 2006). Studies have shown that fear memories can be weakened by blocking the restabilization process with different drugs, such as protein synthesis inhibitors (Nader et al, 2000), N-methyl-d-aspartate (Ben Mamou et al, 2006), or adrenergic receptor antagonists (Przybyslawski et al, 1999; Debiec and Ledoux, 2004) and inhibitors of the mammalian target of rapamycin (Blundell et al, 2008; Jobim et al, 2012). A disadvantage of these pharmacological agents is that most of them are toxic, administered intracranially, and not approved for humans. In order to more easily extrapolate work in animal models to clinical trials, investigated drugs should be safe for human use.

Evidence suggests that among other physiological alterations, there is increased noradrenergic activity in PTSD patients (Southwick et al, 1997, 1999; Boehnlein and Kinzie, 2007). Furthermore, it has been proposed that this hyperactivity is associated with hyperarousal and re-experiencing symptoms present in PTSD (Southwick et al, 1997; Boehnlein and Kinzie, 2007). Consequently, drugs that specifically target noradrenergic system hyperactivity and are safe for human use may be of clinical interest. One of those candidate drugs is the α2-adrenoreceptor agonist clonidine. The effect of clonidine on memory has been shown to be mediated through the α2-adrenoreceptor subtype (Galeotti et al, 2004). These receptors are located both pre- and post-synaptically. Clonidine is thought to act mainly at the presynaptic level by activating the α2-autoreceptor (Southwick et al, 1999; Wilens, 2006), which leads to inhibition of voltage-gated calcium channels and inhibition of norepinephrine release (Southwick et al, 1999; Gilsbach and Hein, 2011). Clinically, clonidine is used to induce sedation, analgesia, and hypotension (MacMillan et al, 1996; Lakhlani et al, 1997), as well as in the treatment of attention-deficit/hyperactivity disorder (Wilens, 2006). Additionally, a few open-label studies have shown beneficial effects of clonidine in treating some PTSD symptoms (Kinzie and Leung, 1989; Harmon and Riggs, 1996; Ziegenhorn et al, 2009), but none of these studies used clonidine specifically in combination with traumatic memory retrieval. In animal models, the use of clonidine has been found to produce memory impairments in step-down (Genkova-Papasova and Lazarova-Bakurova, 1988; Genkova-Papazova et al, 1997), shuttle box (Hawkins and Monti, 1979; Homayoun et al, 2003), and passive avoidance tasks (Galeotti et al, 2004); however, the use of clonidine to block memory reconsolidation has yet to be investigated.

The present study aims to examine the use of clonidine as a potential novel treatment for PTSD by testing its effects on the reconsolidation of a fear memory in rats. We investigated key parameters necessary to develop clinical studies involving reconsolidation blockade with clonidine. We determined the most effective dose through a dose–response curve, established the optimal number of treatments, and verified that the observed effects were reconsolidation specific.

Materials and Methods

Animals

Equal numbers of male and female Sprague-Dawley rats weighing between 250 and 350 g (Harlan Laboratories, Indianapolis, IN) were co-housed with ad libitum access to food and water. Rats were maintained on a 12 h light/dark cycle. All experiments were performed during the light (day) phase. All procedures were approved by McGill Animal Care Committee and complied with the Canadian Council for Animal Care guidelines.

Drugs

Clonidine hydrochloride (Sigma-Aldrich, Canada) was dissolved in sterile saline (0.9% NaCl) to the final concentration (50, 100, or 200 μg/kg) and administered intraperitoneally at a volume of 1 ml/kg (Galeotti et al, 2004).

Behavioral Procedure

Rats underwent auditory fear conditioning, reactivation, and testing in the same experimental chamber to further resemble, in our animal model, a PTSD-like intrusive memory in which cue and context are usually not easily separated. The conditioning chamber consisted of a brightly lit

plexiglass box (25 × 29 × 29 cm) with stainless steel-grid floor that was enclosed within a sound-attenuating box (Coulbourn Instruments, Whitehall, PA).

Experiment 1 Rats were first habituated to the chamber for 5 min on 2 consecutive days. The following day (day 1), rats were conditioned. Conditioning involved 2 min of acclimation to the chamber after which rats received a single pairing of a tone (30 s, 5 kHz, 75 dB) coterminating with a foot shock (1 s, 0.75 mA). Rats remained in the chamber an additional minute before being returned to their home cages. On day 2, the fear memory was reactivated by placing the animals in the experimental chamber and presenting the tone without the shock. Rats were then removed from the context and clonidine (50, 100, or 200 μg/kg) or its vehicle was administered immediately. On days 3 and 10, animals were tested for postreactivation long-term memory (PR-LTM) with the presentation of a single tone.

Experiment 2 Nonreactivated controls were habituated and trained as in experiment 1, but rats did not receive the reactivation and instead remained in the animal colony where they received the clonidine treatment on day 2.

Experiment 3 As a postreactivation short-term memory (PR-STM) control, animals were habituated, trained, reactivated, and given postreactivation clonidine as in experiment 1. They were tested 4 h after the reactivation session on day 2, and again 24 h later.

Experiment 4 Rats underwent the same procedure as in experiment 1 and received clonidine (200 μg/kg) or vehicle following reactivation. After the test on day 10, rats were allowed 2 days of rest before undergoing habituation, new conditioning, and testing in a different experimental chamber. The conditioning chamber consisted of a dimly lit plexiglass and steel box (25 × 29 × 29 cm) with one curved white plastic wall and one black and white striped wall, enclosed within a sound-attenuating box (Med Associates, VT). A smaller steel-grid floor was used in this design and peppermint-scented water was also vaporized inside the box to create a different scent than before. Rats were first habituated to the chamber for 5 min on 2 consecutive days. The following day (day 14), rats were newly conditioned. After 3 and a half minutes of acclimation to the chamber, rats received a single pairing of a different frequency tone (20 s, 3 kHz, 85 dB) coterminating with a foot shock (1 s, 1.1 mA). Rats remained in the chamber an additional 2 min before being returned to their home cages.

Experiment 5 Rats were habituated, trained, and reactivated as described in experiment 1. However, rats underwent reactivation on days 2, 3, and 4, each time followed by an injection of clonidine (100 μg/kg) or its vehicle. Rats were tested on days 5 and 12 using the same procedure as above.

Behavior was recorded using FreezeView software (Actimetrics). Freezing, defined as immobilization with the exception of respiration (Blanchard and Blanchard, 1969), was the conditioned response taken as a measure of fear memory retention. Scores are presented as the percentage of time spent freezing during the total duration of the tone.

Statistical Analysis

A repeated-measures analysis of variance (ANOVA) followed by Fisher's post hoc analysis was used to compare groups across days. Significance was set as $p<0.05$.

Results

For all experiments, no significant sex main effect or interaction was observed for freezing to the tone. A repeated-measures ANOVA across days revealed no difference in freezing scores between males and females for any experiment. This lack of sex differences allowed us to combine the freezing scores for males and females for each experiment.

Pre-tone freezing was also analyzed with a repeated-measures ANOVA across days and no significant main effect of treatment or interaction was observed for any of the experiments. A main effect of sex was observed on pre-tone freezing only for experiments 1 and 3, where there was a lower pre-tone freezing response in the females. In light of these isolated results, the lack of treatment effect on pre-tone freezing, and because our measure of memory retention was tone-related freezing, pre-tone freezing was not further investigated.

Experiment 1: Postreactivation Administration of Clonidine Impairs Reconsolidation of Auditory Fear Memories in a Dose-Dependent Manner

We evaluated whether clonidine is effective at disrupting fear memory reconsolidation when administered systemically at 50, 100, or 200 μg/kg. We conditioned the animals on day 1 and reactivated them the following day by exposing them again to the conditioning chamber and the tone.

After reactivation, animals received an injection of clonidine or its vehicle and were tested for memory retention a day later. To establish if the effects of clonidine were long lasting, rats were also tested again on day 10 (Figure 1a). Clonidine was effective at blocking memory reconsolidation at all tested doses, and its effect was long lasting as the memory impairment was still observed a week after the treatment (Figure 1b–d). A repeated-measures ANOVA revealed a main effect of treatment ($F(1, 34)=6.08$, $p<0.05$ for 50 μg/kg; $F(1, 48)=10.61$, $p<0.01$ for 100 μg/kg; $F(1, 37)=7.99$, $p<0.01$ for 200 μg/kg) and day ($F(2, 68)=9.09$, $p<0.001$ for 50 μg/kg; $F(2, 96)=36.04$, $p<0.001$ for 100 μg/kg; $F(2, 74)=22.05$, $p<0.0001$ for 200 μg/kg). A significant treatment × day interaction was observed for 100 μg/kg ($F(2, 96)=4.66$, $p<0.05$) and 200 μg/kg ($F(2, 74)=5.71$, $p<0.01$). Subsequent Fisher's post hoc tests indicated significant differences between the clonidine-treated group and the controls at both memory retention tests (for 50 μg/kg, $p<0.05$ for both tests; for 100 μg/kg, $p<0.001$ for PR-LTM and $p<0.01$ for PR-LTM 2; for 200 μg/kg, $p<0.001$ for PR-LTM and $p<0.01$ for PR-LTM 2). In addition, significant freezing decreases were observed within the clonidine group between reactivation and both PR-LTM performances (for 50 μg/kg, $p<0.05$; for 100 μg/kg, $p<0.001$; for 200 μg/kg, $p<0.001$). Taken together, the present data suggest that clonidine disrupted fear memory reconsolidation in a dose-dependent manner. Clonidine reached its maximum effect at 100 μg/kg, as increasing the dose further did not lead to a greater impairment of the conditioned response in the treated group.

Experiment 2: Reconsolidation Blockade by Clonidine Is Selective to Reactivated Fear Memories

We assessed whether the effect of clonidine on reconsolidation was dependent on memory reactivation. We injected clonidine at a dose of 100 μg/kg 24 h after training without exposing the animals to the conditioning chamber and tone. Rats were tested for memory retention on days 3 and 10 (Figure 2a). No significant effect of clonidine (repeated-measures ANOVA, $F(1, 22)=0.002$, $p>0.05$) was observed in the absence of reactivation, as compared with the vehicle-injected group 1 day and 1 week after receiving the treatment (Figure 2b). In addition, a repeated-measures ANOVA showed no significant effect of day ($F(1, 22)=1.34$, $p>0.05$) and no treatment × day interaction ($F(1, 22)=0.39$, $p>0.05$). Thus, clonidine disrupts reconsolidation of an auditory fear memory only when administered following reactivation of that memory.

Experiment 3: Postreactivation Administration of Clonidine Does Not Impair Short-Term Fear Memories

To rule out the possibility that nonspecific effects of postreactivation clonidine create temporary dysfunctions of the memory system, we trained and reactivated rats as described before. After reactivation, animals received 100 μg/kg of clonidine or vehicle and were tested for memory retention 4 and 24 h later (Figure 3a). If the memory impairment seen at PR-LTM is due to reconsolidation blockade, then animals should show an intact conditioned response 4 h after reactivation (PR-STM) but reduced freezing behavior 24 h later (PR-LTM). A repeated-measures ANOVA showed a significant main effect of treatment ($F(1, 19)=5.49$, $p<0.05$) and day ($F(2, 38)=10.9$, $p<0.001$), but no treatment × day interaction ($F(2, 38)=2.21$, $p>0.05$; Figure 3b). Nevertheless, Fisher's post hoc test revealed a similar conditioned response for the clonidine-treated rats as compared with the vehicle group at PR-STM ($p>0.05$) but showed a significant decrease in freezing for the clonidine group at PR-LTM as compared with PR-STM ($p<0.001$) and to controls at PR-LTM ($p<0.001$). Hence, the results confirm that postretrieval clonidine selectivity disrupts reconsolidation of long-term memories.

Experiment 4: Reconsolidation Blockade by Clonidine Does Not Impair the Ability to Learn New Fear Memories

To evaluate whether postreactivation clonidine could induce permanent learning impairments, we conditioned animals to fear a different tone using a different auditory fear protocol. After receiving a postreactivation injection of clonidine (200 μg/kg) or vehicle, and a memory retention test 1 and 7 days later, rats were trained again and tested for memory of the new tone (Figure 4a). The highest dose was chosen for this experiment to ensure that if no impairments were observed, it could not be attributed to the use of a low concentration. We hypothesized that if the clonidine-related memory impairment is selective to reconsolidation blockade, then the fear response of the previously treated animals should be similar to the controls when tested for memory of the new tone. A repeated-measures ANOVA revealed no significant main effect of treatment ($F(1, 22)=0.002$, $p>0.05$), day ($F(1, 22)=2.17$, $p>0.05$), and no treatment × day interaction ($F(1, 22)=0.7$, $p>0.05$; Figure 4b). As both groups exhibited similar levels of conditioned response on the two test days, our data indicate that administering clonidine after reactivation does not induce a long-lasting, generalized fear learning impairment.

Experiment 5: Two Postretrieval Treatments of Clonidine Are Sufficient to Induce Maximal Disruption of Fear Memories

To assess whether a greater memory impairment could be achieved using a dose of 100 μg/kg, we trained animals as described before but we reactivated them 3 times over 3 days. Following each reactivation session, rats received an injection of clonidine or its vehicle. Rats were also tested 24 h after the last treatment and 1 week later (Figure 5a). A repeated-measures ANOVA revealed a significant main effect of treatment ($F(4, 116)=9.91$, $p<0.01$) and day ($F(4, 116)=26.04$, $p<0.001$), and a treatment × day interaction ($F(4, 116)=2.70$, $p<0.05$). Fisher's post hoc test found a significant decrease in conditioned response for the clonidine-treated group between reactivations 1 and 2 ($F(4, 116)=26.04$, $p<0.001$) and reactivations 2 and 3 ($F(4, 116)=26.04$, $p<0.05$; Figure 5b). Although the third treatment showed a trend toward additional freezing reduction, it did not have a significant additive effect. The post hoc analysis also revealed a significant difference between the treated rats and the controls at days 2, 3, 4, and 12 (all $p<0.01$). Altogether, the results indicate that reconsolidation blockade by clonidine was effective after one treatment and reached its maximum effect after two treatments.

Discussion

This study demonstrates the effectiveness of clonidine in persistently impairing fear memory retention through reconsolidation blockade in male and female rats. We suggest that the combination of memory reactivation sessions followed by clonidine administration represent a potentially novel therapeutic approach to reduce symptoms in PTSD patients.

Dosage and Number of Treatments

All tested doses of clonidine showed effectiveness in reducing postreactivation fear memory retention in a long-lasting and dose-dependent manner. The dose of 100 μg/kg was determined to be optimally effective because it resulted in a greater memory impairment from reactivation to the PR-LTM test than did the 50 μg/kg dose. However, the dose of 200 μg/kg did not induce a larger reduction in freezing than the 100 μg/kg dose, which suggests that the dose–response curve reaches a plateau, and increasing the dose further will not lead to a more substantial decrease in conditioned responding. On the other hand, we did find that the fear memory could be disrupted further with repeated treatments. Indeed, we established that two reactivation sessions followed by a 100 μg/kg clonidine administration were sufficient to induce maximal memory disruption.

Our results are consistent with studies showing that clonidine has detrimental effects on memory. In animals, clonidine has been found to produce memory impairments in several learning paradigms ranging from shuttle box (Hawkins and Monti, 1979; Homayoun et al, 2003) to avoidance tasks (Galeotti et al, 2004; Genkova-Papasova and Lazarova-Bakurova, 1988; Genkova-Papazova et al, 1997) and to cue detection (Smith and Aston-Jones, 2011; Brown et al, 2012). Some studies in humans have also reported memory impairments associated with clonidine administration in healthy subjects (Riekkinen et al, 1999; Hall et al, 2001) and in Alzheimer's disease patients (Jakala et al, 1999a, 1999b).

It is well known that α2-adrenoreceptor agonists can induce sedation (Lakhlani et al, 1997; MacDonald et al, 1997). However, the possibility that a sedative effect of clonidine influenced the behavioral results in our study can be ruled out as we tested the animals 24 h and again 7 days after injection, the time points well beyond the 30–120 min half-life of clonidine in rats (Conway and Jarrott, 1982).

Reconsolidation Specificity

We have shown that postretrieval administration of clonidine is effective in reducing fear-related memory retention. In order to confirm whether reconsolidation is the mechanism underlying the effect, we examined key elements that define the reconsolidation process. First, our results demonstrate that the effect of clonidine is selective to the reactivated memory, as no memory impairment was observed when clonidine was administered without prior reactivation. Furthermore, when animals were tested a week after treatment, we did not observe any spontaneous recovery of the conditioned response.

Spontaneous recovery is a phenomenon found with extinguished memories, but not after reconsolidation blockade (Duvarci and Nader, 2004). As reconsolidation is a time-dependent process that is known to affect long-term but not short-term memory (Nader et al, 2000; Nader and Hardt, 2009), we also tested the animals 4 h after reactivation. The results revealed an intact conditioned response at that time point but impaired behavior the next day. This demonstrates that clonidine affects postreactivation long-term memory, but not short-term memory. Given that this test

was performed only 4 h after clonidine administration, one could argue that the sedative effects of clonidine altered the results at this shorter interval after drug administration. However, the treated rats displayed low levels of freezing during the pre-tone period, indicating an ability to move; thus, the intact freezing levels observed at PR-STM after clonidine administration are unlikely to be attributable to motor impairments due to sedation in these animals. In addition, it is reasonable to believe that the drug was no longer present in the rats' systems at the time of testing because clonidine has a short half-life (30–120 min; Conway and Jarrott, 1982).

Evaluation of the above-mentioned criteria all rule in favor of the implication of reconsolidation processes in the present study. Our results are consistent with several studies investigating reconsolidation blockers either systemically (Debiec and Ledoux, 2004; Blundell et al, 2008; Taubenfeld et al, 2009; Pitman et al, 2011) or intracranially (Nader et al, 2000; Debiec and Ledoux, 2004; Ben Mamou et al, 2006; Jin et al, 2007). Indeed, it is accepted in the literature that the lack of spontaneous recovery, the selectivity to reactivated memories, and the presence of intact short-term memory are criteria that define the reconsolidation process. Taken together, our results suggest that the effect of clonidine on memory is mediated by reconsolidation blockade.

Clinical Relevance

Currently, there are no specific pharmacological approaches to treat PTSD symptoms. Therefore, there is a need for preclinical research to identify new candidate drugs and to develop novel therapeutic interventions. The present study has implications for the potential clinical use of reconsolidation blockade by clonidine. First, we determined that the dose of 100 μg/kg optimally disrupts fear memory retention in both male and female rats. Conversion from the animal dose to a human equivalent dose in mg/kg may be obtained by applying a formula that takes the body surface area into account. With this calculation, our animal dosage of 100 μg/kg translates into a dose of 1.135 mg for a 70-kg person (Reagan-Shaw et al, 2008). Such a dose is well within the safe range for daily human use that has a maximum of 2.4 mg (Physician's Desk Reference; http://www.pdr.net). Nevertheless, as clonidine is known to induce hypotension, patients being treated with clonidine should be medically monitored. We also found that clonidine-induced memory impairments are selective to the reactivated memory. Thus, we can hypothesize that using clonidine in combination with traumatic memory reactivation will decrease the intensity of that memory without disrupting other unrelated memories. Additionally, we observed that postreactivation clonidine does not affect learning of new fear memories, implying that patients would be able to experience and remember new events normally. These are all valuable aspects for clinical use, as optimal treatments should be specific and not interfere with other processes (Steckler and Risbrough, 2011).

Clonidine has been found to improve symptoms such as hyperarousal (Harmon and Riggs, 1996; Donnelly, 2003), impulsivity (Donnelly, 2003) (Viola et al, 1997), and nightmares (Kinzie and Leung, 1989; Kinzie et al, 1994) when administered chronically to patients. However, some experienced a return of symptoms upon termination of treatment (Porter and Bell, 1999), and the possibility that the beneficial effects would decrease over time remains. A significant advantage of reconsolidation blockade by clonidine in treating PTSD symptoms would be that it does not require chronic administration of the drug, as based upon our animal findings the maximal effect would probably be obtained within a few sessions. Consequently, this would make lasting side effects unlikely. Furthermore, we showed that memory disruption following postretrieval clonidine is long lasting; thus, it is reasonable to hope that combining memory reactivation with clonidine administration could permanently weaken PTSD symptoms such as intrusive memories without the possibility of relapse.

Although fear conditioning models the enhanced fear response upon recollection of the traumatic event, this is only one of the many pathophysiological and behavioral characteristics of PTSD.

Nightmares, avoidance, and hyperarousal are common, and alterations of several neurotransmitter systems have also been observed. Further investigations will be necessary to verify whether clonidine can improve other aspects of this complex pathology in an animal model.

In conclusion, results of this study demonstrate that systemic administration of clonidine after retrieval persistently weakens fear memories through reconsolidation blockade. We show that this effect is maximal after two treatments, is present in both male and female rats, is selective to the reconsolidation time window and to reactivated memories, and does not affect further fear learning.

These preclinical findings indicate potential to further develop clinical approaches using clonidine as a reconsolidation blocker in the treatment of PTSD symptoms.

BACK TO TOP

Manualized therapy for PTSD: Flexing the structure of cognitive processing therapy.

Journal of Consulting and Clinical Psychology
Galovski TE, Blain LM; Mott JM, Elwood L, Houle T.
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Abstract

Objective: This study tested a modified cognitive processing therapy (MCPT) intervention designed as a more flexible administration of the protocol. Number of sessions was determined by client progress toward a priori defined end-state criteria, "stressor sessions" were inserted when necessary, and therapy was conducted by novice CPT clinicians.

Method: A randomized, controlled, repeated measures, semicrossover design was utilized (a) to test the relative efficacy of the MCPT intervention compared with a symptom-monitoring delayed treatment (SMDT) condition and (b) to assess within-group variation in change with a sample of 100 male and female interpersonal trauma survivors with posttraumatic stress disorder (PTSD).

Results: Hierarchical linear modeling analyses revealed that MCPT evidenced greater improvement on all primary (PTSD and depression) and secondary (guilt, quality of life, general mental health, social functioning, and health perceptions) outcomes compared with SMDT. After the conclusion of SMDT, participants crossed over to MCPT, resulting in a combined MCPT sample (n = 69). Of the 50 participants who completed MCPT, 58% reached end-state criteria prior to the 12th session, 8% at Session 12, and 34% between Sessions 12 and 18. Maintenance of

treatment gains was found at the 3-month follow-up, with only 2 of the treated sample meeting criteria for PTSD. Use of stressor sessions did not result in poorer treatment outcomes.

Conclusions: Findings suggest that individuals respond at a variable rate to CPT, with significant benefit from additional therapy when indicated and excellent maintenance of gains. Insertion of stressor sessions did not alter the efficacy of the therapy.

BACK TO TOP

Peers and Peer-Based Interventions in Supporting Reintegration and Mental Health Among National Guard Soldiers: A Qualitative Study

Military Medicine
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December 2012

ABSTRACT

National Guard soldiers experience high levels of mental health symptoms following deployment to Iraq and Afghanistan, yet many do not seek treatment. We interviewed 30 National Guard soldiers with prior deployments to Iraq or Afghanistan to assess mental health treatment barriers and the role of peers in treatment engagement. Interview transcripts were analyzed by a multidisciplinary research team using techniques drawn from grounded theory. The following themes were identified: (1) personal acceptance of having a mental health problem rather than treatment access is the major barrier to treatment entry; (2) tightly connected, supportive peer networks can decrease stigma related to mental health problems and encourage treatment; however, soldiers in impoverished or conflicted peer networks are less likely to receive these benefits; and (3) soldiers are generally positive about the idea of peer-based programs to improve treatment engagement, although they note the importance of leadership support, peer assignment, and unit specialty in implementing these programs. We conclude that some, but not all, naturally occurring peer networks serve to overcome stigma and encourage mental health treatment seeking by soldiers. Formal peer-based programs may assist soldiers not sufficiently benefitting from natural peer networks, although there are barriers to implementation.

INTRODUCTION

Approximately 40% of Army National Guard soldiers have an identified mental health problem 3 months after returning from deployment to a combat zone, and yet only 50% of these soldiers access mental health services. National Guard soldiers experience further increase in mental health problems during the 12 months postdeployment, likely because deactivated National Guard soldiers face the challenges of reintegrating

into civilian work and family life and are no longer embedded in a military infrastructure that provides continuous social support and easily accessible mental health services.

Given the high rate of mental health needs among National Guard service members and limited access to military treatment facilities, reducing the barriers to engaging in community care is likely a critical step in improving outcomes. Soldiers have reported stigma, negative perceptions of mental health treatment, and logistical concerns (e.g., scheduling appointments, getting time off work) as the primary barriers to mental health treatment seeking. Stigma, particularly being perceived as “weak,” was reported as a concern by 65% of soldiers returning from Iraq and Afghanistan who screened positive for a mental health problem. National Guard veterans who served in Iraq also reported concerns that seeking mental health treatment could result in being labeled as “crazy” and affect perceptions of one's leadership abilities, fitness to be deployed, or likelihood of promotion.

Organized peer outreach among National Guard soldiers may be one method for reducing stigma and increasing engagement in care for those with mental health needs. Peers could also limit treatment seeking by reinforcing stigma or, alternatively, by reducing stress and the perceived or actual need for treatment. To date, data on the acceptability and potential efficacy of formal peer programs in helping soldiers cope with mental health problems or seek treatment are limited.

We conducted a series of focus groups and individual interviews of National Guard soldiers who recently returned from deployment in Iraq or Afghanistan to assess the role of peers and peer-based interventions in addressing stressors and mental health conditions that arise during reintegration. The study was intended to provide useful information for military organizations considering implementing formal peer support services.

METHODS

Study Participants

We recruited a convenience sample of National Guard soldiers in a Midwestern state for focus groups and individual interviews during reintegration weekend events or during drill weekends at National Guard armories. Participants were recruited through sign-up sheets after the study was verbally described in a group presentation. Potential participants were informed the purpose of the focus groups/interviews was to “better inform services intended to improve the emotional health of returning soldiers and their families.” Soldiers were given the option of participating in person or by phone. Any National Guard member with a deployment since 2001 was eligible for participation. The study was conducted with approval from a Veterans Affairs Health System and two university institutional review boards.

Data Collection

Focus groups and semistructured individual interviews were conducted from April 2009 to December 2010. Data collection protocols were developed by study team members based on the research questions and using an iterative process (P.P., M.V., and A.B.) to address the following

domains: soldiers' experience with mental health problems, perceived barriers to treatment, possible solutions to these barriers, and the role of peers and peer services. Protocols for interviews and focus groups were identical except for minor changes to wording and ordering.

Interview and focus group sessions were led by four of the authors (P.P., A.B., M.V., and J.F.) and two master's level research assistants. Focus groups and in-person interviews were conducted at two university settings. Study researchers decided to include individual interviews in addition to focus groups because of concerns that participants may be less willing to discuss sensitive aspects of mental health in group settings. Phone interviews were conducted for those who indicated that they were not able to participate in person. Sessions lasted 20 to 80 minutes and were digitally audiorecorded. Participants were provided $50 gift cards after completing the interview or focus group.

Data Analysis

Digital recordings of the focus groups and interviews were transcribed verbatim. Data collection and analysis were conducted concurrently. For each transcript, at least 2 study team members, including a study team member who had not conducted the interview or focus group, read through and completed a structured memo (developed by J.F.) summarizing initial prominent themes from the interview in relation to the primary research questions. Memos were then discussed by the team, and cross-cutting themes were identified using a group consensus process to facilitate and enrich data interpretation and document team findings. Interview guides were modified approximately halfway through the study to collect data on new themes discovered during data collection and concurrent analysis and to further explore prominent themes that were included in the original interview guide. Additional interviews and focus groups were completed until informational saturation of themes had occurred. Codes and their definitions were developed for the identified themes by two study team members (P.P. and J.F.) to exhaustively identify data relevant to each theme. Two study team members (P.P. and E.M.) independently coded three transcripts, compared coding, and achieved consensus on application of the codes to the data. The remaining transcripts were coded by one study team member (E.M.). The codes were then applied to the text of each transcript using NVivo 8 software. Summaries of the text in each code were used by the team to verify the validity of the themes and ensure understanding of variation within themes.

Methodological rigor was enhanced through participation of team members from several disciplines (i.e., psychology, psychiatry, public health), rigorous data collection and code development, and the iterative consensus process.

RESULTS

We conducted 14 individual interviews and 4 focus groups, collecting data from a total of 30 participants. Twelve individual interviews were conducted in person and 2 were conducted by phone. Participants were predominantly male and married, and they had a diverse range of military experience. The major themes identified from the analyses were (1) personal acceptance of having a mental health problem, rather than treatment access, was the major barrier to treatment seeking; (2) the role of peers in treatment seeking depends on the characteristics of a soldier's peer network, which varies from highly supportive to impoverished or conflicted; and (3) soldiers generally had positive responses to the idea of a peer-based program to identify postdeployment mental health treatment needs but were concerned about how it would work in practice.

Major Barriers to Treatment Seeking

The most frequent reason for not seeking help for mental health concerns was described as soldiers failing to recognize or having difficulty admitting to themselves that they needed help. This was often described in the context of military culture and training, which encourages self-reliance and perseverance. Difficulty in personally accepting having a mental health issue was more often described as a form of self-stigma (i.e., viewing oneself as weak), rather than explicit concern about being judged or treated differently by others (i.e., external stigma). A squad leader who had been with the Guard for 3 years described the process soldiers go through in deciding to seek help as: “I think some of them are unsure that, they don't really know if they have a problem or not. I guess it's really sitting down and convincing themselves that they have a problem or that there is an issue. I mean you want to lie to yourself about, ‘I don't need any help, I'm good’, but I think that's probably the biggest thing.”

External stigma, i.e., concerns about being treated differently for addressing a mental health problem, were described as declining within the military and progressively less of a barrier to treatment. Participants noted that the overall Army, the Army National Guard, and high-ranking officers encouraged soldiers to seek treatment if needed and that the necessary information and resources are available. However, participants reported that they believed the consequences of disclosing mental health problems or treatment seeking varied depending on rank and responsibilities. As one participant in a transportation unit said “We're just a bunch of truck drivers and mechanics and no security clearance needed, so I can't imagine anything would affect a career at all.” In contrast, some respondents described soldiers being reluctant to seek mental health treatment because they were concerned that it would harm their career—for example, it could be the deciding factor when competing for a promotion when everything else was equal. A minority of respondents reported being skeptical of increased acceptance of mental conditions and treatment in the military culture, exemplified by the statement, “regardless of what all the reports say, regardless of what the Army says, there absolutely is a stigma associated with seeking help.”

Living far away from military or veteran counseling resources, timeliness and flexibility of appointments, and mismatch with treatment providers were also mentioned as barriers but were generally described as problems with continuing care rather than affecting the initial decision to seek treatment.

Role of Peer Networks on Treatment Seeking

Participants varied considerably on their assessment of the degree to which social ties formed during deployment could play a role in later help seeking. Based on the respondents' descriptions, we have characterized these informal, naturally occurring support networks among soldier peer groups as one of three types: tightly connected and supportive, impoverished, and conflicted.

Tightly Connected and Supportive Networks

These networks were described by several participants and were characterized by frequent contact among soldiers who served together during deployment. Contact could occur either in-person, by phone, e-mail, or on social network sites like Facebook. Participants in supportive peer networks shared problems with each other related to reintegration and mental health. A typical interaction was described as, “One of my friends, he has been going to the VA and getting help as well, he and I talk where he's, you know, had a blow-up at Wal-Mart because some lady cut in

front of him with her cart or something and so we share our funny stories like that. We're like, we might've overreacted in that instance but we're able to discuss and say, 'Hey, that's not right, we probably shouldn't do that next time.'"

When a mental health problem becomes known or suspected, participants in supportive networks described checking in more frequently with that soldier and offering to talk or socialize, as one participant put it, "Even if it's just pick him up and have a few beers with him and let him spill. That might be all they need." When problems appeared to be escalating or severe, respondents described sometimes intervening as a small group to influence a soldier to get help. One such encounter was described as "We use peer pressure and just you know, a couple of us will get together and be like, 'So what you gonna do, just grow a beard and live in a basement? Like control yourself,' and it just, and it clicked with them like, man, this guy, you know obviously we care enough to ask and we've already saw a pattern of that behavior developing while we were over there because of issues and then you say, 'Okay, hey man? You want to live like a hermit or something?' That's when they start saying, 'Yeah, you know what? Maybe I need to go get some help.'"

Another participant described contact from a peer as potentially lifesaving, "One night I found myself in my house with a handgun in my hand and bullet in the chamber, pointing it at my face and fortunately a very good friend of mine called me just to see how I was doing and I went and got help … [He] just happened to call me at home and say, you know, 'How's it going? Everything going okay', you know, and 'we haven't talked in a couple of days' and it was, I don't know, I don't know if anyone here believes in divine intervention but there's a reason that person called me that day and I'm not saying that you know, that somehow magically the angels came down and I felt better and everything but I realized that that wasn't the way to deal with it."

Impoverished Networks

Several participants reported losing contact with other soldiers after deployment, usually as a result of living a long distance from those with whom they deployed or because fellow soldiers were promoted to serve with other units. In some cases, particularly if strong family support was lacking, these participants felt isolated and would have preferred greater interaction with their peers. Participants also described some soldiers (or themselves) as outliers, either "loners" or "the asshole of the group," who were readily identifiable but never integrated into a support networks before, during, or after deployment.

Conflicted Networks

These networks were characterized by competing cliques within the network, such that individuals felt supported by a few close peers but could not trust members of the other cliques. Unit leadership was sometimes described as encouraging this competition or picking favorites. Participants who experienced these networks described a chilling effect when it came to discussing or seeking help for mental health problems because of the concerns that sharing sensitive personal information could eventually be used against you. One participant described his unit as made up of these networks: "This unit actually that I'm in now which, I mean it's, there's a few guys, a few teams in squads that stick together and look out for each other and help each other but I'd say the majority of them are a bunch of backstabbers, being that the smallest mistake, everybody somehow knows about … That's actually a way to tell how tight the team is, is whether they talk about serious personal issues so there's only a few

occasions where that's mentioned and that just goes to show ya that nobody talks about that stuff because there's nobody to talk to or it may be used against you later on down the road."

Peer-Based Programs to Improve Treatment Seeking

Participants were generally supportive of the concept of a formal peer-based program to monitor soldiers for mental health concerns and facilitate treatment seeking, often responding that it is a good idea and has the potential to help reduce both self and external stigma. One respondent suggested that a peer-based program would be particularly effective at addressing stigma if a soldier who was respected for being strong discussed his own issues; other soldiers may then be more willing to accept that their own problems are not a sign of weakness and join in the discussion. Eventually this could lead to soldiers being more likely to seek treatment because, "the first step is being receptive to talking about it with their buddies, then they certainly [w]ould be more accepting [of] discussing it with somebody else."

Successful Implementation of a Peer-Based Program May Vary by Support Network

Participants noted that the effectiveness of a peer-based program to improve treatment seeking would depend on the soldier's existing social group or network. For participants already in tightly connected in supportive networks, there was concern that a peer-based program would be redundant with what was occurring naturally and that formalizing their interactions (e.g., requiring soldiers to call one another at regular intervals or complete check-in reports) might introduce an unnecessary or counterproductive element of artificiality. For participants in conflicted networks, a peer program was considered unlikely to be effective because of the concerns that sharing information could be used against them.

A peer-based program was thought to be particularly likely to be helpful to participants within impoverished networks who would prefer more support but were no longer in regular contact their peers because of geographic separation, operating out of different units, or lacking initiative to maintain ties over time. However, for outliers who never integrated into soldier support networks, respondents expressed skepticism about whether a peer-based program after deployment could successfully reach them. Participants frequently stated that if someone does not want help then there is nothing that anyone else can do for them. A minority of participants felt that there could be a chance for success in reaching out to service members who had not developed strong natural supports, but that it would take a particularly savvy peer soldier to accomplish this. One participant addressed this issue by saying, "You can't approach an asshole with a submissive mindset. It's almost like being able to read the person, your adaptability …. If you approach them as a result-oriented person and say, 'You look like a person that needs results. Well let's get you some results' and then you start introducing them your ideas … they might be more receptive to it …. Some people are just like, 'Well he's an asshole and that's how it's going to be' so they don't even try to get him help because they think he's unreachable. But he's still human, so, everybody's reachable."

Other Concerns Regarding Implementation of a Peer-Based Support Service

In general, participants indicated that whether or not someone would discuss a mental problem with a peer would be largely related to the existing relationship they have with the peer contacting them and whether they trusted and respected that person. As one participant described, "It'd depend upon who it was that called me. If it was some officer from a section that I don't even know, I might hesitate … Buddy to buddy, so friend

to friend, person that you know to person that you know, not someone assigned to the unit as a secondary duty. And you're going to call everyone in the entire unit? Some of the people you don't even know how to pronounce their names, let alone know what they look like, and you're going to ask them how they're doing? You're probably going to get a response with 'Well fine sir, but who are you? I don't even know who you are.'"

The success of a peer-based program was noted also to depend heavily on local implementation in terms of how it is presented and supported by leadership. Implementation strategies may also need to be tailored according to the operational role or specialty of units. As one participant described, "Well the buddy system is actually a brilliant idea but unfortunately that is out of your hands and that's down to the unit itself, it's how the unit works. You're going to have better luck with that with combat arms units than you are with an admin unit. I mean admin, it's all office politics, all day every day. The combat arms unit, it's like, 'you know what, let's get this shit over with, so let's all work together.'"

DISCUSSION

Our findings provide new insights into a culture of increasing awareness and acceptance of mental health problems within the National Guard, the variable role of peer networks in detecting and supporting mental health concerns, and the potential role of peer-based interventions to improve mental health treatment seeking.

Knowledge of mental health problems experienced either firsthand or by fellow soldiers was commonplace among those we interviewed, indirectly suggesting mental health concerns among soldiers often were not hidden out of shame or fear of repercussions. When asked directly about the consequences of seeking mental health treatment, there were mixed opinions regarding whether it could potentially affect career advancement or result in judgment by peers, but there were very few examples of soldiers actually experiencing negative consequences. This is in contrast to a qualitative study of National Guard soldiers conducted in 2006 which reported greater concerns among soldiers about being labeled or experiencing adverse career consequences for receiving mental health treatment. Soldiers we interviewed also perceived military leadership as working to raise awareness and encourage soldiers to get treatment. Together, these findings suggest the military culture overall has moved in the direction of accepting and openly addressing the mental health needs of soldiers. Despite the decline in external consequences for seeking mental health care, self-stigma (i.e., sense of oneself as being "weak" for seeking help) remained as a primary barrier to treatment.

We found the role of naturally occurring peer networks in counteracting stigma likely depended on whether soldiers existed in one of three types of peer networks. Soldiers with tightly connected and supportive peer networks described instances of sharing mental health concerns with one another and banding together to pressure soldiers into seeking treatment when problems become severe. Thus, when these natural support networks work well, they could play an important role in providing social support that buffers against the development of mental health conditions while also normalizing and facilitating mental health treatment when necessary. Soldiers in impoverished or conflicted peer networks appeared much less likely to seek mental health treatment based on interactions with their peers. In impoverished peer networks, soldiers have less frequent interactions with other soldiers and therefore fewer opportunities for support, normalizing, or encouragement for treatment. In conflicted networks, soldiers may obtain support from their few closest peers but may be more concerned about seeking mental health treatment because of a greater possibility of negative repercussions.

Peer-based interventions could address some of the shortcomings of natural support networks and enhance mental health treatment engagement; however, many challenges to implementation were raised. Regardless of the peer network, the success of formalized peer support intervention would largely depend on whether the soldiers had a preexisting trusting relationship. Soldiers are unlikely to disclose mental health concerns to other soldiers, including leaders, they do not trust and would prefer to choose who will be involved in their peer support network. Some soldiers will simply not discuss mental health concerns with other soldiers. Unfortunately, soldiers with mental health needs are more likely to be concerned about stigma, and therefore, the soldiers most likely to benefit from peer outreach may also be the most resistant to it.[4] Alternative methods such as direct involvement by unit leadership or attempts to involve non-National Guard supports may be more successful when a problem is suspected and peer outreach is unsuccessful. Soldiers in impoverished networks who are the “loners” or “assholes” are likely to fit into this category.

Peer-based interventions deployed in conflicted networks may have a greater chance for success if there is also a concerted effort from leadership to disabuse the perception that mental health treatment seeking could be used against someone or affect their career in any way.

This study is limited in that participants who volunteered to discuss mental health issues within the military may not be representative of National Guard soldiers in general. As with most qualitative studies, our goal was to understand a phenomenon, rather than to generalize findings from the study sample to a population. Therefore, we recruited participants from whom we could learn the most about the topic under study or “information-rich cases.” Nonetheless, soldiers who did not volunteer to participate may perceive greater stigma related to mental health treatment or may view peer services less favorably. Our sample also included only one female soldier. Additional studies are indicated to assess the barriers to mental health treatment and the role of peers among women and other minorities in the military. We note, however, that our sample consisted of soldiers from different units and geographic regions, included soldiers of different ages and ranks, and had a wide range of views and experiences related to mental health treatment.

In summary, peer-based interventions to augment natural soldier social support networks were regarded as acceptable to National Guard soldiers during the challenging period of reintegration when mental health problems are prevalent and treatment seeking is limited, potentially because of self-stigma. The effectiveness of peer-based interventions is likely to be dependent on the type of existing peer networks into which the interventions are deployed. Peers conducting outreach should have an established trusting relationship with soldiers they are contacting. Alternative outreach strategies should also be considered for soldiers unwilling to discuss apparent mental health problems with their peers.

BACK TO TOP

Sexual Health

Evaluation of HIV Postexposure Prophylaxis for Occupational and Nonoccupational Exposures at a Deployed U.S. Military Trauma Hospital

Military Medicine

December 2012

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Abstract

Objective: Postexposure prophylaxis (PEP) is an important strategy to prevent human immunodeficiency virus acquisition after occupational and nonoccupational exposures. Since exposures to blood and other body fluids commonly occur in a combat setting, it is important to evaluate PEP utilization in the deployed environment. Methods: This is a retrospective review of Public Health, pharmacy, and medical records for PEP cases at a U.S. military trauma hospital in Afghanistan from February 1, 2007 through June 30, 2012. The decision to initiate PEP and the antiretroviral regimens selected were also evaluated for concordance with published Centers for Disease Control (CDC) guidelines. Results: At total of 31 cases were prescribed PEP over the 65-month study period, including 27 occupational and 4 nonoccupational exposures. Of the 23 cases with sufficient data for evaluation, 18 (78.2%) initiated PEP in concordance with CDC guidelines and the discordant cases were prescribed PEP secondary to patient request. Antiretroviral regimens were in concordance with CDC guidelines in 27 of 31 (87.1%) cases, with most discordant cases prescribed differing durations of PEP. Conclusions: Despite the challenges of health care delivery in a deployed environment, the decisions to initiate human immunodeficiency virus PEP and the selection of antiretroviral regimens were typically concordant with CDC guidelines.

Background

The human immunodeficiency virus (HIV) targets CD4+ T cells leading to immune destruction and eventually the development of acquired immunodeficiency syndrome in untreated cases. HIV is typically transmitted by sexual contact, intravenous drug use, or by mother-to-child transmission. For the military population, sexual contact is the primary method of HIV transmission since prenatal care is readily available and intravenous drug use is rare with an incidence of <1%.1 However, military personnel may incur additional risks for contracting HIV infection during military operations, especially combat settings and during humanitarian missions. This is principally because of exposures to blood and other body fluids as a result of traumatic injuries or by occupational exposures that occur during the provision of health care in these environments.

The overall risk of HIV transmission is estimated to be 0.3% for percutaneous exposures,2 0.09% for mucocutaneous exposures,3 and between 0.1% and 30% for sexual contact depending on the nature of the exposure.4,5 In order to protect exposed persons from acquiring HIV, antiretroviral drugs are often prescribed for postexposure prophylaxis (PEP). The strategy of HIV PEP can be used in the setting of occupational injuries, such as needlesticks and mucocutaneous splash injuries, as well as for nonoccupational (typically sexual) exposures where prophylaxis is termed nonoccupational PEP. Although there are no randomized control trials to demonstrate the efficacy of PEP, a case–control study showed that health care workers who received zidovudine after needlestick injuries were 81% less likely to seroconvert to HIV-positive as a result of the exposure.6 Based on safety and feasibility data for the use of antiretrovirals in this setting, many organizations have developed guidelines for HIV PEP, including the Centers for Disease Control (CDC). Although guidelines were developed to provide recommendations for the initiation of HIV PEP and the selection of antiretroviral regimens, utilization of PEP in clinical practice may differ from published guidelines.7,8

The delivery of health care in the deployed setting poses many challenges because of the complexities of the combat environment and potential limitation in resources. In previous reports from U.S. military trauma hospitals in Iraq and Afghanistan, occupational exposures to blood and body fluids were relatively common with 6.5 and 8.6 exposures per 100 persons each year, respectively (J.F. Okulicz, submitted).9 Although occupational exposures have been well characterized, the utilization of HIV PEP has not been previously reported in a deployed setting. In this study, our first focus was to describe PEP use and exposure scenarios encountered in a U.S. military trauma hospital in Afghanistan. Since both the decision to initiate PEP and the subsequent choice of antiretroviral regimen can be variable, the second focus of our study was to determine if the administration of PEP was in concordance with published CDC guidelines.

Methods

Hospital Facility

Craig Joint Theater Hospital in Bagram Air Field, Afghanistan, provides trauma and medical care to coalition personnel, including U.S. and NATO active duty military members and contractors, as well as Afghans and third-country nationals. The hospital has a 10-bed intensive care unit and a 20-bed inpatient ward; however, bed capacity can increase to a maximum of 33 intensive care and 63 ward beds when a large number of casualties require care. The facility also contains outpatient medical, surgical, dental, and immunization clinics, as well as an inpatient/outpatient pharmacy. In the year 2011, there was a monthly average of 287 hospital admissions and 3,652 outpatient encounters. This project was approved by the Joint Casualty Research Team as part of a performance improvement project.

Data Collection

Pharmacy records were reviewed for dispensing of antiretrovirals between February 1, 2007 and June 30, 2012. The antiretrovirals studied were those available on the U.S. Central Command (CENTCOM) formulary, including nucleoside reverse transcriptase inhibitors zidovudine–lamivudine for a 2-drug regimen and the addition of either the protease inhibitor lopinavir–ritonavir or the non-nucleoside reverse transcriptase inhibitor efavirenz for 3-drug regimens. For the protease inhibitor class, low-dose ritonavir is not considered an active drug and is only used for the purpose of “boosting” the plasma levels of another co-administered protease inhibitor such as lopinavir.10 Medical and Public Health records were examined to collect data for each case prescribed antiretrovirals. Since HIV infection is a nondeployable condition and newly diagnosed cases are not typically treated in the deployed setting, all antiretrovirals dispensed in this study were for the purposes of HIV PEP.

CDC guidelines for prescribing HIV PEP for occupational and nonoccupational exposures were last published in 2005.11,12 Occupational exposures include percutaneous injuries, such as a “needlestick” or laceration with a sharp object, and mucocutaneous exposures to mucous membranes or nonintact skin with blood and other body fluids that are potentially infected with HIV. In addition to blood and visibly bloody body fluids, vaginal secretions and semen are also considered potentially infectious. CDC recommendations for the initiation of PEP for occupational exposures generally depend on the type of exposure and the HIV status of the source patient. Consideration for initiating PEP also depends on the presence of high-risk features for HIV transmission. For example, higher risk features of percutaneous exposures include a needle used to cannulate a blood vessel, visible blood on the surface of the instrument, deep needlesticks, and advanced HIV disease in the source patient have

all been shown to increase the risk of HIV seroconversion.6 For nonoccupational exposures, the body site of exposure (i.e., oral, vaginal, or rectal for sexual exposures) and the HIV status of the source person are important factors for the decision to initiate PEP.

CDC guidelines recommend 28 days of prophylaxis with either 2-drug or 3-drug antiretroviral regimens which, per CENTCOM formulary, include a preferred basic 2-drug regimen of zidovudine–lamivudine, and the preferred agent lopinavir–ritonavir or alternative drug efavirenz for expanded 3-drug regimens. For nonoccupational exposures, CDC guidelines recommend 3-drug regimens; however, clinicians and patients who are concerned about potential toxicity and adherence can consider a 2-drug regimen as an alternative.11 For both occupational and nonoccupational exposures, PEP is usually considered if the exposure occurred within the past 72 hours.

Methods

Cases of occupational and nonoccupational exposures for which PEP was prescribed were evaluated for concordance or discordance with current CDC guidelines.11,12 First, the decision to initiate PEP was evaluated based on the time from exposure (≤72 hours) and the categories and algorithms listed in Table I and Figure 1, respectively. For the purposes of this study, scenarios in which CDC guidelines state “generally, no PEP warranted” and the patient requested PEP, or if the recommendation is on a “case-by-case determination,” the decision to initiate PEP was considered to be in accordance with CDC guidelines unless prescribed >72 hours after exposure.

Second, the prescribed regimen was evaluated for concordance with CDC guidelines based on the decision to prescribe a 2-drug versus 3-drug regimen, as well as dose, frequency, and duration of PEP. CDC guidelines recommend twice daily dosing for zidovudine–lamivudine (300 mg/150 mg fixed dose tablet). In combination with zidovudine–lamivudine for expanded regimens, lopinavir–ritonavir (200 mg/50 mg fixed dose tablet) is dosed 2 tablets twice daily or, as an alternative, efavirenz (600 mg tablet) is dosed once daily at bedtime. Outcomes of PEP, including tolerability, reasons for discontinuing PEP, and follow-up testing for HIV seroconversion were also reviewed.

Results

Of the 31 cases prescribed PEP, 23 cases had sufficient data to evaluate for concordance with CDC guidelines. For occupational exposures, 16 percutaneous and 3 mucocutaneous exposures were evaluated. Of these 19 cases, 14 (73.7%) were in-hospital occupational exposures and the remaining occurred at other military camps or among the local civilian population. Specifically, cases no. 2, 4, and 14 occurred in medics drawing blood in local villages and cases no. 8 and 16 occurred in security forces personnel while performing routine bag inspections, with a needlestick and a laceration from a personal razor, respectively. HIV risk factors were reported in 2 cases involving Afghan source patients, with one testing positive for both hepatitis B and C (case no. 13) and the second involving a source patient with diffuse cutaneous mulluscum contagiosum and a history of multiple unprotected sexual encounters (case no. 15).

Most percutaneous exposures were determined to be CDC risk less severe (n = 8; 50%) and involved source patients of unknown HIV status (n = 11; 69%). The 3 mucocutaneous exposures were from sources with unknown HIV status and involved splashes to the eyes; 2 with blood and 1 with nonbloody urine. The decision to initiate PEP was in concordance with CDC guidelines in 17 of 19 (89.5%) occupational exposure cases. For

the first discordant case (no. 14), the exposed patient was prescribed PEP even though the source patient had tested negative for HIV infection. The second discordant case (no. 17) involved the initiation of PEP for an ocular exposure with nonbloody urine.

For nonoccupational exposures, all 4 identified cases were evaluated for concordance or discordance with CDC guidelines. Each case was considered "substantial exposure risk" from a source with unknown HIV status. HIV risk factors were known in 2 cases where the exposed patient had sexual exposures with a commercial sex worker. The decision to initiate PEP was in concordance with CDC guidelines in 3 of 4 (75%) cases, with one discordant case prescribed PEP at the request of the exposed patient 11 days after unprotected oral sex with a commercial sex worker.

Evaluation of PEP Regimens

All 31 PEP regimens were evaluated, with 27 (87.1%) cases concordant with CDC guidelines for regimen selection, dose, frequency, and duration of therapy. Of the 4 discordant cases, 3 were as a result of differing durations of therapy. In contrast to the recommended 4 weeks of PEP, two cases were prescribed PEP for ≥6 weeks (case no. 5 and an additional case not shown) and 1 case was prescribed PEP for 2 weeks (case no. 6). The remaining discordant case (no. 8) was prescribed zidovudine–lamivudine three times daily rather than the twice daily recommended dose.

Zidovudine–lamivudine 2-drug regimens were prescribed in 30 cases (96.8%), with the remaining case prescribed a 3-drug regimen including efavirenz. Although the single case prescribed a 3-drug regimen involved a source patient with "unknown HIV status"(case no. 15), the provider presumed the source patient was HIV-infected as a result of the presence of diffuse cutaneous molluscum contagiosum, a history of multiple unprotected sexual encounters, and refusal to be tested for HIV infection. Since 3-drug PEP is recommended for "more severe" exposures in an HIV-infected source patient (Class 1 or 2), the decision to treat with a 3-drug regimen in this case was determined to be in concordance with CDC guidelines. The provider also indicated a preference to prescribe lopinavir–ritonavir as the third drug for expanded PEP; however, lopinavir–ritonavir was not available and efavirenz was chosen as an alternative agent.

Outcomes of PEP

Of the 22 cases with data regarding the discontinuation of PEP, 11 (50%) exposed patients stopped PEP after the source patient tested negative for HIV by rapid testing, 10 (45.5%) completed the entire course, and 1 (4.5%) discontinued 2-drug PEP after 4 days secondary to abdominal discomfort and diarrhea (case no. 21). After excluding the 12 cases in which the source patient tested negative for HIV, 19 cases were reviewed for potential HIV seroconversion in the exposed patient. Of these, 16 patients had complete follow-up data and there were no reported cases of HIV seroconversion.

Discussion

Health care providers in a deployed environment commonly encounter blood and other body fluid exposure scenarios where HIV PEP may be indicated. In our study, we found that PEP was prescribed approximately 6 times per year at a U.S. military trauma hospital in Afghanistan. The

decisions to initiate PEP and the selection of antiretroviral regimens were typically concordant with CDC guidelines. Although the majority of occupational exposures occurred in the hospital, one-fourth of these cases occurred in outlying military camps or in local civilian villages, with all outside cases initiating PEP within 24 hours because of rapid transport to our hospital for evaluation. In a deployed environment, this scenario poses a considerable challenge for initiating antiretrovirals in a timely manner and providing the comprehensive evaluation and follow-up necessary when prescribing PEP. Since nonoccupational exposures were also recorded, additional educational outreach may be necessary in deployed settings.

The decision to initiate PEP is highly dependent on the type of blood and other body fluid exposure and the HIV status of the source patient. Rapid assays for detecting bloodborne pathogens have been used for several years in the deployed setting because of the high sensitivity and specificity of these platforms13. For example, another study from our hospital showed no false negative or positive results by HIV rapid testing compared to standard HIV antibody testing in 54 source patients (J.F. Okulicz, submitted). Thus, the use of rapid tests to exclude HIV infection in source patients appears to be appropriate in the deployed setting. Although exposure characteristics can usually be ascertained by history from the exposed patient, the HIV status of the source patient is often unknown. In our study, nearly half of the cases prescribed PEP involved either unknown source patients or scenarios where the source patient was unavailable for HIV testing. In these situations, HIV prevalence data in the local population can be used to help estimate the risk of HIV transmission to the exposed patient. In Afghanistan, however, the HIV prevalence in the local population is incompletely understood. A study of injection drug users in 3 large Afghan cities reported an HIV prevalence of 1.8%, whereas another report of Afghan refugees in Pakistan showed a prevalence of 5.9%.14,15 In contrast, a study of 4,452 intrapartum women in Kabul, Afghanistan, had no reported cases of HIV infection.16 The limited testing and reporting of HIV infections in Afghanistan poses challenges for evaluating scenarios where the HIV status of the source patient is unknown. As a result, it is reasonable for clinicians to have a more aggressive approach to PEP in Afghanistan or other areas where HIV prevalence is incompletely defined. Although source patients that are U.S. military members are presumed to be very low risk because of mandatory HIV screening before deployment, it should be noted that cases of HIV-positive service members have been identified during deployment.17

In contrast to countries with limited public health data regarding HIV infection, military operations performed in areas with high HIV prevalence pose several additional challenges. For example, there are 9 countries in Sub-Saharan Africa with an HIV prevalence of >10%, with Swaziland the highest at 26%.18 In these high prevalence areas, the probability for HIV infection in an unknown source patient is estimated to be much higher and PEP should be strongly considered. World Health Organization HIV treatment guidelines are utilized in Sub-Saharan Africa and typically include zidovudine–lamivudine plus a non-nucleoside reverse transcriptase inhibitor such as nevirapine or efavirenz for initial therapy in HIV-infected patients.19 Nevirapine is also commonly used to prevent mother-to-child transmission of HIV during the peripartum period. Because of widespread use, drug resistance to these antiretrovirals may be present in the local HIV-infected population. If antiretroviral drug resistance to these agents is present in the source patient, then prescribing the same agents for PEP may not be efficacious in preventing HIV seroconversion in the exposed patient. This is particularly important if an non-nucleoside reverse transcriptase inhibitor is chosen as the third drug for PEP since this antiretroviral class has a low genetic barrier for resistance and requires only a single mutation to develop high-level resistance.10 In contrast, the protease inhibitor lopinavir–ritonavir has a high genetic barrier to resistance, requiring a minimum of 3 or more mutations to develop high-level resistance.20,21 Based on the current CENTCOM formulary, the use of lopinavir–ritonavir in combination with zidovudine–lamivudine should be

preferred for military personnel with blood and other body fluid exposures in areas with high HIV prevalence because of the higher genetic barrier of resistance for protease inhibitors compared to non-nucleoside reverse transcriptase inhibitors.

In addition to guidelines for occupational and nonoccupational exposures, the CDC has also published guidelines for PEP following blast injuries.22 This is relevant to the military population as a result of the high frequency of blast injuries encountered during Operation Iraqi Freedom and Operation Enduring Freedom. Blood and body fluid exposures may result from injured victims in the vicinity of the blast or from enemy combatants such as suicide bombers. CDC guidelines state that HIV PEP is generally not warranted following blast injuries, unless the exposure is to a known or highly likely HIV-infected source. Since no data is available regarding HIV transmission following blast exposures, PEP may be considered during military operations when the local HIV prevalence is high or if there is suspicion of HIV-infected source patient(s) in the area where the blast occurred. This could not be evaluated in our study as there were no cases prescribed PEP secondary to blood and other body fluid exposures from blast injuries.

The decision to initiate PEP in our study was concordant with CDC guidelines in 87% of cases, with all discordant cases given PEP secondary to patient request. In clinical practice, overtreatment of occupational exposures is common.7 This conservative approach is often chosen to give the best opportunity to avoid HIV seroconversion, even in low-risk scenarios. The negative aspects to overtreatment include the potential for adverse drug reactions and the cost of treatment. From the patient perspective, offering PEP provides reassurance that everything possible is being done to prevent HIV transmission. There is evidence that this conservative approach is effective, as there have been no new cases of HIV transmission from occupational exposures in the United States in more than 5 years and very few cases of serious toxicities from PEP have been reported.7

Antiretroviral regimen selection and prescribing was also highly concordant with CDC guidelines in our study. The majority of discordant results were attributable to differing lengths of therapy with 2 cases prescribed ≥6 weeks and another prescribed 2 weeks of PEP. The recommendation of 4 weeks of PEP is widely accepted as the standard duration for PEP. This is largely derived from nonhuman primate macaque models, which showed that shorter courses of PEP conferred incomplete protection compared to 28 days of therapy.23 In our study, HIV seroconversion did not occur in the case prescribed 2 weeks of therapy and there were no reported side effects for the cases prescribed ≥6 weeks of PEP.

Although the duration of PEP is standard across major guidelines, there are notable differences between the CDC and other published guidelines. For example, the recommendation for initiating PEP within 72 hours of exposure is derived from macaque studies showing a greater benefit for PEP initiated within 36 hours compared to 72 hours after exposure.24,25 As a result, most international guidelines recommend PEP initiation within 72 hours, with the exception of European guidelines which recommend a limit of 48 hours.26–29 In the United States, the state of New York endorses a 36-hour window in contrast with CDC recommendations. Despite these differences, the principal point is that PEP should be administered as soon as possible and never be delayed. Guidelines do not imply that PEP cannot be given beyond the recommended time window; however, there is no evidence of efficacy when initiated beyond 72 hours from exposure.

HIV PEP guidelines also differ in recommendations regarding selection of antiretrovirals. The CDC, World Health Organization, and Australian guidelines are less prescriptive about which drugs comprise a 2-drug regimen and also the indications for prescribing a 3-drug regimen.11,12,26,27 Although the original CDC case–control study6 in health care workers showed benefit with zidovudine monotherapy, all

guidelines recommend multidrug regimens that should theoretically provide greater efficacy. CDC guidelines recommend 3-drug therapy for higher risk exposures; however, increasing numbers of antiretrovirals have been associated with incremental adverse effects which, if leading to discontinuation, can result in higher failure rates.30 It is also important to note that PEP is not completely effective and HIV seroconversion has been reported in several cases where 3 or more antiretrovirals were initiated less than 2 hours from the time of exposure.31 Mathematical modeling that includes adverse effects, efficacy, and cost has shown that 3-drug regimens including a protease inhibitor would be favored if the background rate of HIV drug resistance in the source population is greater than 15%.32 During military operations, however, the background rate of antiretroviral drug resistance in the local population may be unknown. Ultimately, the decision to initiate PEP and the number of antiretrovirals selected should be individualized based on the exposure scenario, as well as the risk tolerance preferences of both the clinician and the exposed patient.33

Antiretrovirals have been available to treat HIV infection for more than 25 years and the options for PEP are continuing to expand. Nucleoside reverse transcriptase inhibitor basic regimens as well as other protease inhibitor and non-nucleoside reverse transcriptase inhibitor drugs for expanded regimens are listed in Table IV. In addition to the CENTCOM formulary agent zidovudine–lamivudine, the combination tablet of tenofovir–emtricitabine is also a CDC preferred agent for basic 2-drug PEP. Tenofovir–emtricitabine has several advantages over zidovudine–lamivudine, including once daily dosing and greater tolerability.34 This agent is likely to replace zidovudine–lamivudine as the preferred agent for 2-drug PEP for military members in the future as a result of convenience and improved side effect profile.

For expanded 3-drug regimens, lopinavir–ritonavir has a high genetic barrier for antiretroviral resistance, but diarrhea is a common side effect which makes this a significant disadvantage for use in the deployed environment. Adverse effects may be temporized by antidiarrheals and antiemetics; however, this increases the overall pill burden. The CDC alternative agent atazanavir offers daily dosing with a lower pill burden, but has the potential to cause asymptomatic jaundice and less commonly nephrolithiasis. Darunavir, the most recent protease inhibitor on the market, has many advantages including the highest genetic barrier to resistance of all antiretrovirals, daily dosing with a low pill burden, and a lower rate of adverse effects compared to other protease inhibitors.37 Despite higher costs, the newer protease inhibitors atazanavir or darunavir combined with low-dose ritonavir offer considerable advantages and may be preferred over lopinavir–ritonavir if available in the deployed setting in the future.

For the non-nucleoside reverse transcriptase inhibitor class, efavirenz is an alternative agent for 3-drug PEP which, as a combination tablet of efavirenz–tenofovir–emtricitabine, offers the greatest convenience as a one tablet per day regimen. However, efavirenz is associated with significant central nervous system side effects making this agent less suitable for PEP, especially for military members performing operations in a combat setting. Since the potential for teratogenicity is also a concern, efavirenz should be avoided in women of childbearing age. Other antiretrovirals can also be considered for PEP including newer non-nucleoside reverse transcriptase inhibitor agents, the integrase inhibitor raltegravir, and the entry inhibitor maraviroc. However, there are limited data for use of these agents as PEP and consultation with an Infectious Disease or HIV specialist is advised before considering these antiretrovirals.

Blood and other body fluid exposures commonly occur during military operations, particularly in combat settings and during humanitarian missions. HIV PEP is an important strategy to prevent HIV seroconversion in exposed patients. In a deployed trauma hospital in Afghanistan, the initiation of

PEP and selection of antiretrovirals was typically in concordance with CDC guidelines. As additional antiretrovirals become available, there will be greater opportunity to tailor PEP to the individual patient. This is especially important as many antiretrovirals have side effects that may be incompatible with duties performed by military members in an operational setting.

BACK TO TOP

Substance Abuse

Substance Use Disorders in the U.S. Armed Forces, 2000-2011

Armed Forces Health Surveillance Center
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Drug misuse is associated with serious health consequences and has detrimental effects on military readiness. During 2000 to 2011, 70,104 service members received an incident diagnosis of a substance use disorder (SUD) (excluding alcohol and tobacco-related disorders). Incidence rates declined with increasing age, time in service, rank, and number of combat deployments. Service members in a combat occupation had 1.2 times the rate of individuals in a health care or administration/supply occupation. The median time to discharge after an SUD diagnosis was longest in the Air Force (327 days) and shortest in the Navy (133 days). The substances with the highest incidence rates were cannabis (160 per 100,000 person years [p-yrs]), “mixed/unspecified/other” (125 per 100,000 p-yrs), and cocaine (61 per 100,000 p-yrs). Incidence rates of cannabis and cocaine use diagnoses generally declined while rates of mixed/unspecified/other and opioid use increased over the surveillance period. The increasing trend in opioid-related diagnoses since 2002 may reflect an increase in prescription drug misuse. The Department of Defense recently expanded its drug testing program to screen for hydrocodone and benzodiazepines. A preeminent concern regarding the health of members of the U.S. Armed Forces is the impact on mental health of more than a decade at war. Significant attention has been focused on conditions like post-traumatic stress disorder (PTSD), depression and anxiety, and suicidal behaviors. Concomitant with these concerns has been an increasing focus on the incidence of substance use disorders (SUDs) among military members, especially the misuse of prescription medications. During the years 2000 to 2011, substance abuse and dependence diagnoses accounted for 4.1 percent (n=73,623) of all incident mental disorder diagnoses; while the 2011 incidence rates of SUDs were lower than those in 2009, they were higher than all of the years prior to 2009.

Other studies have noted increasing rates of SUDs in military populations, often in relation to deployment. The 2008 Department of Defense (DoD) Survey of Health Related Behaviors found that self-reported drug use has been increasing since 2005; 12 percent of military members surveyed affirmed substance use (including prescription medications) in the past 30 days. A recent DoD-sponsored Institute of Medicine (IOM) report on

substance use disorders in the U.S. Armed Forces stated that outdated treatments and prevention as well as a lack of standardization of policies have led to increases in alcohol and substance use disorders – and most notably, prescription drug misuse. Any history of drug or alcohol abuse or dependence is generally considered disqualifying for entry into the military. For service members, all branches of the U.S. Armed Forces have a zero tolerance policy for illicit substance use, but the implementation of these policies differs by service.

This report summarizes counts, rates, and trends in diagnoses of substance use disorders (excluding alcohol and tobacco related diagnoses), overall and by specific drug categories (e.g., opioid, cocaine, cannabis, etc.), among active component U.S. service members over a 12-year surveillance period. The report also summarizes times to separation after diagnoses of substance use in each of the Services.

METHODS

The surveillance period was 1 January 2000 to 31 December 2011. The surveillance population included all individuals who served in the active component of the U.S. Armed Forces at any time during the surveillance period. All data used to determine incident substance use disorder diagnoses were derived from records routinely maintained in the Defense Medical Surveillance System (DMSS). These records document both ambulatory encounters and hospitalizations of active component members of the U.S. Armed Forces in fixed military and civilian (if reimbursed through the Military Health System) treatment facilities. Records of medical care in the Central Command theater of operations were obtained from the Theater Medical Data Store (TMDS).

For surveillance purposes, SUDs were ascertained from medical encounters that included ICD-9-CM codes for substance use diagnoses in the first or second diagnostic position (see specific codes below); diagnoses of alcohol and tobacco abuse (305.00-305.03, 305.1) were excluded. A case was defined as one inpatient medical encounter with any of the defining diagnoses in the first or second diagnostic position, two outpatient encounters (which could include TMDS encounters) within 180 days of each other with the defining diagnoses in the first or second diagnostic position, or one outpatient medical encounter in a psychiatric or mental health care specialty setting (defined by Medical Expense and Performance Reporting System (MEPRS) code: BF) with the defining diagnosis in the first or second diagnostic position. Diagnoses of misuse of specific substances were identified by ICD-9-CM codes as follows: opioid: 304.0 and 305.5; sedative, hypnotic, anxiolytic: 304.1 and 305.4; cocaine: 304.2 and 305.6; cannabis: 304.3 and 305.2; amphetamine and other psycho stimulants: 304.4 and 305.7; hallucinogen: 304.5 and 305.3; and all other to include unspecified drugs, other specified drugs, and combinations of drugs: 304.6, 304.7, 304.8, 304.9, 305.8, 305.9.

ICD-9-CM coding does not explicitly specify prescription drug misuse; individuals abusing prescription medication and receiving a diagnosis of an SUD would be categorized based on the class of medication. Individuals with SUD diagnoses prior to the beginning of the surveillance period or during the first 180 days of service were excluded as prevalent cases. Service members who were diagnosed with more than one SUD during the surveillance period were considered incident cases in each category for which they met case-defining criteria.

The summary measures utilized were incidence rate (IR) per 100,000 person- years and incidence rate ratio (IRR). Demographic characteristic-specific IRRs were adjusted for age, military pay grade, branch of service, and gender. Time to separation was determined based on the time from an incident diagnosis of a substance use disorder of interest to the end of the affected service member's active military service (as documented by

the latest military demographic record in the DMSS archive); by this method, terminations of active service by administrative separation, end of obligated service, and retirement, were ascertained. Times to separation were summarized by calculating median times to separation after diagnoses of interest and the percentages of affected individuals remaining in service at various time points following diagnoses.

Individuals who were diagnosed with an SUD and subsequently died prior to separation were excluded from time-to-separation analysis.

RESULTS

During the 12-year surveillance period, 70,104 active component service members met the case definition for an incident diagnosis of SUD; the overall incidence rate was 414 per 100,000 person years (p-yrs) (Thirty individuals were diagnosed with an SUD within the first 180 days of service; they were considered prevalent, not incident, cases and were excluded from analyses.)

Incidence rates declined with increasing age, time in service, rank, and number of combat deployments. Those patterns generally held when adjusting for age, military rank, gender, and branch of service. The youngest service members had 1.8 times the incidence rates of the oldest service members and junior enlisted had 17.6 times the rates of officers. Individuals with no combat deployments had 25 times the incidence rate of those with four or more combat deployments. Individuals with 0-5 years of service had 77 times the incidence rate of individuals with more than 20 years of service.

By race and ethnicity, white, non-Hispanics had the highest incidence rate at 438 per 100,000 p-yrs, followed closely by black, non-Hispanics, then Hispanics. Males had 1.5 times the incidence rate of females. Single individuals had 1.2 times the adjusted incidence rate of married individuals. Service members in combat occupations had 1.2 times the rate of those in healthcare or admin/supply occupations.

Of all service members with at least one incident SUD diagnosis during the period, 134 died prior to discharge (and were excluded from time to discharge analyses). Among all others, the median time to discharge aft er an incident diagnosis of substance abuse was 232 days. The Army consistently had the highest incidence rates of SUD, peaking in 2009, and the Air Force had the lowest. The Marine Corps experienced a steady increase in incidence since 2006.

Incidence rates peaked in the 17-20 year age group in 2008; incidence rates in the 21-25 year age group surpassed those of the 17-20 year age group in 2011. When evaluating time to discharge, the Air Force had the longest median time to discharge and, consistently throughout a 360 day follow-up period, a lower proportion of airmen were separated from service than members of the other services.

By 360 days after an incident diagnosis, the Marine Corps had the lowest (32%) and the Air Force had the highest percentage (47%) of individuals remaining in service. The median time to discharge after an SUD diagnosis was longest in the Air Force (327 days) and shortest in the Navy (133 days). By military grade, median times to discharge after SUD diagnoses were shortest among junior enlisted service members (E1-E4) (205 days after diagnosis) and longest among warrant officers (695 days).

During the period, the substances with the highest incidence rates of diagnosis were cannabis (160 per 100,000 p-yrs), “mixed/unspecified/other” (125 per 100,000 p-yrs), and cocaine (ICD-9-CM 304.2, 305.6) (61 per 100,000 p-yrs). Incidence rates of diagnoses of cannabis and cocaine use generally declined while rates of mixed/unspecified/other and opioid use increased during the surveillance period. Cannabis was the substance most frequently diagnosed in the Army and Marine Corps; “mixed/unspecified/other” substances predominated in the other Services.

EDITORIAL COMMENT

During a 12-year surveillance period, 70,104 service members were diagnosed with a substance use disorder; cannabis was the most frequently reported specific substance on records of incident diagnoses of substance abuse. Rates of cannabis-related diagnoses declined over the surveillance period. In contrast, rates of diagnoses of mixed/other related disorders and opioid related disorders increased over the period.

The recent IOM report on SUDs in the military highlighted the long history of alcohol and drug misuse in the U.S military. The report herein examines diagnoses of substance use disorders excluding alcohol misuse (which was the subject of a recent *MSMR* report);7 the report expands previous *MSMR* estimates of the incidence of drug abuse and dependence diagnoses by providing more granularity on diagnoses related to specific drugs. Drug misuse is associated with serious health consequences and has detrimental effects on performance, military discipline and readiness. DoD policy has long discouraged drug abuse. Since the early 1980’s, the DoD has emphasized zero tolerance of illicit drug use, and all services developed programs aimed at deterring such use. Drug testing of urine specimens has played a key role in this effort. While this no-tolerance policy extends across all services, the services differ in terms of policies related to separation of individuals who are determined to be drug users.

The increasing trend in the incidence rate of opioid-related diagnoses since 2002 may reflect an increase in prescription drug misuse; rates of prescription drug misuse have been increasing over the past several years among both military members and civilians. Although overall drug use is generally lower in the military. Service policies for actions following identification of substance use disorders in service members

SERVICE POLICY

Navy - Mandatory separation to include separation for self-referral. No timeline. Must offer treatment if dependent.

Marine - Corps Mandatory separation to include separation for self-referral. No timeline. Must offer treatment if dependent.

Coast Guard - Mandatory separation; no statement on separation for self-referral. No timeline. Must offer treatment if dependent.

Army - Mandatory separation review board to include separation review board for self-referral, separation process must begin within

Air Force - No mandatory separation is required. Individuals who self-refer are protected from use of that information against them. No timeline. Treatment is encouraged.

*30 days of notification of positive drug test. Must offer treatment if dependent.

Mandatory separation policies do not apply to alcohol and tobacco use disorders compared to civilian populations, prescription drug abuse has been increasing at a greater rate in the military over the past several years.5,8,9 The DoD has been evaluating and implementing strategies to combat this increase; notably, the DoD recently expanded its drug testing program to screen for hydrocodone and benzodiazepines (a class of drugs that includes Valium® and Xanax®).

There are several limitations to these analyses that should be considered when interpreting the findings. The estimates of the incidence of specific substance use disorders underestimate the true incidence of these conditions for several reasons. The rates were derived by applying a surveillance case definition to administrative medical records; this process requires that individuals have a specific diagnosis of an SUD in their electronic medical record. The methodology would fail to capture individuals with SUDs who did not have a medical encounter during which an SUD was documented.

It is uncommon for military members with SUDs to self-refer for medical care; thus, documented diagnoses of SUDs most oft en reflect command-directed referrals after SUD-related incidents or aft er positive urine tests for drugs. In addition, until 2012, urine drug testing failed to capture many of the commonly abused prescription drugs; as a consequence, the rates of anxiolytic and opiate-related diagnoses reported here likely underestimate the actual rates of abuse of these substances during the period of interest in this report. The analysis of median time to discharge after SUD diagnoses by service is an indirect way of examining the potential impact of service-specific policies regarding separation from service for substance abuse. The data indicate that the median time to discharge is longest in the Air Force, which has different policies regarding separation than the other services

However, because the data used for this report did not differentiate between separations due to SUD diagnoses and other reasons for discharge (e.g., end of service obligation, retirement), the natures and magnitudes of the impacts of service specific policies on times to discharge after detection of SUDs could not be assessed definitively.

BACK TO TOP

Medical Protocol and Training

GBD 2010: Understanding disease, injury, and risk

The Lancet
Richard Horton
15 Dec 2012

Publication of the Global Burden of Disease Study 2010 (GBD 2010) is a landmark event for this journal and, we hope, for health. The collaboration of 486 scientists from 302 institutions in 50 countries has produced an important contribution to our understanding of present and future health priorities for countries and the global community.

What is the GBD 2010? Launched in 2007, it is a consortium of seven partners: Harvard University; the Institute for Health Metrics and Evaluation (IHME) at the University of Washington, Seattle; Johns Hopkins University; the University of Queensland; Imperial College London; the University of Tokyo; and WHO. GBD 2010 is the first systematic and comprehensive assessment of data on disease, injuries, and risk since 1990. That initial exercise was commissioned by the World Bank. This latest round was supported by the Bill & Melinda Gates Foundation. The project has dramatically expanded in scope. In 1990, 107 diseases and injuries, together with ten risk factors, were assessed. For 2010, 235 causes of death and 67 risk factors are included.

What are the headline findings? First, although 52·8 million deaths occurred in 2010 (in 1990, the figure was 46·5 million deaths), great progress is being made in population health. Life expectancies for men and women are increasing. A greater proportion of deaths are taking place among people older than 70 years. The burdens of HIV and malaria are falling. Far fewer children younger than 5 years are dying. Infectious diseases are increasingly being controlled. In some parts of the world, there has been substantial progress in preventing premature deaths from heart disease and cancer.

But this hopeful picture is being challenged by old and new threats. Huge gaps remain in progress for some regions of the world. Tuberculosis and malaria are estimated to have killed around 1·2 million people each in 2010. 8 million people died from cancer in 2010, over a third more deaths than 20 years ago. One in four deaths was from heart disease or stroke. 1·3 million deaths were due to diabetes. Deaths from road traffic injuries increased by almost half. Blood pressure is the biggest global risk factor for disease, followed by tobacco, alcohol, and poor diet. And young adults are emerging as a new and neglected priority in global health: GBD 2010 finds that young adults, especially men, are dying in far higher numbers than previously appreciated. But the most afflicted continent remains Africa. Here, maternal, newborn, and child mortality, along with a broad array of vaccine-preventable and other communicable diseases, remain urgent concerns.

GBD 2010 also puts an important spotlight on disability—from, for example, mental health disorders, substance use, musculoskeletal disease, diabetes, chronic respiratory disease, anaemia, and loss of vision and hearing. Disability from disease and injury will become an increasingly important issue for all health systems. More people will be spending more years of their lives with more illnesses. Women are hit especially hard by disability. Women aged 15—65 years lose more healthy life to disability than men. Yet disability has been almost ignored as a central policy priority during the era of the Millennium Development Goals.

What should happen next? These reports should add energy and momentum to efforts to improve the measurement of health, especially commitments to strengthen civil registration and vital statistics systems in countries. There is also every prospect that, instead of the GBD being a single event every few years, it will evolve into a continuous process of reviewing and updating data as new and more reliable information,

together with better methods, become available. The 1990 GBD reports led to important shifts in health priorities. Non-communicable diseases, especially mental ill-health, justifiably achieved much greater prominence. The success of the GBD, then and now, is that it provides a level playing field to assess independently (and dispassionately) the health priorities that face countries.

In the meantime, everyone concerned with health—health workers and policy makers, those working in technical agencies (across the UN system), development partners, civil society, and the research community—should use these latest findings to sharpen understanding of trends in disease, injury, and risk. We should use them to spark global, regional, and national debates about their meaning for policy and practice. We should use them to hold one another accountable for progress towards internationally agreed development goals and to plan for the post-2015 era of sustainable development, where the scope of health as an indispensable part of human development will be broadened still further. And, finally, we should use them as a platform to advocate ever more vigorously for the growing consensus that universal health coverage could be the third great global health transitionn. GBD 2010 is an extraordinary collaboration. Our collective responsibility is to turn it into an extraordinary opportunity.

BACK TO TOP

A Model for Patient-Centered Army Primary Care

Military Medicine
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12 Dec 2012

Abstract

This pilot evaluated a novel method of primary care delivery in a military family practice setting. A registered nurse, registered nurse case manager, and primary care provider formed the patient management team. Approximately 2,500 empanelled patients participated in a pilot program that applied a patient-centered approach to primary care. The pilot tracked outcome measures, which included (1) panel size, (2) access to care, (3) care utilization, (4) continuity of care, (5) nurse and provider productivity, (6) Healthcare Effectiveness Data and Information Set measures, and (7) satisfaction measures. When compared to the standard family practice clinic, the patients in the pilot were able to access the family practice clinic more frequently ($p < 0.05$), were less seen in the urgent care ($p < 0.05$), and had a lower no-show rate ($p < 0.001$) for scheduled appointments. The providers were able to see their own empanelled patients significantly more frequently ($p < 0.05$) and virtually all Healthcare Effectiveness Data and Information Set markers improved with colon cancer screening, low-density lipoprotein annual exams, low-density lipoprotein control, and breast cancer screening/mammogram being significantly improved over the comparison group ($p < 0.05$). These

results suggest a change in staffing and a focus on patient-centered care can significantly improve outpatient care access and population health maintenance.

Background

Army Primary Care

Army primary care has seen a significant increase in utilization over recent years. In 2010, there were 19,227,110 ambulatory visits among active component service members alone. That figures to about 13 ambulatory visits by each service member over the preceding year, which represents a 9.4% increase over 2009 and a 64.1% increase since 2001.1 This increased demand has caused a strain on the current primary care model, which has resulted in a decrease in access to care, poor tracking of patients, and increasing frustration among both patients and providers because of inability to achieve continuity of care.

Primary Care Teams

The traditional provider-centric model in primary care has been transitioning to a team approach as a more efficient model of care. This team approach has many benefits for both the patient and the team. Establishing semiautonomous teams could improve the system productivity, clinical quality, increase patient satisfaction, and employee morale.2 Cohesive teams are associated with better clinical outcome measures and higher patient satisfaction. Making the patient a member of that collaborative team has also been shown to improve health outcomes such as better control of blood pressure, treatment effectiveness for pain and emotional problems,5 and improved outcomes for patients with diabetes and heart failure.

Nursing Role in Primary Care

An integral part of this team concept is an active nursing role. It is clear that nursing must take a more active role in the management of primary care patients. With the advent of increasing acuity and workload coupled with a shortage of primary care providers, it is imperative that nursing take on a more autonomous role. The concept of this transition was depicted well by Schroeder, et al7 which encouraged nurses to shift from episodic care to planning on a continuum of care through coordination and outcome monitoring of groups of people. Nursing must assume an active role with the patient and the patient's family and be an integral part of each care encounter. However, in order to safely achieve this level of autonomy and independence, primary care clinics need to begin staffing with bachelor level degree nurses. The Army has strongly encouraged certification in areas such as critical care or emergency services but has not stressed the need to have certified ambulatory care nurses in the outpatient clinics.

Nursing Outcomes in Primary Care

Although it is understood that nursing must participate in any transition to a team-based approach in primary care, there is a scarcity of research done in this area. A recent article that purports to give appropriate measurements for successful implementation of Patient-Centered Medical

Home (PCMH) fails to include any measurements of nursing outcomes8 and National Committee for Quality Assurance PCMH certification site lacks any mention of nursing at all.9 Past research, however, has shown that nursing expertise will improve many health outcomes in ambulatory care. A meta-analysis of 23 articles10 found improvement in registered nurse (RN)-specific outcomes to include increased patient satisfaction related to continuity of care and communication with providers, as well as general improvements in client self-efficacy; self-care; quality of life; and physiological markers such as blood pressure and glycosylated hemoglobin (A1C). Also noted were fewer hospital visits and emergency room visits as a result of improved operational efficiency and demand management. Wong and Cummings11 found that allowing more autonomy in the nursing leadership role resulted in increased patient satisfaction and reduced adverse events. Other studies have also found that RN outpatient management improved outcomes of chronic diseases like diabetes,12,13 anticoagulation treatment,14 and heart failure.15 Demand management can be controlled and managed through the use of nursing triage or nursing appointments. Nursing triage has yielded positive effects in primary care16 while not increasing untoward or negative health effects.17 Nursing appointments allow a new avenue of access for patients. These appointments are generally positively received18 and have shown enhanced communication and better education on general health behaviors resulting in improved health behaviors.19 Primary care nursing case management is a concept that is receiving increased interest with the new team-based model. A study done in a civilian hospital on patients with congestive heart failure found that careful case management by an RN can result in fewer emergency room visits, unplanned hospitalizations, cost avoidance, as well as showing high patient satisfaction and an improved quality of life.15

The issues of poor team structure, limited access to primary care, and dissatisfaction on the part of both the patient and the provider were the basis for the development of a new model for primary care. This pilot specifically sought to address expanded nursing roles, population management, demand management, and increased access to care.

Methods

The pilot proposed to implement a shift in the focus of primary care from that of task completion within the clinic to population management of the patients overall. This model proposed making the provider, the RN, and the RN case manager all equally responsive and responsible for the empanelled patient population. The model introduced the “My RN” concept, which assigned an RN to each patient as is traditional with providers. This ensured each patient would know his/her nurse and the nurse would know each patient. This provided a level of stability and continuity in a setting where military providers rotate frequently. The licensed practical nurse (LPN) worked with one provider/RN dyad and assumed the responsibility for the daily workload and patient throughput within the clinic. The certified nursing assistant (CNA) was a shared asset between teams and was responsible for room transitions, lab runs, and other tasks within the clinic. An RN case manager was also added to the team to support complex patients requiring additional education and monitoring.

The project was approved and funded through the U.S. Army Medical Command. The Command at Moncrief Army Community Hospital was able to support the pilot with two providers: one physician and one physician's assistant. The Moncrief Family Care Clinic (FCC) also provided the front desk clerk for appointment check-in and one active duty Army Nurse as the team leader. The remainder of the staff that was hired for this pilot

included one RN, two RN case managers, two LPNs, one CNA, and one data assistant. The staff was aligned into two teams so that the same support staff and provider always worked together and the CNA was shared by both teams.

Start-up training was conducted to ensure the staff understood the enhanced care concept. Basic training included computer training, introduction to population management, clinical practice guideline familiarization, and general clinic job descriptions. A specific training package was developed for the primary care RNs, which drew from the American Academy of Ambulatory Care Nursing core curriculum and culminated with the opportunity for the RN to sit for the Ambulatory Care Nurse certification exam. Other project-specific training included data to be gathered for population management markers, the “My RN” concept, template management, customer service, and being responsive to the population of patients either in the clinic or outside the hospital. The training for the RN case managers used an online case manager course, which was available at no cost. At the completion of the training, the RN case manager was also eligible to sit for the Case Manager Certification exam. The LPNs were given further training on patient screening and how to initiate documentation by beginning the subjective portion of the patient's encounter note.

Measures

This project was designed to compare changes over time in specific measures. Therefore, measures were chosen which were already routinely collected. This allowed a comparison of data from before the pilot began as well as allowing a comparison of data to the rest of the family practice clinic without the need to specifically collect data from that sector. All calculations were based on per 1,000 patients enrolled. The outcome measures that were used for the pilot were (1) comparison of panel size, (2) comparison of access, (3) comparison of utilization, (4) continuity of care, (5) nurse and provider productivity, (6) Healthcare Effectiveness Data and Information Set (HEDIS) measures, and (7) satisfaction measures. Access to care used the five subgroups, each based on clinic utilization per 1,000 enrolled, of (1) access to all outpatient services, (2) access to FCC (3) access to specialty care, (4) access to Urgent Care Clinic (UCC), and (5) inpatient dispositions. Utilization comparison evaluated (1) no-show incidence and (2) unbooked appointments. Continuity of care included patient continuity (ability to see assigned primary care manager) and provider continuity (ability to see patients assigned to their panel). Provider productivity was measured using the relative value units (RVUs) per full time equivalent per month. The only mechanism currently available to measure nursing workload was a telephone consult. Population health measures included the ten HEDIS markers of asthma control medication, chlamydia screening, colorectal screening, annual A1C exam, A1C control, A1C < 7, annual low-density lipoproteins (LDL) exam, LDL control, mammogram, and cervical cancer screening. Patient satisfaction was measured using the Office of the Surgeon General sponsored survey called the Army Provider Level Satisfaction Survey (APLSS), which is sent out to beneficiaries after an outpatient visit to determine satisfaction with care. Provider satisfaction was collected as part of the exit survey with the providers in the pilot.

Analysis

This pilot was conducted in a family practice clinic in a military community hospital with approximately 77,000 beneficiaries. This population consisted of 19,000 active duty, 18,000 dependents, and 39,600 retirees with dependants. The providers practicing at this facility included family

practice physicians, family nurse practitioners, and physician assistants. Of these providers, 12 were in the comparison group while two, a family practice physician and a physician assistant, were in the pilot group.

The statistical analysis for this pilot was performed by a data analyst working with the Department of Defense Medical Metrics database. The analysis was based on a comparison between the pilot team and the remainder of the FCC. Two statistical calculations were utilized for evaluation of study results. The first was a one-tailed F-test to determine equality of variance as the numbers of providers in the comparison and pilot group were unequal. All variances were insignificant except where noted otherwise. The second statistical test utilized was a one-tailed Student's t-test to compare means between groups.

Results

Overall, the pilot program was able to show significant improvements in all categories except productivity.

The pilot providers were able to manage a significantly greater number of empanelled beneficiaries compared to the comparison group (1,193 vs. 1,127; $p < 0.05$). The pilot group also showed a higher average monthly access to care compared to the comparison group for all aspects although only FCC and UCC access were statistically significant. Although there was significant variance between groups in UCC utilization rates, the pilot group was still able to show a significant difference in usage rates compared to the comparison group (41.1 vs. 44.4; $p < 0.03$). The pilot group showed significantly better utilization rates with a significantly lower no-show rate (7.1 vs. 9.9; $p < 0.001$), which interestingly was counterbalanced with a higher monthly average of unbooked appointment requests. The pilot group showed a significantly higher average monthly probability of provider continuity while patient continuity was also improved although it did not achieve statistical significance. Both measures of productivity failed to achieve statistical significance as well as showing a significant variance between groups.

The pilot showed improvement on all but one of the ten HEDIS measures, with four of the improvements being statistically significant.

The asthma control medication marker likely failed to improve as a result of sample size. At the time of the final measurement, one of the pilot providers had one of the three asthmatics in his panel miss a follow-up. Patient satisfaction scores according to the APLSS were very good for both the pilot group and the comparison group. Although the pilot group had a better average APLSS score post-pilot than the comparison group (96.8% vs. 91.9%), it also started out with a better score (95.3% vs. 91.1%) and therefore the change was not significant.

Discussion

The cost for delivering health care within the Department of Defense military treatment facilities has increased substantially over the last decade. As the number of ambulatory visits has increased, so has the workload on providers and support staff. More requirements are being placed on the patient encounter, which may not relate to why the patient sought care. To solve this dilemma requires innovative strategies by which health care is delivered. The present project focused on a novel method for implementing a more effective process in which to deliver primary care within a military family practice setting. Although this pilot has many similar aspects, it is important to note that this project was begun before the movement to PCMH had gained momentum within the Army.

Panel size per provider is a balance between enrollment and access to care. Because of resource constraints in a capitated budget, the Army will never be able to care for all eligible beneficiaries strictly within the military medical facilities. However, if more patients can be well-managed within the military health system, many of those extra costs can be managed, which results in more cost-effective care. The fact that the pilot was able to efficiently manage more patients in the military facility means fewer people are seeking care in civilian facilities. This will result in cost savings in both the short and long term. Also important, the pilot was able to manage a greater number of patients while improving metrics such as access to care, satisfaction, and patient/provider continuity.

Access to care using this model was better overall when compared to the regular team approach being used at the military facility. Patients in the pilot group were able to achieve better access care in the primary care setting, which was the primary outcome, but there was also a sizable increase seen in accessing specialty care. Since there was no direct access to a specialty clinic in this setting, this increase is hypothesized to be attributable to better access through the primary care clinic. It was also noted that the pilot group was hospitalized more often. As the providers and their panels were selected for being representative of the general population, the difference in hospitalization rates were more likely attributable to increased access to primary care, which translated to increased specialty visits and therefore more hospitalizations for surgeries or medical treatments. Increased patient satisfaction was seen in the no-show rates and, conversely, in the number of appointments which could not be booked (e.g., unbooked appointments) because of limited space in the scheduling templates. As seen in this project, engaged and satisfied patients are more likely to show for their regular scheduled appointments. However, an interesting finding was that although the pilot group had more unbooked appointment requests, the satisfaction remained high. This may be attributable to the ability to directly access the team RN for advice and ability to meet their immediate needs outside the clinic. It may also be a result of reaction by the population of “build it and they will come.” This phenomenon of increasing unbooked appointments began to crescendo as the word of the clinic got out into the community. People were voicing increasing satisfaction knowing this project was focusing on improving access; so, more people were attempting to access the clinic to be seen. The pilot did not increase scheduling template slots nor did the pilot decrease the number of empanelled patients to each provider; so, this increased demand was coming from patients previously seen by the two pilot providers. Despite the increased unbooked appointments, the patients' satisfaction scores remained high. It is also important to mention that near the end of this 1-year pilot program, the template slots were no longer filling up and the providers began to have openings as the initial rush for appointments began to slow.

A major marker for this study was continuity. This project succeeded in improving both sides of patient and provider continuity. The comparison group showed that both perspectives of continuity were about 50%, which means the empanelled patient/provider would only get to see each other half the time—or the same odds as flipping a coin. This project was able to improve on that by allowing the patient/provider dyad to see each other almost 75% of the time. Because of the improved access, the majority of the backlogged patient visits were handled in the first 4 to 5 months of the project. The team decided to open a select few appointments to nonempanelled patients if the appointments were not filled within 24 hours of appointment to maintain RVU production.

Provider RVU production under this new model did not show significant changes. This was expected at the inception of the project. The project development team noted the frustration of primary care providers because of increasing burden within patient encounters. The pilot's intent was to off-load nonessential tasks from the provider to allow a more meaningful patient interaction. Scheduling templates were not adjusted for this reason. Minor increases in RVU production were expected by allowing more time within the appointment to address more issues and allowing

more time to chart with increased coding accuracy. This goal was seen in the improved access to providers, increased patient satisfaction, and the ability to accept nonempanelled patients because of vacancies in their own schedule.

This pilot increased the standard RN staffing significantly. It was therefore important to show how this RN presence was improving patient care. Unfortunately, within the current system, there are no workload metrics that measure the workload of an ambulatory care RN. The only workload marker found to be tracked for RNs were telephone consults. However, if the telephone consult was forwarded to the provider for information or action, all workload was transferred to the provider, leaving no evidence of the work the RN had contributed. Although there is currently work ongoing to develop workload metrics for ambulatory nursing in the Army, no other accurate metric was available at the time of this pilot.

There are limitations to this project. The ability to interpret significant findings is suspect when variances between the pilot and comparison groups are significant, as occurred in several of the measurements. As a nonrandomized program, it is also possible that the pilot providers were more clinically astute, or the patient population was healthier, relative to the comparison. This project was conducted in one clinic at a community hospital, which limits generalizability. Further replication at larger test sites would be required to improve generalizability. A final limitation that needs to be addressed in future research is the cost of this program. The intent of this pilot was not to track costs or cost savings beyond the surrogate measures of clinic access and urgent care access. A valid measure for the cost of “wellness” was felt to be beyond the scope of the proof-of-concept pilot. This must be addressed in future research to determine feasibility of application in a capitated financial system.

Conclusions

It is important to note that a finding can be clinically significant while not being statistically significant. This project was conducted by comparing the pilot to an outpatient model that the Army has been using for years with some success. The ambulatory care system in place at the time of this pilot obviously worked as thousands of patients successfully traversed the system every day in the Army. This project may not have found statistically significant differences in all areas; however, it was able to show improvements in every area measured.

This new paradigm for staffing a primary care clinic is able to improve all markers of productivity, satisfaction, and access to care across the board. The patients truly appreciated being recognized by name at their visits or on the telephone. More importantly, they appreciated the ability to talk to someone who knew them and not necessarily inside a clinic appointment.

It is time to acknowledge that the majority of patient care is occurring within the outpatient arena and to staff the setting accordingly. Studies have shown that having appropriate inpatient staffing improves outcomes, increases satisfaction, and improves patient safety. This small pilot project has shown the first two hold true in the outpatient arena and it seems likely the third will also hold true.

While the outpatient care moves toward the PCMH model, it is important to note that while the model as a whole has been shown to improve outcomes, the role of staff within the model has not been adequately explored or defined. This model does both. This model provides an excellent basis for a new paradigm of staffing model in the primary care setting.

BACK TO TOP

Using Social Media to Improve Continuing Medical Education: A Survey of Course Participants

Mayo Clinic Proceedings
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Objective

To determine continuing medical education (CME) course participants' use of social media (SM) and their attitudes about the value of SM for enhancing CME education and to examine associations between participants' characteristics and attitudes toward SM.

Participants and Methods

We conducted a cross-sectional survey and validation study of 539 participants at a Mayo Clinic Internal Medicine CME course in November 2011. The Social Media Use and Perception Instrument (SMUPI) consisted of 10 items (5-point Likert scales) and categorical response options. The main outcome measures were psychometric characteristics of the SMUPI scale, course participants' use of SM, and their attitudes regarding the importance of SM for enhancing CME.

Results

Of 539 CME course participants, 327 (61%) responded to the SMUPI survey. Most respondents (291 [89%]) reported using SM, with the most common types being YouTube (189 of the 327 participants [58%]) and Facebook (163 of 327 [50%]). Factor analysis revealed a 2-dimensional assessment of course participants' attitudes. Internal consistency reliability (Cronbach α) was excellent for factor 1 (0.94), factor 2 (0.89), and overall (0.94). The CME course participants' favorable attitudes toward SM were associated with younger age (20-29 years, mean score 3.13; 30-39 years, 3.40; 40-49 years, 3.39; 50-59 years, 3.18; 60-69 years, 2.93; and ≥70 years, 2.92; P=.02), using SM frequently (never, mean score 2.49; less than once monthly, 2.75; once monthly, 3.21; weekly, 3.31; and daily, 3.81; P<.0001), and professional degree (PhD, mean score 3.00; MD, 3.05; DO, 3.35; PA, 3.42; and NP, 3.50; P=.01).

Conclusion

We describe the first validated measure of CME course participants' use of and attitudes toward SM. Our results suggest that CME course directors should guide SM strategies toward more youthful, technology-savvy CME participants and that SM will become increasingly worthwhile in CME as younger learners continue to enter the profession.

Social media (SM) (eg, Facebook, Twitter, and YouTube) consists of Internet- and mobile device–based technologies that enhance interactivity among individuals and organizations. The strengths of SM include wide accessibility and personalized user profiles that allow the targeting of specific audiences for entertainment, marketing, and education. Facebook has more than 500 million users, 50% of whom access their accounts daily. Although SM is considered a phenomenon of the millennial generation (also called Generation Y [those born between approximately 1980 and 2000), more than 30% of Facebookers are over age 35, and users older than 50 years are the fastest growing cohort. Remarkably, nearly 70% of all Internet users have Facebook accounts, and during 20 minutes of Facebook use globally, more than 1 million links are shared and nearly 3 million messages are sent. Similar statistics exist for YouTube; as of 2011, there were approximately 500 million unique visitors and 3 billion hours spent on YouTube per month among all users combined. Social media websites can reach large populations and have been widely used for business-related purposes. Recent marketing research by the University of Massachusetts Dartmouth found that corporate and academic utilization of SM is substantial, with 20% of Fortune 500 companies, 45% of Inc. 500 companies, 50% of US colleges and universities, and 100% of the top US charities using SM.

Social media has the potential to enhance continuing medical education (CME). Web-based learning in medical education has already been established and validated during recent years, although the advantage of Web-based learning over conventional teaching methods remains unclear. The popularity of SM among medical learners and faculty physicians has generated studies about the implications regarding professionalism associated with this new technology. A recent report by the Robert Wood Johnson Foundation highlighted potential professionalism issues regarding the use of SM among health care professionals, including breaches of the patient-physician relationship and patient confidentiality. This concern for professionalism has led the American Medical Association and numerous US medical schools to publish guidelines on the appropriate use of SM by health care professionals. However, while the use of SM in medicine is widespread, its utility for enhancing learning remains poorly understood.

An estimated 45% to 90% of medical students, residents, and fellows use SM. Recent surveys revealed that 67% of practicing physicians use Facebook and 48% use Twitter. Although many studies have described students' attitudes about the professional use of SM in medicine, few have examined physicians' attitudes on the use of SM for academic purposes. For instance, a recent survey of medical students and practicing physicians demonstrated a high awareness of existing SM tools for medical education but showed a lack of knowledge regarding the use of these technologies for learning.

The potential application of SM to CME has been recognized. However, we are unaware of published research on the use of SM to deliver CME knowledge content to practicing physicians or studies on physicians' attitudes regarding the use of SM to market CME activities. Our objective was

to conduct a cross-sectional survey of US physicians attending a Mayo Clinic Internal Medicine CME course to determine their use of SM and evaluate their attitudes regarding the value of SM for enhancing CME.

Participants and Methods

Study Design and Participants

We conducted a cross-sectional survey and validation study that included all 539 participants at the Mayo Clinic 2011 Clinical Reviews course. Clinical Reviews is an annual week-long course accredited by the Mayo School of Continuous Professional Development that provides 22.5 hours of CME credit. The format consists of 20- to 30-minute podium presentations. Presenters are encouraged to use clinical cases and the audience response system whenever possible. Faculty members from the Mayo Clinic College of Medicine are selected by the course directors to give one or two presentations. Participants at Clinical Reviews typically represent health care professionals from the midwestern United States. All course participants were asked to voluntarily complete the Social Media Use and Perception Instrument (SMUPI) during a break between speaker sessions. A water bottle with a Mayo Clinic logo was offered on survey completion. This study was deemed exempt by the Mayo Clinic Institutional Review Board.

Survey Instrument Development

The SMUPI was designed to determine CME participants' general knowledge and use of SM and to evaluate their attitudes regarding the value of SM for enhancing CME use and marketing. Content for this instrument was derived from the existing literature, discussions with 3 college-age students of the millennial generation and an SM consultant, and input from Mayo physicians with experience in scale design, validation, and CME assessment. The initial iteration generated 19 items, 9 of which were initially chosen and further refined. Further iterations included a 10th item, “Social media will be increasingly utilized for CME in the future.” The final version was agreed on by 4 of the authors (A.T.W., N.P.S., C.M.W., and T.J.B.) and consisted of 10 items structured on 5-point scales (1 = strongly disagree, 2 = disagree, 3 = neutral, 4 = agree, and 5 = strongly agree) along with categorical response options for demographic variables.

Statistical Analyses

Factor analysis was performed on scores from the 10 Likert-scaled survey items. Factors were extracted using the minimal proportion criteria. Items with factor loadings of 0.60 or more were retained. Interrater reliability for individual items was calculated using intraclass correlation coefficients with 95% CIs. Intraclass correlations were interpreted as follows: coefficients less than 0.4, poor; 0.4 to 0.75, fair to good; and greater than 0.75, excellent. Internal consistency reliability for items comprising each factor and overall were calculated using Cronbach coefficient α, in which $\alpha > 0.7$ is considered acceptable.

The SMUPI scores were reported as means and SDs for the 10 instrument items. Participant characteristics, which were treated as categorical variables, were the following: age (20-29, 30-39, 40-49, 50-59, 60-69, and ≥70 years), sex, geographic region (western, northeastern, midwestern, and southern United States and Canada), practice type (academic, private-urban, private-rural, and resident or fellow in training), degree

(MD/MBBS, DO, NP, PA, PharmD, and PhD), medical specialty (internal medicine, internal medicine subspecialty, family medicine, surgery, emergency medicine, and pediatrics), types of SM use, frequency of SM use (never, less than once a month, monthly, weekly, and daily), purpose of SM use (personal, CME, general education, and professional), and means of learning about the CME courses (SM, mail brochure, e-mail brochure, journal/newspaper ad, another Mayo CME course, word of mouth, previous attendance, Internet search, and other). Associations between SMUPI scores and CME participant–related variables were determined using the Kruskal-Wallis test. Statistical significance was set at $P<.05$. Statistical analyses were conducted using SAS version 9.2 (SAS Institute Inc).

Results

Factor analysis revealed a 2-dimensional assessment of CME course participants' attitudes, with factor 1 representing the value of SM to course participants (items 1-5) and factor 2 representing the value of SM to CME course directors (items 6-9). One item was eliminated due to an ambiguous item loading. Overall, the extracted factors accounted for 100% of the shared variance among the original variables. Internal consistency reliability (Cronbach α) was excellent for factor 1 (0.94), factor 2 (0.89), and overall (0.94). Regarding survey responses, participants expressed the most agreement with items stating that SM would be useful for disseminating information about CME opportunities, that the use of SM in CME is ethical, and that SM will be increasingly utilized for CME in the future.

The survey was completed by 327 of the 539 CME participants, yielding a response rate of 61% (some respondents did not answer all questions, however). The majority of the participants were male (193 of 321 [60%]) and older than 50 years (215 of 323 [67%]). Most participants were from the midwestern United States (307 of 321 [96%]), but participants also represented the western, northwestern, and southern United States and Canada. Of the 308 respondents who specified practice type, 149 (48%) were in private-rural practice, 88 (29%) were in private-urban practice, 65 (21%) were in academics, and 6 (2%) were residents/fellows in training.

Nearly all participants reported having used at least one type of SM (291 of 327 [89%]), and very few (54 of 322 [17%]) reported never using SM. Most of the 327 participants utilized SM for personal use (251 [77%]); others used SM for general education (64 [20%[), CME purposes (21 [6%]), and other professional use (50 [15%]).

Among the 327 participants who responded to the survey, the most common SM tools were YouTube (189 [58%]), Facebook (163 [50%]), and Skype (142 [43%]). The types of SM that were rarely or never used were Doximity (5 [2%]), Sermo (4 [1%]), and Second Life (4 [1%]). The following types of SM were used less than 1% of the time: fring, SlideShare, foursquare, Digg, Friendster, reddit, and tumblr.

The CME course participants' favorable attitudes toward SM were associated with characteristics of younger age (20-29 years, mean score of 3.13; 30-39 years, 3.40; 40-49 years, 3.39; 50-59 years, 3.18; 60-69 years, 2.93; and ≥70 years, 2.92; $P=.02$), using SM frequently (never, mean score of 2.49; less than once monthly, 2.75; once monthly, 3.21; weekly, 3.31; and daily, 3.81; $P<.0001$), and professional degree (PhD, mean score of 3.00; MD, 3.05; DO, 3.35; PA, 3.42; and NP, 3.50; $P=.01$). There were no significant associations between participants' attitudes toward SM and participant sex, geographic region, type of practice, or medical specialty.

Discussion

We describe the first validated measure of CME participants' attitudes regarding personal use of SM and the value of SM for CME. The vast majority of CME participants utilized SM for personal reasons and/or education. The most common types of SM used by CME participants were YouTube, Facebook, and Skype. Participants' favorable attitudes toward SM utilization for CME were associated with younger age and frequency of SM use. These findings have important implications for CME course directors and future research on using SM to enhance CME.

The CME course participants in this study reported using SM frequently. Notably, SM use represents a high behavior-level outcome, which is not commonly reported in education research. Additionally, CME course participants expressed some agreement that use of SM for CME is ethical, desirable for distributing CME content, and likely to increase over time; however, course participants older than age 50 were less likely to view SM as a professional medium of communication. A recent pilot study revealed that only 24% of CME professionals had a formal strategic plan for incorporating SM into their CME courses and that 67% had no plans to incorporate SM in the future. Given the overall popularity of SM use among CME participants and the significantly negative association between SMUPI scores and participant age, it appears that CME course directors should consider adopting a strategy of targeting CME marketing and educational content to CME participants, especially younger ones, through the use of SM.

Our findings regarding type and frequency of SM use are similar to those of other studies among health care professionals including nurses, pharmacists, medical students, residents, fellows, and practicing physicians. As in previous studies, we found that CME participants use SM for personal, more than for professional or educational, purposes. Nonetheless, the desirability of SM for educational use has been recognized. Potential barriers to using SM for education include inadequate knowledge about how to access electronic information, lack of educational content in SM compared with other forms of media, poor quality control, and limited time to access SM for learning.

Our results suggest that clinicians with DO, NP, or PA degrees view SM more favorably than do those with MD or PhD degrees. Several studies indicated that nurses and physician assistants may be more likely than physicians to use SM for professional reasons. According to recent surveys, 65% of nurses reported using SM in their professions, whereas 60% of physicians were interested in using SM at work. Another survey revealed that only 3% of physicians and 10% of physicians in training used SM for professional reasons. An additional investigation showed that 21% of physicians used SM, compared with 36% of physician assistants. Alternatively, the varying opinions toward SM among CME participants with different professional degrees in our study might have been due to participant age; the average age of DOs, NPs, and PAs was 31 years and that of MDs was 40 years, whereas the single PhD was in the sixth decade of life.

Many experts have examined SM regarding what constitutes professional use and the prevalence of unprofessional behavior. Related to this issue, health care professionals have been wary of SM because of concerns about maintaining patient confidentiality and anecdotes of physicians and nurses who have been terminated for inappropriate Facebook posts. Therefore, health care organizations, medical schools, and professional societies such as the American Medical Association have issued guidelines on the appropriate use of SM, including suggestions for separating personal and professional content online. Similarly, the Alliance for Continuing Medical Education has provided standards for the appropriate use of SM. Our experiences as CME course directors have revealed that incorporating SM into large-scale CME offerings can be accomplished without difficulty and at exceedingly low risk. Indeed, we have yet to experience any incidents in which SM has compromised the integrity of our CME courses, presenters, or participants.

Although we are unaware of any research describing the use of SM for marketing in CME, it is noteworthy that industry studies have revealed that more than 90% of marketers utilize SM to sell their products. Based on industry standards and the current study findings, it would seem advantageous for CME course directors to take full advantage of SM for the promotion of their courses.

Our method for measuring CME participants' attitudes about SM is supported by validity evidence, which includes the categories of content, internal structure, response process, criteria, and consequences. In this study, *content* evidence was supported by survey items from previous literature on SM and CME and input by experts in education. *Internal structure* evidence was supported by factor analysis that showed a 2-dimensional assessment of CME participants' attitudes regarding the use of SM in CME and excellent reliability. *Criterion* evidence was supported by associations between attitude scores and other variables including CME participants' ages and frequencies of SM use. Notably, previous literature reviews revealed that content, internal structure, and relationships to other variables are the most commonly reported validity evidence categories in medical education studies.

Our study has some limitations. The majority of the respondents resided in the Midwest, and there was only limited representation from other regions of the United States and Canada. Most of the participants were family and internal medicine physicians, with only a minority of the participants practicing in surgical specialties or internal medicine subspecialties. Although findings from this study should be generalized to other settings with caution, we found no compelling evidence that the results would have been strongly influenced by variations in geographic or practice distributions. Furthermore, the demographic characteristics of our study sample, including CME participant practice type, medical specialty, and educational degree, are similar to those reported in large systematic reviews of CME. Our collection of demographic variables could have been more robust to include questions regarding issues such as socioeconomic status and broadband access availability, but as noted previously, the demographic profile of our sample appears to be similar to that of participants in other published CME studies. Lastly, we acknowledge that survey nonresponders may have had different attitudes than responders regarding SM. However, the response rate in this study was favorable compared with that typically seen in physician surveys.

Conclusion

To our knowledge, this study represents the first validated measure of CME participants' attitudes regarding personal use of SM and the value of SM for attaining CME. Our findings indicate that the most fruitful categories of SM for CME use and marketing may be Facebook, YouTube, and Skype. The identified association between positive attitudes on using SM in CME with younger age and increased frequency of SM use suggests that CME course directors might want to direct SM learning strategies toward more youthful, technology-savvy CME physicians and that the utilization of SM in CME will become increasingly worthwhile as junior physicians enter the profession. More research on developing methods, including SM interventions, for enhancing CME is needed.

BACK TO TOP

The Anatomy and Physiology of the US Health Care System in 2050? An Exercise in Prognostication, Fantasy, and Hope

American Journal of Medicine

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The debate concerning the appropriate structure for the American medical system goes on. Almost every day, one reads a newspaper or magazine article focusing on the strengths and flaws of our health care network. Should we imitate successful systems elsewhere in the world? How can we insure all of our citizens without bankrupting the economy? How many physicians, nurses, and hospitals do we need and how many will we need in the future? These are just some of the questions that constantly bombard us. Like all physicians in the US, we have given these questions and many others considerable thought, which we will now share with the readers of *The American Journal of Medicine*. These are our own personal ideas and do not reflect the official attitudes or positions of *the Journal*, Elsevier, any political party, or the University of Arizona.

We anticipate that the current trend towards central control of medical care will continue, and that by 2050, most physicians will work for a health care system such as the one being formed by our university health care network here in Tucson.

Accountable care organizations involving community hospitals such as Tucson Medical Center already have been formed with community doctors and their Medicare patients. These will expand to incorporate more primary care and specialty physicians, along with patients outside of Medicare age.

Individual practitioners and small groups of physicians will gradually disappear, with large numbers of doctors working for the local or regional health system. Centralization will be focused in local entities rather than in Washington, DC or individual state capitals. Physicians will be salaried by these large health networks, with incentives given for productivity and performance.

The networks will contain many components, for example, inpatient and rehabilitation hospitals, outpatient clinics, ambulatory surgical and imaging centers, as well as satellite outpatient clinics and hospitals in outlying areas. The emergency medical system will be a patchwork of state, local community, and private entities that will work closely with the large health systems. Smaller cities may have only one health care network while major urban centers may contain a number of these integrated systems. It also is possible that some of the larger networks will have insurance companies embedded in their structure. Duty hours will be strictly regulated for both trainees and full-time employees.

Most, if not all, Americans will have some form of health insurance, with many still having coverage tied to employment. However, many individuals will receive insurance from regional or federal plans paid for, in part, by state and federal taxes. The federal government will continue to

have a role in covering the Medicare and Medicaid populations. Thus, the future health insurance system will be an enlarged and more universal version of our current system. There will be continuing efforts to reduce waste and nonindicated services, with considerable emphasis on constant quality improvement in both in- and outpatient areas by sharing data among all areas of the health care system.

The practice of medicine will become progressively more digital, with most networks connected to huge computer systems involving multiple fail-safe backup programs and servers. Patient records will all be digitized and entered by voice-activated programs or keyboard typing. Clinical software will continuously interact with physicians utilizing a variety of standardized algorithms for diagnostic and therapeutic strategies. These programs also will monitor patient compliance through connections to pharmacies in order to ascertain if individual patients are actually filling their prescriptions. Drug dosage and avoidance of harmful drug interactions will be an important part of the clinical software, which will be constantly updated from national databases containing clinical guidelines and pharmaceutical information. Thus, the practice of medicine will become considerably more standardized compared with our current system. Pharmacy and therapeutic decisions will be locally or nationally regionalized, thereby standardizing the use of pharmaceutical agents throughout a region or nationally, enabling negotiating to achieve lower pharmacy costs. Data from the health networks will be collected, analyzed, and used to improve patient protocols and outcomes.

It is even possible that patients will have small embedded microchips, inserted subcutaneously, containing large volumes of detailed medical information, or carry security-encoded flash drives on key chains with their medical information. Patients would control access to this information except in emergency situations. The information on the chip or drive would be updated constantly. This will help medical personnel to know the most recent clinical and laboratory information on each patient. A simpler version of such a system is already in use by many veterinarians who deal with domestic pets. Another innovation will be routine genomic characterization for each individual. Primary care physicians and nurse clinicians will be aware of a particular patient's disease proclivities based on this genomic information. This information will be used for both preventive counseling and disease intervention.

Many patients will be more medically sophisticated than today. This will be the result of widespread educational efforts, particularly in young schoolchildren who will grow up with considerably more health knowledge than their parents, as well as with an increased ability to evaluate the quality of the information received. The Internet also will play an important role here.

Medical malpractice litigation will be much less common than today because of more standardized evaluation and treatment algorithms and because of, at long last, tort reform in this area. Malpractice tribunals or no-fault courts will function in many states and will adjudicate the overwhelming majority of patient complaints and poor outcomes.

Medical education will be substantially cheaper than today because of an “all players” tax that will subsidize medical education. These taxes will be imposed on insurers, health care networks, and taxpayers throughout the country. Physician salaries and insurance payouts to health care networks will be regulated nationally and will be based on anticipated effort corrected for the mean cost of living for the different regions of the US.

Telemedicine will become more and more widely used to assist with health care in remote locations. It is even possible that surgery will be performed using such a system. Many imaging tests will be interpreted by remote readers utilizing digital technology. It is even possible that some forms of health care will be delivered internationally through cyber systems.

Public health efforts to curb obesity and smoking, the major drivers of health care costs, will be accepted, and there will be a greater effort to limit fast foods and farm subsidies for corn products by making them more expensive, while at the same time lowering the cost of healthy food items. Cigarette taxes will increase and graphic labels on cigarette packs will become standard, lowering smoking rates.

In conclusion, the anatomy and physiology of future US health care will resemble our current system in many ways. However, technology, centralization, and standardization will be the hallmark of these futuristic networks that will employ the vast majority of health care workers including physicians, nurses, mid-level providers, and pharmacists.

There are pitfalls to this approach in that standardization and centralization may slow down innovation. In addition, we have not yet found a way to communicate health information across systems. The correct balance may take time to work out. Nevertheless, we hope that this future system will provide universal, high quality medical care at a reasonable cost.

BACK TO TOP

The Promises and Perils of the MHS' Implementation of the Patient-Centered Medical Home

Military Medicine
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With increasing resource scarcity and rising costs of health care, the Military Health System (MHS) must transform from a chronically inefficient and costly health care system that is overly reliant on specialty care and large institutions into a cost-effective and outcome-based system of health. Over the past 2 decades, the United States has witnessed economically unsustainable rises in health care costs in both the civilian and the federal sectors. During this period, however, the country has seen little improvement in access to and quality of health care. Multiple studies show primary care providers improve health care cost and quality, yet few initiatives have focused on reestablishing the primary care physician as the center of health care delivery.

The Patient-Centered Medical Home (PCMH) model rejuvenates the use of primary care providers as the central source of individual medical care. The PCMH is a commonly understood model; it is a modern adaptation of the classic, small town physician practice. Simply put, this is the

patient's home for all things medical. The PCMH uses a team of care providers to deliver continuous and comprehensive primary care and to ensure that the needs of the patient are met. In addition, specific focus is placed on preventive care and population health. Patients have increased access to providers on a continuous basis and can communicate with their care team via modern technology tools, such as secure messaging. Current research indicates improved patient experiences, better coordination of care, and decreased emergency department visits and inpatient admissions. All these improvements are essential for sustainability in today's economic environment.

DOD GUIDANCE

In 2009, the Department of Defense (DoD) directed the immediate implementation of the PCMH model. Reasons for PCMH adoption include better outcomes, decreased spending, lower utilization and admission rates, and reduced emergency room visits; all of which are needed to improve the quality of care delivered and to reduce health care costs. All primary care centers at military treatment facilities (MTFs) are required to assign all beneficiaries to primary care providers by name with access to their providers 24 hours a day, 7 days a week.

The key to effective implementation of this model is integration of primary care resources (providers, nurses, and support staff) into teams with a clearly identified leader. DoD guidance recommends 3 to 5 providers per team but does not delineate the actual numbers of patients or support staff per team. In addition, leadership encourages the use of open-access scheduling, increased online services, and innovative use of telephone triage and advice lines. Finally, it provides clear identification of reporting metrics. MHS leadership will use these access measures, coupled with patient satisfaction scores, to assess the PCMH's effectiveness.

To assist in the implementation of this program, TRICARE Management Activity published the MHS PCMH guidelines in June 2011. These guidelines “provide information and recommendations” but are not “a substitute for Service-specific guidance.” The Air Force began transitioning its primary care practices to a PCMH model in 2008 at Edwards and Ellsworth Air Force bases and expects full implementation in 2012 at all 76 Air Force MTFs. The reasons behind this early conversion were to address declining patient satisfaction and staff retention issues within the Air Force. The Navy's Bureau of Medicine and Surgery (BUMED) launched a specific patient home Web site where beneficiaries can learn about the PCMH initiative. Per its Web site, the Medical Home Port's mission is to “ensure that care is all-inclusive and integrated with all other care provided within our health care system.” The Army's Medical Command published its official order in January 2011 to coordinate individual MTF efforts and leverage enterprise services to provide “a common framework and methodology for the Army PCMH.” Per this order, 100% of direct-care enrollees will be in a PCMH no later than the beginning of fiscal year 2015.

IMPLEMENTATION AND EVALUATION

A change of culture, for both providers and patients, is required for full adaptation and success of the PCMH. Specifically, a renewed focus on quality and true accountability of patient outcomes is necessary for successful implementation. The Army model proposes 3 to 5 providers per team and 3 to 5 teams per home (COL Mark Reeves, personal communication). Additional team members for the 3 providers include 2 Registered Nurses, 6 Licensed Practical Nurses, and 1 Medical Clerk. The Navy's model is very similar to the Army with 3.75 support personnel per full-time equivalent (FTE). The Air Force model incorporates 1 physician, 1 mid-level provider, 1 nurse, and 5 medical technicians into each team. This

team is responsible for 2,500 impaneled patients and requires an estimated 90 appointments per week per provider. Army and Navy guidance for impanelment is 1,000 to 1,200 patients per FTE and 1,100 to 1,300 patients per FTE, respectively (CAPT Maureen Padden, personal communication).

Evaluation metrics for the PCMH is essential to verify its provision of cost-effective, improved outcomes. Patient surveys on satisfaction with care and accessibility are the cornerstone of this evaluation. In addition, PCM enrollment, percentage of services provided by each PCM, patient outcomes, and adherence to clinical practice guidelines will be used for evaluation of this model in the MHS. Additional areas of analysis include availability of support staff during clinical hours, pre- and post-PCMH implementation, patient and staff satisfaction surveys, ambulatory complexity case mix, Healthcare Effectiveness Data and Information Set (HEDIS) measures, and emergency room and urgent care utilization by enrollees. As with any program, accurate enrollment is essential for meaningful interpretation of these metrics.

A key threshold for each PCMH is National Committee for Quality Assurance (NCQA) recognition. Just as the MHS uses Joint Commission accreditation as an external evaluation of care and as a mechanism to show value to the tax payers, the NCQA recognition allows for the MHS PCMH to measure against an industry standard. BUMED policy expects each PCMH to achieve Level 1 recognition within 4 months of creation and Level 2 recognition within the following 6 to 12 months (CAPT Maureen Padden, personal communication). Through this external evaluation, MTF PCMHs can earn recognition in the MHS and throughout the medical community.

CHALLENGES

Incorporating this model into the MHS will be a cumbersome and complicated process. One of the fundamental challenges is standardization since TRICARE Management Activity chose an advisory role instead of dictating the model's implementation. Given service differences, this approach is understandable. However, since each service has the leeway to explore and create their own processes, there will be inevitable waste and disconnects between newly created systems and existing software. The use of technology to maximize clinical efficiency and communication with patients is essential. The MHS must rapidly incorporate interoperable software to facilitate the transition to PCMH and improve patient outcomes. Burdensome, complicated systems that fail to communicate with other services' systems are useless.

Another major challenge lies with the unique nature of the military and the MHS. Any effort to quantify the value of military health care must assess the price of readiness. Unfortunately, no such system exists. The inability to translate readiness into monetary terms affects the accuracy of comparisons between the military and civilian institutions and hampers the funding of MHS programs and initiatives. Furthermore, line commanders must value any shift in care delivery. Regardless of internal benefits and comparative evaluations, if military line commanders find the system unresponsive or unable to maximize readiness, it will fail.

Personnel shortages are another potential showstopper of this model. Without enough providers to adequately staff these medical homes, increased access and the overall benefits of this model will not occur. Further complicating this issue is the dual role many providers serve. Since many active duty providers are also leaders, officers in charge, and teaching staff, their availability is decreased. This impacts the staffing model

and number of FTEs available to serve the beneficiary population. In addition, teams must also have adequate clinical space to evaluate and treat their patient population efficiently.

Financial success of any process change is a fundamental requirement, especially in today's financially constrained environment. The PCMH must show value and profitability; unfortunately, defining these metrics will also be challenging. The MHS is not configured to capture preventive care financial savings. It, like most civilian models, reflects value in procedures and diagnoses. The needed transition is from overvaluing interventions to focusing on areas of improved outcomes and cost savings. Since “fee for service encourages overutilization, capitation encourages underutilization, and pay for performance encourages cherry-picking and clinically illogical care.” the solution is a hybrid method as encompassing as the model it is trying to quantify.

CONCLUSION

LTG Schoomaker, the former Army Surgeon General, while speaking during the Army Medical Home Transformation Conference, categorized the PCMH as a “pivotal initiative for Army Medicine” (April 26–28, 2011, San Antonio, Texas). The MHS contains the resources, personnel and organizational culture, and focus to make this successful. As an organization dedicated to the care of those who serve or have served in the military and their families, all members of the MHS recognize the need to provide coordinated and comprehensive care to our beneficiaries. The overall service delivered, which is cost-effective, high-quality care, is the true measure of profitability. With continuing tightening of the budget purse strings, the PCMH model must show profitability; the future of military medicine may depend on it.

BACK TO TOP

Sleep

Excessive daytime sleepiness in sleep disorders

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Abstract

Excessive daytime sleepiness is a significant public health problem, with prevalence in the community estimated to be as high as 18%. Sleepiness is caused by abnormal sleep quantity or sleep quality. Amongst others, multiple neurological, psychological, cardiac and pulmonary disorders may contribute. Risk factors for excessive sleepiness include obesity, depression, extremes of age and insufficient sleep. In the clinical setting, two of

the most commonly encountered causes are obstructive sleep apnoea and periodic limb movement disorder. There is continuing discussion of the mechanisms by which these disorders cause daytime symptoms, with intermittent nocturnal hypoxia, sleep fragmentation and autonomic dysregulation identified as important factors. The increased prevalence of obstructive sleep apnoea in obese subjects does not fully account for the increased rates of daytime sleepiness in this population and there is evidence to suggest that it is caused by metabolic factors and chronic inflammation in obese individuals. Sleepiness is also more common in those reporting symptoms of depression or anxiety disorders and significantly impacts their quality of life. Clinicians should be aware of factors which put their patients at high risk of daytime sleepiness, as it is a debilitating and potentially dangerous symptom with medicolegal implications. Treatment option should address underlying contributors and promote sleep quantity and sleep quality by ensuring good sleep hygiene. However, stimulant medication may be indicated in some cases to allow for more normal daytime functioning.

Introduction

Excessive daytime sleepiness (EDS) is the primary concern for many patients presenting with sleep disorder and a significant public health problem. The International Classification of Sleep Disorders (ICSD2) includes EDS as an essential feature for three diagnostic categories: narcolepsy, hypersomnia and behaviourally induced insufficient sleep syndrome. However, it is also associated with a wide range of diseases, including psychiatric and neurological disorders, pulmonary and cardiac conditions (Table 1). Frequently, there may not be an identifiable cause and the only diagnosis possible is that of idiopathic hypersomnia. However, the most common causes may be found in a disturbance of sleep quality, sleep quantity or other contributors. Most frequently, insufficient sleep duration is responsible for this symptom. This review will give an overview of some of the most common causes of EDS encountered in clinical practice and identify important risk factors for sleepiness in the community.

Prevalence of EDS

The prevalence of self-reported insufficient sleep or excessive daytime sleepiness in the general population has proved difficult to estimate. This is partly due to the lack of a standard definition of EDS, with some studies asking subjects to estimate the severity of their daytime sleepiness, others the number of days per week they experience EDS and others using the Epworth Sleepiness Score (ESS) to assess sleepiness. This score ranges from 0, indicating no daytime sleepiness, to a maximum of 24 (1). The latest “Sleep in America” poll conducted by the American Sleep Foundation found that 18% of respondents scored 10 points or more on the ESS, qualifying them as excessively sleepy (2). Other findings vary significantly. For example, a Japanese study which asked participants “Do you fall asleep when you must not sleep (for example when you are driving a car)?” identified a prevalence of 2.5% (3), whilst a recent Norwegian study in which the ESS was administered over the telephone found that 17.7% of participants had an ESS of 10 or more (4). A US study where EDS was identified based on a moderate or severe rating for the questions “do you feel drowsy or sleepy most of the day but manage to stay awake?” and “do you have any irresistible sleep attacks during the day?” reported a prevalence of 8.7% (5).

EDS is associated with poor performance in the workplace (6) and reduced quality of life with serious economic consequences: a recent Australian study estimated the economic costs of sleepiness at $AUS 4.5 million (approximately £4 million or $4.6 US Dollar), or 0.8% of GDP (7).

Importantly, sleepy drivers are at greatly increased risk of involvement in road traffic accidents, which are also more likely to be fatal due to the driver's failure to brake before impact (8).

Measuring sleepiness

Multiple Sleep Latency Test (MSLT) and ESS

The ESS is the most widely used subjective measure of sleepiness. This takes the form of a questionnaire where patients rate their perceived likelihood of falling asleep in eight everyday situations, to give a score from 024 points (1). Although the test is quick and easy to administer, it is dependent on the subject's interpretation of the rating system. It may be less reliable in very sleepy patients and can be affected by social, cultural and psychological factors such as anxiety or depression, and gender. The best available objective measure of sleepiness is mean sleep latency, as measured by the MSLT, where patients take successive naps at 2 hour intervals and the time to sleep onset is measured using polysomnographic criteria. Generally, a mean sleep latency of less than 15 minutes is considered being mildly sleepy, less than 10 minutes is moderately and less than 5 minutes qualifies as severely sleepy (11). However, both objective and subjective measures of sleepiness may be confounded by factors such as the patient's motivation to stay awake, sleep hygiene or the previous night's sleep quality and quantity.

Hypersomnia vs. fatigue

When investigating potential causes of EDS, it is important to distinguish between fatigue and excessive sleepiness, or hypersomnia. Fatigue is, like hypersomnia, a common complaint in general practice; it is a poorly defined feeling of exhaustion or strain associated with many chronic diseases and psychiatric disorders (13). Importantly, severely fatigued patients will not necessarily be sleepy, suggesting that the underlying pathologies are distinct. However, in clinical practice it can be difficult to distinguish between the two and there are recognised cases where fatigue and sleepiness may not be clearly defined (Table 2).

Causes of EDS

Sleep apnoea and sleep-disordered breathing

The most commonly encountered cause of EDS in a clinical setting is obstructive sleep apnoea (OSA). Sleep apnoea results from total or partial occlusion of the upper airway during sleep, causing apnoeas and hypopnoeas that lead to intermittent hypoxia, arousal from sleep with resulting sleep fragmentation and disturbed sleep architecture. OSA can be reliably diagnosed by using overnight polysomnography studies to assess the number of apnoeashypopnoeas per hour of sleep: the apnoeahypopnoea index (AHI). According to the American Academy of Sleep Medicine criteria, an AHI of 515 events per hour represents mild OSA, an AHI of 1530 as moderate OSA and an AHI>30 as severe. However, this criteria also considers the degree of EDS, which may not correlate with the severity as measured by the AHI. OSA is common worldwide, with the proportion of 3060 year old adults in the USA with an AHI ≥5 estimated at 24% of men and 9% of women (9). In Europe, estimates of 26% of men and 28% of women with an AHI ≥5 have been reported (14), whilst 9% of Hong Kong males were found to have an AHI ≥5 (15). The percentage of participants with OSA associated with EDS was lower in both the USA study (4% of men and 2% of women) and the Hong Kong study (4% of

participants), suggesting that OSA is highly prevalent but often asymptomatic. In the USA, it is estimated that 7580% of those with symptomatic OSA are undiagnosed, representing a significant population who could benefit from treatment (16).

Patients are rarely aware of nighttime disturbance other than snoring, but may complain of excessive sleepiness during the daytime or involuntarily falling asleep. Well recognised risk factors for this condition include an increased BMI, neck circumference, increased age, alcohol use, male gender and anatomical variations which narrow the upper airway.

A hypothesised mechanism for sleep disruption in obesity is that excess tissue around the pharynx narrows the airway, impacting on the critical occlusion pressure of the upper airway (17) and disrupting breathing during sleep. However, this theory has been criticised by a number of authors, who argue that the physical effects of increased fat cannot account for the degree of disruption to breathing.

The factors determining EDS in OSA are not well understood; the severity of OSA measured by AHI does not correlate well with the presence or degree of daytime sleepiness. Early studies found no link with sleep fragmentation and inconsistent results regarding the significance of intermittent nocturnal hypoxaemia (INH). However, nasal continuous positive airway pressure (CPAP) to correct INH in OSA, has proved to be an effective treatment for EDS, especially for those with a high AHI or severe sleepiness (20). Colt et al. suggested that this may be due to the correction of sleep fragmentation, rather than the elimination of INH. They studied OSA patients with nasal continuous positive airway pressure (CPAP) treatment to avoid apnoeas and hypopnoeas and correct sleep fragmentation, with or without the induction of INH. INH was induced by the intermittent addition of 100% nitrogen to the air delivered via CPAP. After 2 nights of treatment, there was no significant difference in the change of mean sleep latency in the MSLT observed in each group, leading the authors to suggest that nocturnal hypoxemia was not relevant to the pathogenesis of EDS. However, this study involved only 2 nights of INH and in this short-term design EDS may not significantly change; it is therefore unlikely to be a valid model of the pathological mechanism in OSA. OSA patients experience nocturnal hypoxemia over many years, a chronic process which is thought to cause daytime cognitive dysfunction and damage wake-promoting networks (21) and experience shows that sleep apnoea patients, even when controlled with CPAP therapy, may require weeks or even months of treatment to experience significant changes in their level of sleepiness.

Many studies may have failed to identify clear risk factors for hyper-somnolence because they attempted to evaluate a large number of variables in OSA patients with varying degrees of EDS. In a comparison of two groups of OSA patients with either severe EDS {mean [standard deviation, SD] ESS 17 [3] points, MSLT 4 [1] min} or no EDS, {ESS 5 [2] points, MSLT 16 [3] min}, Median et al. found that the EDS group had significantly increased sleep efficiency and worse nocturnal intermittent hypoxaemia (22). No significant difference was found in the apnoeahypopnoeaindex (AHI), arousal index or architecture of sleep phases. However, this study failed to control for the possible presence of obesity hypoventilation syndrome (OHS) in the EDS group (23). OHS patients are those who are obese and hypercapnic ($PaCO_2$ >45 mmHg or >6 kPa) without other causes of hypoventilation. In contrast, OSA patients are neither hypoxic nor hypercapnic by day (24). Patients with OHS are known to suffer worse daytime sleepiness than isolated OSA patients matched for age, AHI and body mass index (BMI) (25), potentially confounding the results of Mediano et al. Despite this, the consistent association between nocturnal hypoxaemia and EDS suggests that there may be a linking pathogenic mechanism.

Autonomic arousals during sleep have been discussed as another cause of EDS in patients with sleep-disordered breathing. These arousals involve brainstem nuclei which control sleep and wake cycles as well as cardiac function, leading to autonomic changes without changes to the EEG (26). OSA patients with EDS have an increased ratio of low to high frequency heart rate power (LF/HF) during sleep, a feature which is used to describe vagal and sympathetic tone (27). An elevated LF/HF power ratio indicates an increase in sympathetic output to the heart, possibly caused by repeated autonomic arousals. The significance of the LF/HF power ratio remains when OHS patients are excluded, whilst no difference in AHI and nocturnal hypoxaemia is found between patients with or without EDS (28). This evidence suggests that lower oxygenation and increased sympathetic cardiac tone during sleep are key factors contributing to EDS in patients with sleep-disordered breathing.

Periodic Limb Movement Disorder (PLMD) and Restless Legs Syndrome (RLS)

Periodic limb movement disorder (PLMD) is another commonly-encountered sleep disorder and potentially a cause of daytime sleepiness. It was initially identified in patients with RLS, with approximately 80% of RLS patients undergoing polysomnography found to have PLMD (29). However, PLMD is recognised as a separate condition from RLS (11). PLMD patients experience involuntary, but non-epileptic, stereotypical movements of their limbs, especially during non-rapid eye movement (NREM) sleep and during the 1st half of the night (30). Up to 25% of those presenting with other sleep disorders, such as OSA, rapid eye movement (REM) sleep behaviour disorder or narcolepsy may also suffer from PLMD (31) which, in part, explains the difficulties in understanding the effects of isolated PLMD. PLMD is commonly thought to be underdiagnosed, with prevalence in the community estimated at 3.9% (32). Several studies have suggested a role for dysregulation of dopaminergic transmission in the pathogenesis of PLMD, supported by the observation that dopamine agonists can be an effective treatment (33).

Recent work to establish the cause of EDS in PLMD has focused on the presence of autonomic arousals seen in this disorder. It is not obvious whether PLMs cause the arousals or are a reflection of altered autonomic function, although the periodic nature of movements in PLMD has led to comparisons with the “cyclic alternating pattern” (CAP) sometimes visible on the EEG and used as a marker of arousal instability during sleep (34). This pattern consists of the background EEG pattern (phase B) interspersed with bursts of delta wave activity (phase A). In 1996, Parrino et al. demonstrated that PLMs are mostly present during periods of CAP, and that there are increased limb movements during phase A activity. Ferrillo has suggested that this signifies that cortical arousals in PLMD are synchronised with a brainstem network regulating cardiovascular and respiratory changes, an arrangement which also underlies the CAP (35).

More recently, polysomnographic data from PLMD patients was used to examine the temporal relationship between changes in the EEG, heart rate and limb movements in both REM and NREM sleep. A number of studies have detected autonomic activation several seconds before either limb movement or EEG changes, suggesting that sympathetic activation leads to subcortical activation and facilitation of both cortical arousal and PLM (36). This, similarly to patients with sleep-disordered breathing, implies that sympathetic overactivity and not the PLMs may be the cause of sleep disruption, resulting in EDS.

EDS in the general population

Outside of the clinical setting, EDS is a widespread problem in the community, with estimated prevalence as high as 18% (2). A number of factors contribute to EDS and this may range from chronic insufficient sleep to poor sleep hygiene, use of modern media in bed and female gender. However, it can be difficult to identify significant risk factors. Interviews with 1997 1693 year olds in the UK, carried out by Groeger et al., found that 18% of subjects reported insufficient sleep on most nights; 58% of participants had suffered sleep problems on at least one night during the previous week (37), which was similar to the US sleep survey findings (2). However, only 5% of respondents reported sleeping less than 5 hours a night, with little gender difference in self-reported sleep duration (37).

The importance of long-term sleep insufficiency is unclear. Bonnet and Arand have argued that even small reductions of sleep time may have significant effects on the mean sleep latency and that reduced awareness due to sleepiness should be a serious public health concern (38). A study showed that loss of two hours of sleep can cause a 32% reduction in MSL (39). However, there is conflicting evidence, including animal studies, indicating that sleep times extend beyond those required if there are few incentives to stay awake, and this may have serious implications considering the social background of subjects and potential associations with underlying depression. Additionally, normal subjects will sleep for longer than usual in the right environment, even when EDS is not detected in the MSLT (40), suggesting that sleep times alone are of little use in estimating the severity of sleep disorders in the community.

Obesity and EDS

Obesity is a factor consistently linked to daytime sleepiness (41), with obese subjects twice as likely to report EDS than non-obese individuals (5). Whilst the increased prevalence of OSA in obese subjects may account for some of this difference, obesity is associated with hyper-somnolence even in the absence of sleep-disordered breathing. The reasons for this are not fully understood, although a number of factors have been shown to be predictive of EDS in obese patients, suggesting that the underlying mechanism is multifactorial.

Perhaps unexpectedly, a study of obese patients presenting for bariatric surgery found that AHI is not predictive of daytime sleepiness (44), suggesting that other factors may be more important than the presence of OSA. A recent cross-sectional study of OSA patients also found that obesity and depressive symptoms, but not AHI, were predictive of EDS (45). Even snoring has been found to be a predictor of sleepiness independently of AHI and other sleep parameters (46). The importance of factors other than sleep disordered breathing could also explain why CPAP therapy sometimes fails to correct EDS, especially in those with mild OSA (20).

Metabolic disruption and chronic inflammation in obesity may be more relevant to EDS than the mechanical effects of excess weight. This hypothesis may be underlined by the fact that adipose tissue is the largest endocrine organ, producing multiple adipokines. Vgontzas and colleagues have suggested that daytime sleepiness in obesity is a manifestation of a metabolic abnormality leading to hyperarousal at night and hypoarousal during the day. This was based on their observations that obese subjects have shorter sleep latencies and maintain sleep more effectively during the day, but have difficulty falling asleep and maintaining sleep at night. They also identified differences in sleep architecture, with obese patients experiencing more REM sleep in the early hours and less REM sleep in the later part of the night compared to controls. This latter point could indicate a circadian shift of REM sleep in the obese. In addition, levels of insulin and proinflammatory cytokines such as

interleukin6, tumour necrosis factor alpha (TNFα) are increased in the obese, supporting the hypothesis that obesity is a chronic inflammatory state.

Vgontzas's group examined whether these metabolic disturbances directly cause hyper-somnolence by trialling the use of etanercept, an antiTNF drug, to treat EDS in obese patients with OSA over three weeks. The mean sleep latency of the treatment group increased by 3.1 (1.0) min in the MSLT ($P<0.05$) (47), but, although this is a statistically significant result, this study involved only eight patients and large-scale studies may be needed to provide further understanding of the efficacy of such medical treatment.

Depression and EDS

In both obese and non-obese subjects, depression is strongly associated with sleepiness. However, 70% of those with depressive disorder complain of difficulty initiating and maintaining sleep and, thus, insomnia and fatigue rather than daytime sleepiness are often regarded as the most important problems, with a number of studies confirming the importance of insomnia as an independent predictor of suicidal ideation and behaviour. Most clinical rating scales for depression enquire about fatigue and tiredness rather than EDS specifically, so the significance of sleepiness in depression may be underestimated (50). Daytime sleepiness has been shown to correlate with increased depression tendency scores in the general public (51) and, in addition, patients with OSA have high rates of depressive disorders (1556% of patients vs. 67% of the healthy population) (52,53).

Examination of the link between sleepiness and depression is further complicated by the fact that both are influenced by other factors such as medication, comorbid systemic disease, alcohol use and anxiety. One approach to further understand these interactions has been to explore the role of genetic factors; both depression and daytime sleepiness are moderately associated with heritability (coefficients between 3848% for EDS and 1655% for depression. A large number of genes show an association with depression, especially within the serotonergic system, but only a small number of gene association studies for EDS has been completed. A cross sectional study of elderly twins found a significant genetic correlation of 0.4, suggesting the presence of genes which affect both conditions (50). Association of EDS has been found with variations in the orexin/hypocretin gene OC2R (60), and in narcoleptic patients with the catecholOmethyltransferase (COMT) gene necessary for degradation of dopamine (61).

Age and EDS

The prevalence of EDS also changes with age, with a number of studies finding increased EDS in the very young and very old. Prevalence of EDS decreases in those over 35 year olds, and increases again in the over 75 year olds range (5). EDS in the young is most likely due to insufficient sleep, whilst sleepiness in the old is more commonly associated with health problems such as diabetes and cardiovascular disease. Additionally, both sleep efficiency and sleepiness become less common in middle age, suggesting that EDS in older people is not solely due to less efficient sleep, but may also hint at changes in the everyday routines that working life demands. Another suggested mechanism is that hormonal sleep homeostasis is disrupted in older people. This is supported by the observation that administration of an arousal-promoting hormone, such as corticotrophin-releasing hormone, at the beginning of sleep causes more sleep disturbance in older subjects than younger (62).

Other risk factors for EDS

Cross-sectional studies have proved useful in identifying other risk factors for EDS in the general population, including shiftwork, poor sleep hygiene (e.g., using mobile phones before bedtime) and loneliness. Shift work sleep syndrome, a type of circadian rhythm disorder in which patients have difficulty falling asleep and waking up, is a well recognised cause of EDS (65) estimated to affect about 10% of those who work irregular hours (66). Working outside of daylight hours disrupts the circadian sleep-wake cycle and decreases both the duration and efficiency of sleep (67). A recent study of over 3,000 people found that night workers were 2.7 times more likely than day workers to feel moderately to severely sleepy at work (68). Additionally, sleepiness is a commonly encountered symptom in serious systemic disease. Examples include cardiac failure, respiratory illness (e.g., COPD), malignancy and a range of neurological conditions (6973).

Medication

People suffering from EDS may self-medicate or use caffeine, exacerbating the problem. Caffeine increases sleep latency and reduces both total sleep time and the percentage of stage 4 sleep (74). These effects are most likely due to its antagonism of the A1 and A2A adenosine receptors distributed widely throughout the central nervous system (CNS). Adenosine is known to inhibit cholinergic neurons located in the basal forebrain which are involved in arousal, so caffeine may promote wakefulness by disinhibiting this system (77). However, it is difficult to assess the impact of caffeine in the population due to the wide variety of caffeine sources and the inconsistency of caffeine intake. A British population-based study found that high consumption (>6 cups of tea or coffee per day) was associated with higher rates of severe sleepiness (78) compared to moderate caffeine intake. However, it remains unclear to what extent lifestyle issues may contribute to these results. Therefore, lifestyle adjustment and sufficient sleep quantity and quality (sleep hygiene) should be at the centre of therapeutic efforts, but if such measures are insufficient adjunct stimulant therapy (e.g., modafinil) may be used.

Summary

Daytime sleepiness is a common, debilitating and potentially dangerous symptom, which is likely to be under-recognised. It can be caused by multiple contributors, usually interfering with sleep quantity and sleep quality (Table 3). Patients with OSA often, but not invariably, suffer from hyper-somnolence as a result of poor nocturnal oxygenation and dysregulation of autonomic function. It is thought that these factors damage neural networks involved in wake promotion and disrupt sleep through autonomic arousals. In PLMD, the finding that autonomic changes precede the cortical activation causing leg movement suggests that an underlying disorder of autonomic regulation leads to disrupted sleep. Additionally, clinicians should be aware of factors which put their patients at high risk of EDS, including shift work, obesity, depressive symptoms and poor sleep hygiene. Of these, further investigation of the hypothesised mechanisms by which obesity may cause EDS are of particular interest, due to the widespread prevalence of both of these conditions. Treatment should always focus on the underlying cause, promoting appropriate sleep quantity and quality by establishing good sleep hygiene. Available stimulant therapy may be used as adjunct in certain cases. To optimise treatment of patients with EDS, it will be important to consider the wide range of unidentified risk factors which may be contributing to this symptom.

BACK TO TOP

Body mass index and obstructive sleep apnoea

Primary Care Respiratory Journal
Shneerson, John
4 Dec 2012

The article by Wall et al. in this issue of the PCRJ1 is one of the largest epidemiological studies ever to be carried out to assess the link between obstructive sleep apnoea (OSA) and obesity. Data were analysed from over a million subjects aged 50 years or over, and the body mass index (BMI) had been calculated in as many as 88%. The aim of the study was to assess the prevalence of OSA and snoring, and to evaluate any correlation with BMI, age, gender and social class.

The study suffers from the disadvantage that the diagnosis of OSA was based purely on whether or not this was recorded as a Read computer code in the primary care notes. This clearly leaves scope for significant underestimation, since in most cases the diagnosis would only be made after referral to secondary care with a confirmatory sleep study and clinical assessment. OSA would be more likely to be recorded if it was clinically severe and typical in its presentation, and if the subject requested (or had access to) secondary care assessment. These factors may at least partly explain the lower prevalence of OSA in the lower socioeconomic group as well as the underdiagnosis overall. Only 0.6% of this population were found to have OSA compared to previously ascertained figures of 4% in men and 2% in women. In addition, OSA was almost four times more common in males than females in those with a raised BMI, but in reality this may be an exaggeration. Women with OSA are more likely to present with insomnia or fatigue than men and with less excessive daytime sleepiness, and are therefore less likely to be diagnosed using conventional criteria.3

Interestingly, there does appear to be a “dose-response” curve between BMI and the prevalence of OSA. The odds ratio for OSA was 27.4 if the BMI was greater than 40kg/m2 whereas it was only 6.5 if the BMI was 3040kg/km2. This large increase may be real, but there may also have been inconsistencies in the measurement of BMI since there was no standardisation of how height or weight were recorded. There is also no information from the data about the interval between recording the BMI and the diagnosis of OSA. Other measurements of obesity such as the neck circumference have been found to be more closely linked to OSA than the BMI.4 Despite these reservations, the implication of this dose-response curve is that any reduction in weight in the obese may well have a significant therapeutic benefit in reducing the risk of developing OSA5 and probably its severity and complications such as hypertension, stroke or the obesity hypoventilation syndrome.6

The peak age prevalence of OSA in this report was between 60 and 64 years which is in line with other epidemiological studies. However, studies on individual patients with OSA have shown an increasing prevalence even in older age groups. This discrepancy is probably because older patients have fewer symptoms of OSA and are therefore less likely to be recognised in epidemiological studies.9 Apart from this, there are other

reasons why OSA may be missed in older people. Firstly, they may not present to primary care as readily as younger subjects since they may feel that their OSA symptoms are part of normal aging. Secondly, they are less likely to be aware of some symptoms such as snoring. And thirdly, other comorbidities may obscure the clinical features of OSA. For all these reasons, one of the messages of this study1 is that primary care physicians should be more alert to the possibility of OSA in older subjects presenting with unexplained symptoms – even if they are not the classical features of OSA seen in younger people such as snoring, excessive daytime sleepiness and witnessed apnoeas.

Many of the same considerations apply to the apparent underdiagnosis of OSA in the lower socioeconomic group. These patients may be reluctant to present to medical practitioners, other medical conditions related to social deprivation can obscure the diagnosis, and some subjects may have difficulty in expressing the symptoms which might trigger consideration of OSA as a diagnosis.

Cross sectional studies of this type can never establish a cause and effect between a diagnosis such as OSA and even closely correlated features such as a raised BMI, but the findings should make all primary care clinicians consider OSA when dealing with obese subjects. Conversely, strenuous attempts to reduce the BMI should be made once the diagnosis of OSA has been established. This survey highlights the importance of clinicians being aware of the difficulties in diagnosing OSA in certain patient groups – especially the elderly, women, and those in low socioeconomic groups.1 The epidemic of obesity in almost all developing countries makes Wall and colleagues' findings relevant to almost every medical practitioner who treats adult patients.

BACK TO TOP

Other

Costs of war: excess health care burdens during the wars in Afghanistan and Iraq (relative to the health care experience prewar)

Medical Surveillance
December 2012

Abstract

This report estimates the health care burden related to the wars in Iraq and Afghanistan by calculating the difference between the total health care delivered to U.S. military members during wartime (October 2001 to June 2012) and that which would have been delivered if prewar (January 1998 to August 2001) rates of ambulatory visits, hospitalizations, and hospital bed days of active component members of the U.S. Armed Forces had persisted during the war. Overall, there were estimated excesses of 17,023,491 ambulatory visits, 66,768 hospitalizations, and 634,720

hospital bed days during the war period relative to that expected based on prewar experience. Army and Marine Corps members and service members older than 30 accounted for the majority of excess medical care during the war period.

The illness/injury-specific category of mental disorders was the single largest contributor to the total estimated excesses of ambulatory visits, hospitalizations, and bed days. The total health care burdens associated with the wars in Afghanistan and Iraq are undoubtedly greater than those enumerated in this report because this analysis did not address care delivered in deployment locations or at sea, care rendered by civilian providers to reserve component members in their home communities, care of veterans by the Departments of Defense and Veterans Affairs, preventive care for the sake of force health protection, and future health care associated with wartime injuries and illnesses.

Introduction

The United States military has been continuously engaged in combat operations since October 2001. The most apparent medical effects of the war –musculoskeletal and internal organ injuries, traumatic brain injuries, vision and hearing decrements, and combat stressrelated mental disorders – have been described and discussed in detail.17 In addition, however, there are many disabling effects of wartime service that are not directly related to combat (e.g., family stressrelated conditions, gynecological and fertility disorders, skin disorders, drug and alcohol abuse, motor vehicle accidents, depression, suicide ideation, sleep disorders).

On the other hand, some medical problems affect military members less during war than peace time. For example, while military members are serving in war zones, they are at lower risk of conditions that are endemic to the United States but not to war zones, are closely associated with recreational activities (e.g., bicycle, snow ski, swimming accidents), and so on. Also, military members may defer seeking care for some conditions while serving in war zones.

Because some illnesses and injuries that affect service members while deployed are not war-related (e.g., cancers), while others that affect nondeployed service members are war-related (e.g., injuries during deployment-specific training, sleep disorders), it is difficult to precisely characterize the types and amounts of care delivered during wartime that are directly related to war fighting.

However, the health care burden related to war fighting can be indirectly estimated by calculating the difference between the total health care delivered to military members during wartime and that which would have been delivered if participation in the war had been averted. Such assessments require comprehensive records regarding the natures and frequencies of medical encounters of military members during the war period (“observed experience”) – and a method of estimating the natures and frequencies of medical encounters of military members that would have occurred during the war period absent participation in the war (“expected experience”). The continuous surveillance for more than 15 years of the ambulatory visits and hospitalizations of U.S. military members (using standardized electronic medical records integrated in the Defense Medical Surveillance System)8 enables such estimates in relation to the wars in Afghanistan and Iraq.

This report summarizes differences between the medical care experience of active component members of the U.S. Armed Forces since the beginning of the wars in Afghanistan and Iraq and the medical care experience that would have occurred if the experience immediately prior to the war had persisted during the war.

Methods

The surveillance period was divided into prewar and during war periods. The prewar period was defined as 1 January 1998 through 31 August 2001; the war period was defined as 1 October 2001 through 30 June 2012. The surveillance population included all individuals who served in the active component of the U.S. Army, Navy, Air Force, or Marine Corps any time during the surveillance period.

Medical encounters for all illnesses and injuries of interest were identified by ICD9CM diagnostic codes between 001999 that were reported in primary (first listed) diagnosis positions on standardized records of ambulatory visits and hospitalizations. Encounters that were documented with records with other than illness or injury-specific diagnosis codes (ICD9CM 001999) in primary (first-listed) diagnostic positions were analyzed separately (detailed results not included in this report). Such encounters included those for care not specifically related to current illnesses or injuries (e.g., medical examinations, immunizations, screening tests) (V codes) and those documented with records that indicated the external causes (E codes) rather than the natures of injuries in primary diagnostic positions.

All records used for the analyses were routinely transmitted to the Armed Forces

Health Surveillance Center (AFHSC) and integrated in the Defense Medical Surveillance System (DMSS) for health surveillance purposes.8 The analyses included records of health care to military members in fixed U.S. military and civilian (contracted/reimbursed care) medical facilities but not records of care delivered in deployed medical facilities or those at sea.

Health care burdens were summarized in relation to the ambulatory visits, hospitalizations, and hospital bed days that were required for the assessment, treatment, and rehabilitation of illnesses and injuries in 25 categories. The conditions included in each illness/injury category were specified by the Global Burden of Disease study (as modified for use by the AFHSC).9, 10

For the prewar and war periods, the total days of military service by members of the active components of the U.S. Armed Services and the numbers of ambulatory visits, hospitalizations, and hospital bed days associated with each illness and injury-specific category of interest were enumerated. This was the “observed experience” during estimates of excess/deficit war-related medical encounters. Rates of ambulatory visits, hospitalizations, and hospital bed days during the prewar and war periods were calculated by dividing the numbers of the respective encounters by the total person-years of active component service. Rates were expressed as encounters per 1,000 person-years of service.

The numbers of ambulatory visits, hospitalizations, and hospital bed days that would have occurred during the war period if the prewar experience had persisted were calculated by multiplying the relevant rates during the prewar period by the cumulative time of military service of active component members during the war period. This was the “expected experience” during estimates of excess/deficit war-related medical encounters.

“Excess/deficit” numbers of ambulatory visits, hospitalizations, and hospital bed days during the war period (relative to the experience during the prewar period) were calculated by subtracting the “expected” from the respective “observed’ numbers.

Results

During the 44month prewar period, active component members experienced 22,116,340 ambulatory visits (crude rate: 4,454.5 per 1,000 person-years [pyrs]), 272,381 hospitalizations (crude rate: 54.9 per 1,000 pyrs), and 1,202,578 hospital bed days (crude rate: 242.2 bed days per 1,000 pyrs) for evaluation, treatment, and rehabilitation of illnesses and injuries. During the prewar period, crude rates of ambulatory visits, hospitalizations, and hospital bed days were higher among service members who were female, in the Army, black non-Hispanic, and in health care occupations compared to their respective counterparts. In relation to age, crude rates of ambulatory visits were highest among the oldest (40+ years), and rates of hospitalizations and bed days were highest among the youngest (<20) service members (Table 1).

During the 129month war period, active component members experienced 84,021,447 ambulatory visits (crude rate: 5,586.4 per 1,000 pyrs), 891,903 hospitalizations (crude rate: 59.3 per 1,000 pyrs), and 4,277,740 hospital bed days (crude rate: 284.4 bed days per 1,000 pyrs) related to illnesses and injuries. During the war period, crude rates of ambulatory visits, hospitalizations, and hospital bed days were higher among females, Army members, black non-Hispanics, and those in health care occupations than their respective counterparts. In relation to age, crude rates of ambulatory visits, hospitalizations, and hospital bed days were highest among the oldest (40 and older), 2024 year olds, and youngest (<20 years) aged military members, respectively (Table 1).

The ratios of crude overall rates (war period versus prewar period) of ambulatory visits, hospitalizations, and hospital bed days were 1.25, 1.08, and 1.17, respectively.

By military/demographic subgroups:

Among all military/demographic subgroups, the largest relative increases in crude rates from the prewar to war period were among 40+ year olds for ambulatory visits (relative rate: 1.39), 3039 years for hospitalizations (relative rate: 1.19), and those in combat-specific occupations for hospital bed days (relative rate: 1.40) (Table 1).

The largest absolute increases in rates from the prewar to war period were among 40+ year olds for ambulatory visits (rate difference: +2,208 per 1,000 pyrs) and hospitalizations (rate difference: +9.49 per 1,000 pyrs) and those in combat-specific occupations for hospital bed days (rate difference: +88.1 per 1,000 pyrs). Of note, among females, rates of hospitalizations and hospital bed days were lower during the war than prewar period. Also, among service members younger than 20 years, hospitalization (but not bed day) rates were lower during the war than prewar period (Table 1).

Overall, there were estimated excesses of 17,023,491 ambulatory visits (mean: +131,965 per month), 66,768 hospitalizations (mean: +518 per month), and 634,720 hospital bed days (mean: +4,920 per month) during the war period relative to that expected based on prewar experience (Table 1).

Army and Marine Corps members accounted for approximately one-half (50.4%) of all excess ambulatory visits, two-thirds (64.8%) of excess hospitalizations, and three-fourths (77.9%) of excess hospital bed days during the war period. Service members in combat-specific occupations accounted for 11.3 percent, 33.6 percent, and 42.6 percent of all war period-related excesses of ambulatory visits, hospitalizations, and hospital bed days, respectively. Of note, during the war period, females accounted for nearly one-fifth (18.8%) of all excess ambulatory visits but had "deficits" of hospitalizations and hospital bed days (Table 1).

By illness and injury-related categories: During the prewar period, injuries/poisonings, musculoskeletal disorders, and respiratory infections accounted for the most ambulatory visits; the most hospitalizations were attributable to maternal conditions, injuries/poisonings, and mental disorders; and the most hospital bed days were attributable to mental disorders, maternal conditions, and injuries/ poisonings (Table 2).

During the war period, injuries/poisonings, musculoskeletal disorders, and mental disorders accounted for the most ambulatory visits; the most hospitalizations were attributable to maternal conditions, mental disorders, and injuries/poisonings; and the most hospital bed days were attributable to mental disorders, injuries/poisonings, and maternal conditions (Table 2, Figure 1).

From the prewar to the war period, mental disorders accounted for the largest illness/injury-specific increases in rates of ambulatory visits, hospitalizations, and hospital bed days. During the war period (relative to the expected based on prewar experience), mental disorders accounted for more than six million excess ambulatory visits, nearly 42,000 excess hospitalizations, and more than 300,000 excess hospital bed days. Remarkably, mental disorders accounted for 35 percent, 63 percent, and 48 percent of the total estimated excesses of ambulatory visits, hospitalizations, and hospital bed days, respectively, during the war period (Table 2, Figures 1,2).

As with mental disorders, during the war compared to the prewar period, ambulatory visit rates were much higher for musculoskeletal conditions and "signs, symptoms, and ill-defined conditions"; hospitalization rates were markedly higher for maternal conditions, skin diseases, and injuries/poisonings; and hospital bed day rates were remarkably higher for injuries/ poisonings.

Together, mental disorders, musculoskeletal disorders, and signs, symptoms, and ill-defined conditions accounted for 69 percent of all excess ambulatory visits; mental disorders, maternal conditions, skin diseases, and injuries/poisonings accounted for 93 percent of all excess hospitalizations; and mental disorders and injuries/poisonings accounted for 90 percent of all excess hospital bed days (Table 2, Figures 1,2).

Of note, of the 25 illness and injury-related categories of conditions of interest, three accounted for lower ambulatory visit rates, six accounted for lower hospitalization rates, and nine accounted for lower bed day rates during the war than in the prewar period. The category of infectious and parasitic diseases was the only one that accounted for lower ambulatory visit, hospitalization, and bed day rates during the war than in the prewar period.

BACK TO TOP

Providing Support Through Life's Final Chapter for Those Who Made It Home

Military Medicine
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Abstract

Military personnel are exposed to unique environmental hazards and psychological stressors during their service to our nation. As a result, military service personnel are at high risk not only for physical injury but for psychological trauma as well that may result in post-traumatic stress disorder, depression, substance abuse, and homelessness. These medical and psychosocial issues may hasten the development of life-limiting illnesses and may complicate the delivery of end-of-life care. Community-based hospice agencies often lack the resources and expertise to address the special needs of veterans. This article highlights the efforts of the Department of Veterans Affairs to provide comprehensive and co-ordinated end-of-life support for “those who served.”

Introduction

Hospice care is a guaranteed health benefit for all Department of Veterans Affairs (VA) enrollees, many of whom do not have Medicare or another payor source. To fulfill this obligation, the VA provides hospice care through its medical centers and through contracts with community hospice providers. Approximately 1,000 veterans receive VA-paid home hospice services each day.

The VA has had a long-standing interest in the development and assessment of end-of-life care models. The VA was the site of several initial landmark studies assessing the benefits of hospice care. In addition, the “Veterans Health Care Eligibility Reform Act of 1996” provided significant funding to evaluate a variety of VA- and community-based models for the delivery of hospice care. The VA was an important site for the evaluation of inpatient hospice and palliative care consultation services. The VA has also taken the initial steps in developing home telehealth monitoring for palliative care patients.

Currently, all VA medical centers are required to have a hospice and palliative care consult service. In a study by Penrod et al, veterans who received an inpatient palliative care consult were more likely to set goals of care with the health care staff. As a result, these veterans were less likely to be admitted to the intensive care unit and had fewer diagnostic and laboratory tests. Additionally, both veterans and family satisfaction survey scores were positively affected. In 2009, 59% of veterans who died in VA facilities received care from a palliative consult team. Fortunately, hospice and palliative care efforts extend beyond the acute care setting to provide comprehensive and longitudinal end-of-life care that focuses specifically on the needs of veterans.

The Special Needs of “Those Who Served”

Military service is associated with significant life stressors that are largely unparalleled in the community workforce. Many combat veterans suffer from chronic pain because of service-related injuries. Traumatic brain injury, spinal cord injury, and amputations are common among combat veterans.

As a result of their service to our nation, many veterans have been functionally and/or cognitively impaired for years preceding their terminal diagnosis. Older veterans enrolled in the VA have a higher rate of dependency than age-matched nonveterans.

In addition, there are medical conditions relevant to each generation of military service. For example, veterans of the World War II and Korean War era may have complications related to exposures to cold injury and radiation. Large numbers of Vietnam era veterans were exposed to agent orange.10 Before 1975, tens of thousands of veterans were enrolled in medical experiments involving radioactive, chemical, and biological agents.11 Some veterans may perceive that they are underappreciated for their service and that the extreme sacrifice of their fallen comrades has been forgotten by our nation. Veterans also encounter civilian health care professionals who are often unaware of the special demands of being a soldier and the heroic sacrifices of America's heroes.

Major depression and other mental health disorders are also common among combat veterans with specific biological, psychological, and social vulnerabilities.12 Of great concern is the high prevalence of post-traumatic stress disorder (PTSD) among combat veterans. PTSD is an anxiety-related disorder that is associated with re-experiencing (nightmares/ “flashbacks”), hyperarousal, emotional numbing, and social avoidance. It is estimated that 11 to 20% of veterans from Operations Iraqi and Enduring Freedom and 30% of Vietnam veterans suffer from PTSD symptoms.13 If untreated, PTSD can have a major impact on the patient's psychological and physical health. Many veterans are never diagnosed, especially those who had not sought care at a VA facility. Even for those who seemed to have successfully transitioned to civilian life, there may be a resurgence of PTSD symptoms during episodes of delirium.14 In addition, Alici et al reported that 17% of veterans had PTSD-related symptoms during the last month of life.15 Early recognition is important, as PTSD can have a strong negative impact on the dying process.14,15

Issues of substance abuse, divorce, unemployment, and homelessness are common in combat veterans with underlying mental health and cognitive disorders.12 Despite representing only 8% of the population, veterans account for 23% of the homeless population.16 Another 1.5 million veterans are considered to be at risk for homelessness. Homeless veterans are older and more educated than homeless nonveterans with similar rates of alcohol and drug abuse problems. As with the general homeless population, 45% suffer from mental illness and 70% have alcohol or drug abuse problems.

Psychosocial issues often amplify in the setting of an advanced illness or a life-limiting prognosis. Broken marriages and strained family relationships can reduce the social capacity that a veteran has to cope with the changes that arise during the dying process. Families of former soldiers may have been serving as caregivers for years, and in some cases, decades before the additional stressors associated with end-of-life care arise. Community-sector hospice providers may have difficulty in addressing these psychosocial issues because of insufficient resources or expertise. The VA recognizes the challenges facing veterans and their families and has implemented multiple system-based changes to overcome many of the barriers faced by community-based hospice providers.

Recent Trends Among Community-Based Hospice Providers

Community-based hospice agencies are reimbursed on a per diem rate. Over the last decade, median enrollment has remained stable at 18 days; however, the average length of stay has increased from 54 to 86 days.17 In its 2009 report, the Medicare Payment Advisory Commission noted a positive correlation between hospice profit margins and average length of stay.18 As Medicare faces increasing fiscal austerity measures, hospice agencies will face ever-tighter budgetary constraints. Such scrutiny will likely focus on those patients with longer lengths of stay. The concern is that community-based agencies will be forced to provide shorter periods of service and restrict the services that they provide to patients.

For patients enrolled in a Medicare Advantage Plan, the election for hospice requires the patient disenroll from their current plan and re-enter the fee-for-service system for their nonhospice care needs. Community-based hospice programs, even those that are owned by a health care system, often operate as interdisciplinary teams working in relative clinical isolation from other health care professionals (hospitals, physician offices, emergency departments, etc.). With the proliferation of accountable care organizations and the proposed piloting of payment bundling demonstration models, there is increased interest in the co-ordination of clinical services across the health care continuum. Fortunately, the VA has taken the initiative to develop a model where hospice and palliative care services are an integral part of the comprehensive health care package. In an era of emerging health care reform, this model may serve as a replicable model for non-VA health care systems.

Role of VA Hospice and Palliative Care

What has emerged is the VA's commitment to integrate palliative care across the health care continuum (acute care, primary care, and long-term care). The entire VA health care system uses an electronic health record to facilitate communication between long-term care, palliative care, inpatient, and outpatient health care professionals. Access to a dynamic, accessible, and comprehensive medical record minimizes the risk of duplicating medical services and provides the hospice and palliative care team with the information needed to have impactful end-of-life discussion.

Current Medicare hospice reimbursement applies to patients with an estimated life expectancy of 6 months or less. Unfortunately, many veterans have chronic end-stage illnesses with longer trajectories that will have episodes requiring greater palliative management before referral to hospice care. VA services are not confined by the Medicare hospice benefit restrictions and the potential financial pressures of community-based hospice agencies to “game the system” by the underuse of resources. The VA can, therefore, be able to provide high-cost palliative care interventions that could potentially improve the patient's quality of life. In selected cases, interventions, such as blood transfusions, palliative radiation, tube feedings, and intravenous antibiotics could improve the patient's quality of life. In other cases, veterans and care givers may need time to digest their prognosis and fully establish their goals of care.

Community hospice agencies provide several days of inpatient care for patients who are unable to achieve crisis symptom control in the home environment. Home health aides may also be provided by the agency. However, even with increased home support, some veterans become too weak to care for themselves and may lack sufficient family support to assist with their activities of daily living. In such cases, nursing home care is

not included in the Medicare hospice benefit. The VA fortunately recognizes this common clinical predicament and provides up to 90 days of inpatient hospice care at its Community Living Centers (nursing homes).

The ability to provide extended housing support also allows the VA to provide effective end-of-life care to the homeless veteran. Most community-based hospice agencies lack the resources and expertise to address the social needs of these socially disadvantaged veterans. The VA has a variety of mechanisms to provide funds for temporary housing or long-term care depending on the homeless veteran's needs. In addition, the Community Living Centers are also a potential resource for homeless veterans in need of a place to live while receiving hospice care.

Residents in a Community Living Center share the common history of military service. Large numbers of Community Living Center staff are also veterans. A resident may develop a camaraderie that for some veterans may be comparable to family relationships. These relationships are of particular value to both veterans and their support system as they face the challenges of life-limiting illness.

Another important component of VA hospice care is the recognition of the Veteran's military service. As part of this recognition, many VA Community Living Centers provide ceremonies honoring the military service of the deceased Veteran. For example, at the Orlando VA Medical Center, when a death occurs (regardless of time of day or day of week) staff are notified and gather in the room and halls. The gurney carrying the veteran is draped with the American flag. During regular hours, taps is played overhead alerting the veteran's comrades that one of their own has died. If family members are available, they are joined by staff and proceed to the memorial wall for a prayer service and the lighting (electric) of the memorial candle with a prayer service. The procession then proceeds to the entrance for the removal of the body. The halls are lined with the veteran's brothers and sisters in arms along with the VA Community Living Center staff for the rendering of a final salute.

All VA facilities have palliative care co-ordinators who collaborate with community-based hospice programs to facilitate seamless transitions of care. They also serve as an educational resource for both patients and VA staff. The VA can leverage its significant resources in mental health services to provide extensive expertise in the assessment and management of PTSD, substance abuse, and depression. In addition, the Home-Based Primary Care Program can be used to provide comprehensive interdisciplinary clinical care services for the nonhospice health care needs of homebound veterans.

The VA has also invested significant resources in the development and implementation of end-of-life educational programs. The VA collaborated with the Center to Advance Palliative Care (CAPC), the End-of-Life Nursing Education Consortium, and the Education in Palliative and End-of-Life Care program to incorporate veteran-specific needs and approaches to these educational programs.

The VA also provides additional support, training, and expertise for community-based hospices to address veteran-specific issues at the end of life. To improve the capacity of community-based programs to provide high quality hospice care for veterans, the National Hospice & Palliative Care Organization (NHPCO) and the VA developed the program, “We Honor Veterans.” Part of the program's mission is to set the standards for “partnership” between community hospice providers and the VA. There are 4 levels of partnership based on the provider's ability to meet Veteran-specific educational and system targets.19 In addition, the NHPCO and the VA have developed Hospice Veteran Partnership (HVP) programs.

HVPs are coalitions of VA facilities, community hospices, end-of-life care or community organizations, and others working together to advocate for veterans in need of end-of-life care.

The VA has taken the lead in instituting system-wide outcome measurements to assess the quality of hospice care provided to its beneficiaries. As part of this effort, the VA developed the Quality Improvement Implementation Resource Center to help measure and respond to identified issues and to share best practices across all VA sites. The results are then shared both in-house and as to the community through collaboration with the NHPCO, CAPC, and other interest groups. The goal of this collaboration is to make this expertise available wherever veterans are accessing palliative and hospice care.

The VA also utilizes the national Performance Reporting and Outcomes Measurement to Improve the Standard of Care at End-of-Life survey. This survey involves the interviewing of family members of all veterans who passed away within a month of receiving VA inpatient or long-term care. The survey focuses on the family's perception of the VA's ability to address the issues of communication, emotional and spiritual support, pain management, and personal care needs.

Conclusion

Because community agencies are largely dependent upon capitated reimbursements, impending Medicare cutbacks and greater regulatory constraints will likely increase the financial pressures on community-based hospice agencies to limit services to those who are dying. Whether such cutbacks will negatively impact the ability of these agencies to meet the needs of patients remains unknown.

The VA continues to invest substantial resources in developing hospice and palliative care policies and programs. In fiscal year 2013, $7.2 billion (up $550 million from fiscal year 2012) is being appropriated to expand institutional and noninstitutional long-term care services including palliative care services. This commitment has positioned the VA to sustain its commitment to the burgeoning number of veterans needing comprehensive hospice and palliative care services. Future studies are needed to compare the quality and costs of care for veterans provided by the VA versus that provided through contracted community services.

BACK TO TOP

Promoting Reintegration of National Guard Veterans and Their Partners Using a Self-Directed Program of Integrative Therapies: A Pilot Study

Military Medicine
William Collinge, MPH, PhD; Janet Kahn, PhD; Robert Soltysik, MS

ABSTRACT

This article reports pilot data from phase I of a project to develop and evaluate a self-directed program of integrative therapies for National Guard personnel and significant relationship partners to support reintegration and resilience after return from Iraq or Afghanistan. Data are reported on 43 dyads. Intervention was an integrated multimedia package of guided meditative, contemplative, and relaxation exercises (CD) and instruction in simple massage techniques (DVD) to promote stress reduction and interpersonal connectedness. A repeated measures design with standardized instruments was used to establish stability of baseline levels of relevant mental health domains (day 1, day 30), followed by the intervention and assessments 4 and 8 weeks later. Significant improvements in standardized measures for post-traumatic stress disorder, depression, and self-compassion were seen in both veterans and partners; and in stress for partners. Weekly online reporting tracked utilization of guided exercises and massage. Veterans reported significant reductions in ratings of physical pain, physical tension, irritability, anxiety/worry, and depression after massage, and longitudinal analysis suggested declining baseline levels of tension and irritability. Qualitative data from focus groups and implications for continued development and a phase II trial are discussed.

INTRODUCTION

Psychological distress and adjustment difficulties among military veterans returning from Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) and their relationship partners are well documented. Screening efforts suggest that up to 42% of National Guard veterans and roughly one-third of all returning veterans have problems that warrant mental health treatment, yet most are not receiving treatment. Many returnees express concerns about interpersonal conflict, highlighting the potential impact of deployment-related psychological distress on the well-being of veterans' family members, friends, and coworkers.

Perceived stigma associated with seeking behavioral health services remains a barrier to needed treatment. Sayer et al reported both individual and sociocultural barriers cited by veterans as reasons for not seeking treatment. With the numbers of veterans that will be reintegrating into community life in the coming years, the long-term impact of untreated or undertreated mental health problems is expected to impact communities for years to come.

As a distinct population, members of the National Guard face circumstances different from those of veterans of other branches of the military in terms of access to services during reintegration. Rather than returning to a base that may offer a comprehensive range of services and the camaraderie of others who have shared their experiences, they return to their home communities as “citizen soldiers.” Although eligible for Veterans Administration (VA) benefits, distance to VA facilities and Vet Centers may pose an obstacle that limits their use of those opportunities, particularly in rural states. Although other veterans who return to a base spend their days among those who recognize their service, rank, and experiences, and may also be alert to signals of mental difficulties, National Guard veterans returning to prior jobs may well be earning less pay, having less responsibility, and receiving less respect from coworkers who have never experienced them in their military capacities. From a

community health perspective, National Guard veterans are a population at significant risk of being underserved in terms of mental health needs. Thus, innovative interventions that overcome the psychological, geographical, and financial obstacles to accessing formal services and help this population reintegrate and adjust to community life in the long term are needed. Of particular interest are interventions that target maladaptive coping strategies commonly addressed in cognitive behavioral interventions such as worry, self-punishment, and social avoidance, and that bolster social support as these may reduce combat-related symptoms in this population.

This article reports pilot data from a phase I National Institute of Mental Health–funded study of a behavioral health intervention designed for autonomous use at home by National Guard veterans and partners of their choice to promote reintegration and well-being. The project is entitled "Mission Reconnect: Promoting Resilience and Reintegration of Post-Deployment Veterans and Their Families." The intervention, delivered by CD, DVD, and print, integrates instruction in evidence-based complementary therapies supporting both individual and relationship well-being. The program is designed to be self-directed with its different elements used at home, at work, or anywhere the participant finds them helpful. People may use each element of the program as frequently or infrequently as they like. Using it requires neither travel to VA or other facilities nor labeling oneself as in need of mental health care. The wellness-oriented techniques in this program are appropriate for people across a broad spectrum of mental health status and may be used by themselves or as an adjunct to individual or group therapies. Thus, the program may be able to reach people who are geographically isolated from services as well as people who are reluctant to use mental health services.

Mission Reconnect includes meditative, contemplative, and relaxation techniques and use of touch with a partner in the form of simple massage. Hundreds of small clinical trials indicate that mindfulness-related practices may offer significant benefits for a broad spectrum of health and mental health outcomes including stress, depression, and post-traumatic stress disorder (PTSD), including with military populations. However, given the size and quality of these studies (many, for instance, lacked plausible comparison groups), their findings must be taken as suggestive rather than definitive. A recent systematic review of complementary and alternative medicine (CAM) therapies for depressive and anxiety disorders concluded that "For anxiety disorders, there is limited evidence on the effectiveness of meditation (n = 2 studies) …. Relaxation and/or breathing retraining show promise as a CAM therapy …. Mindfulness-based stress reduction has shown positive effects on anxiety and depressive symptoms. However, studies are poor to fair quality." Other systematic reviews have drawn similar conclusions.

The literature on massage is somewhat stronger, with massage methods, including simple relaxation massage, having been established as beneficial for a broad spectrum of conditions, with reductions in anxiety and pain among the most common benefits.

While using these often-studied techniques, this investigation breaks new ground in part by delivering the instruction solely through self-directed media. In our own prior research, we found not only that people are able to learn simple touch and massage techniques from video with no personal instruction but also that the resulting massages produced reductions of pain, fatigue, anxiety, and depression, on a par with those of professional massage therapists. Although mind–body techniques are now taught in many medical schools, and their use is fairly widespread, we found no research on the effects of these techniques when taught exclusively by CD and/or audiotape even though tapes and CDs teaching mind–body techniques are ubiquitous. Although both massage and mind–body techniques are increasingly used in VA and Department of Defense sites around the country, our program's emphasis on self-directed media delivery of instruction is, to our knowledge, novel for the military population.

A key aspect of this program is targeting the dyadic system of a veteran and trusted partner for intervention. As stated in the Iraq War Clinician Guide, “The primary source of support for the returning soldier is likely to be his or her family. We know from veterans of the Vietnam War that there can be a risk of disengagement from family at the time of return from a war zone. We also know that emerging problems with ASD (acute stress disorder) and PTSD can wreak havoc with the competency and comfort the returning soldier experiences as a partner and parent.”

Although it is clear that formal mental health support is warranted for a large number of returning veterans, the people in their significant relationships are seriously affected as well. Early support for both the veteran and family may increase the potential for successful reintegration and family cohesion and reduce the likelihood or severity of future problems. Thus, the goal of Mission Reconnect is to offer an integrated program that leverages the relationship bond to encourage compliance, teaches stress-management skills to both the veteran and partner, and strengthens the relationship through joint use of wellness-related practices and guidance in generating compassion and appreciation for self and partner. This article reports on a phase I feasibility study of the approach.

METHODS

Recruitment and Sample

Recruitment was conducted with the cooperation of the Family Support and Assistance Programs (FSAPs) of the Army National Guard in both Vermont and Oregon. Subjects were recruited through presentations at postdeployment Yellow Ribbon events and through announcement in FSAP e-newsletters. Subjects were consented in person or by phone by the first author, and institutional review board oversight was provided by the New England Institutional Review Board, Newton, Massachusetts.

Baseline Phase

Subjects completed a 30-day baseline phase (no intervention) with survey data (described below) collected at the beginning (baseline 1) and end of the 30 period (baseline 2) to establish stability of baseline levels on standardized instruments.

Intervention Phase

Intervention began with a 2-hour orientation meeting in which subjects were given the intervention package (CD, DVD, manual, described below), viewed the materials as a group, and received instructions for home practice and data collection.

Intervention activities were of two types: (1) mind/body practices (meditative, contemplative, and relaxation techniques) taught by audio CD and print instruction and (2) massage for stress reduction (taught by video DVD and print/photographic instruction). Subjects were instructed to practice their choice of practices at least 3 to 4 times per week for 8 weeks and to try them all at least once during the course of the 8-week intervention period.

For massage, we instructed the subjects to practice massage techniques of their choice as often as they mutually agreed each week, suggesting that they may benefit from sessions of just a few minutes on up to 30 minutes or more. This would allow us to collect data on preferences and utilization patterns. In addition to these general instructions, we asked all dyads to do one 20-minute session per week as a “massage reporting session.” This would allow us to collect data on change in veterans' symptoms after a uniform dose of partner-delivered massage across the sample. (This weekly reporting session was not assumed to be representative of all sessions because of expected variations in duration.) We used this approach successfully in a prior study for assessing the ability of caregivers to provide relief through massage at home.

Data Collection

All data were collected online via PsychData.com. Data were collected both monthly and weekly. The monthly survey package was administered to both veterans and partners at baselines 1 and 2 (30 days apart), 4 weeks after beginning intervention, and again at 8 weeks (end of intervention). We used the PTSD Checklist—Civilian Version (PCL-C) for both the veteran and the partner. The PCL-C is a 17-item self-report scale that assesses the Diagnostic and Statistical Manual for Mental Disorders (Edition 4) diagnostic symptoms of PTSD using a Likert-type response format. It has demonstrated excellent internal consistency and test–retest reliability and correlates highly with other measures of PTSD. The PCL-C is used rather than the PCL-Military because it is important to assess veterans' responses to military and nonmilitary traumatic events. The PCL-C was used with partners and veterans since partners of veterans with PTSD may experience secondary trauma stress; veterans with PTSD have increased tendency toward intimate partner violence, and women who have experienced intimate partner violence have increased incidence of PTSD. The incidence of PTSD among partners of OIF/OEF veterans remains understudied.

To assess depression, we used the Beck Depression Inventory II (BDI-II). This is one of the most widely used instruments for measuring depression and uses a 21-item scale with reliability and validity established in numerous studies. Respondents are asked to rate their symptoms and attitudes using a 4-point scale. Normative values for a variety of patient populations are available as reliability figures, and comparison data on OIF veterans are provided in the section “Results.”

Subjects completed the Perceived Stress Scale (PSS-10), a 10-item Likert-scaled instrument to determine perceived stress levels over a 1-month recall period. The PSS is a validated and widely used scale for community samples with at least a junior high school education. The items are general in nature and free of content specific to any subpopulation group.

To assess capacity for compassion toward others, we used the Compassionate Love Scale (“Close Other” version), 21 items with a single score that assesses compassionate or altruistic love. Studies with three samples (N = 529) were used to create the scale that was tested in three new studies (N = 700) for validation and to identify correlates of compassionate love. Correlates were seen with indices of prosocial behavior such as helping others, social support to close others, and empathy with others (α = 0.95).

We also used the Self-Compassion Scale, a 26-item, 5-point Likert measure of 6 different aspects of self-compassion: self-kindness, self-judgment, common humanity, isolation, mindfulness, and overidentification. The scale has an appropriate factor structure and demonstrates concurrent validity (e.g., correlates with social connectedness), convergent validity (e.g., correlates with lower anxiety, depression, and

perfectionism, and greater satisfaction with life), discriminate validity (e.g., no correlation with social desirability or narcissism and appears to promote better coping than self-esteem), and test–retest reliability ($\alpha = 0.93$).

To assess quality of life, we used the Quality of Life Inventory (QoLI), a 32-item questionnaire with evidence for concurrent, discriminant, predictive, and criterion-related validity. It includes subscales for health, self-esteem, goals and values, money, work, play, learning, creativity, helping, love, friends, children, relatives, home, neighborhood, and community and an overall score. It was validated in a study involving 3,927 clients from various clinical settings and has been found sensitive to treatment-related change in naturalistic clinical settings and samples.

In addition to the above monthly survey instruments, both veteran and partner submitted a weekly report online each week during the 8-week intervention phase. The weekly reports recorded (1) frequency and duration of use of each intervention method offered plus (2) data from both the veteran and partner specific to the massage reporting session. Massage session data for the veteran comprised pre- and postsession ratings (recorded at time of massage on a two-sided, 5 × 8-inch session card) for levels of physical pain, physical tension, irritability, anxiety/worry, and depression, each rated for severity on a 0 to 10 scale. Massage data for the partner comprised areas of the body massaged and duration of the reporting session. All session card data were later entered by the subjects individually on their online weekly report.

Subject compensation was $20 for each weekly report and $25 for each monthly survey.

Instructional Materials

Video Instruction

A DVD was professionally produced with the following contents: (a) Introduction to Mission Reconnect by LTC Wayne Jonas, MD (Ret.), U.S. Army Medical Corps (welcoming and endorsing the program, 2:15), (b) Overview of the Project (W.C., purpose and goals, 1:45), A Word on PTSD (W.C., responding if symptoms arise during exercises, 1:21), How to Participate (W.C., setting aside time daily for wellness practices, willingness to test practices, 0:50), The Tools (W.C., types of practices, frequency and duration of use, 1:05), and (c) Instruction in Massage for Stress Reduction (J.K., overview, communication, preparation, affirming nonsexual intention; instruction in light massage techniques for the head and face, neck, shoulders, back, feet, and hands, using home furniture, 29:00).

Audio Instruction

The first two authors (W.C., J.K.) produced and recorded an audio CD with the following guided mind/body practices: “Centering” (basic mindfulness meditation instruction, 11:36, male and female voice versions), “Connecting” (contemplative guided meditation to encourage appreciation, compassion, and well-wishing for the partner and self, 7:03, male and female voice versions), “Deep Relaxation” (progressive relaxation through the body, 20:12, male voice), “Sound Into Silence” (following the tone of a struck chime into silence to facilitate meditative state, 4:16, female voice), “Movement Into Stillness” (seated, gentle rocking in progressively reduced movements until still, 5:32, female voice), and “Therapeutic Yawning” (evocation of the yawning reflex for a series of six to twelve yawns, 3:16, female voice). Subjects were encouraged to download the exercises to their mobile devices for practice any time of day they wished (though we did not collect data on devices used).

Printed Manual

The project manual (47 pages) includes the text of the introductory DVD material, descriptions and specific instructions for each of the guided mind/body exercises, and instructions for the massage techniques accompanied by photos.

Follow-Up Focus Groups

A convenience sample of 12 dyads (self-selected), who were able to attend at the scheduled meeting times, participated in two 90-minute follow-up focus groups after the completion of intervention. The purpose was to provide qualitative data on perceived impact of the program, usability of the materials, and recommendations for future development. The meetings were recorded, transcribed, and analyzed using QSR NVivo software for thematic analysis and coding of participant comments. Participants were compensated $50 for attendance.

Deployment-Related Interruption

Hurricane Irene struck New England roughly midway through the intervention phase for the Vermont cohort, requiring temporary deployment of some subjects. Given study's primary goal of assessing feasibility of the instructional approach, we decided to accommodate this by instructing affected dyads to pause their weekly reporting regimes until after the soldier returned so as to have 8 weeks of complete data from participating dyads.

RESULTS

Sample

Forty-three dyads were consented (27 Vermont, 16 Oregon). Of these, 23 veterans had 1 deployment, 18 had 2 deployments, and 2 had 3 deployments; 8 were OIF only, 20 OEF only, and 15 had been in both OIF and OEF. The sample includes service members with return dates ranging from 2002 to 2011. In all cases of dropout for which we were able to attain information, reasons given were related to time commitment involved to do project activities.

Fidelity

Subjects averaged over six times per week using one or more of the mind/body exercises and more than 2.5 times using massage; thus, for both modalities, fidelity exceeded the minimum instructions. Minutes per week devoted to both modalities combined averaged 61 for veterans and 63.3 for partners.

Mind/Body Practices

Of mind/body exercises, the Therapeutic Yawning, Centering, and Deep Relaxation exercises were most used. Subjects reported using the mind/body practices an average of 6.3 times per week; veterans averaged 27 minutes (SD 17.6), and partners 27.6 minutes (SD 15.6).

Massage Data

Mean duration of the 136 massage reporting sessions conducted was 22.7 minutes (SD 5.5), and the most prominent areas massaged were shoulders (75%), neck (72%), back (68%), head (36%), and feet (27%). Veterans reported highly significant reductions after massage for physical pain, physical tension, irritability, anxiety/worry, and depression. Change over time in veterans' presession ratings of symptom levels was analyzed by splitting each veteran's weekly reporting sessions into an early series and a late series, and then comparing the two series using Kendall's tau-b. Significant declines were seen over time in presession ratings for “physical tension” and “on edge/irritable.”

Survey Data

For all survey instruments, two baseline testings showed no significant differences; thus, the mean scores of two baseline testings were calculated for each subject for reporting as their “baseline”

Post-Traumatic Stress Disorder

Baseline scores for veterans on the PCL-C (mean 34.7, SD 13.6) were close to those of a study of 355 OIF veterans by Erbes et al (mean 35.5, SD 13.6, using the Military version of the PCL). The VA National Center for PTSD suggests cutoffs for screening and diagnostic purposes, with a screening cutoff of 25 for both active duty OIF/OEF veterans and civilians and diagnostic cutoffs of 28 and 30 to 38, respectively. Thus, there appeared to be substantial risk of PTSD in both veterans and partners in our sample, and both veterans and partners showed significant, though modest, improvements at both follow-ups.

Depression

Baseline depression scores for veterans (mean 12.6, SD 11.5) were higher than that of Erbes et al sample (mean 9.78, SD 7.95). The cutoffs used for the BDI-II are 0 to 9 for minimal depression, 10 to 16 for mild, 17 to 29 for moderate, and 30 to 63 for severe. Both veterans and partners showed significant reductions from the mild range to the minimal range at follow-up.

Other Scales

The PSS-10, Compassionate Love Scale, and Self-Compassion Scale are not diagnostic instruments, so there are no cutoffs. Partners showed significant reductions in perceived stress, and both partners and veterans had significant improvements in self-compassion at first follow-up and a trend at second follow-up. There were no significant changes on the Compassionate Love Scale, although over half of the subjects improved their scores at both follow-ups. The QoLI showed no significant outcomes on any subscales or total score. Those data are not presented here but are available on request.

Qualitative Data (From Focus Groups)

Participants reported practicing the exercises at home, at work, and in their vehicles. They viewed the project and each of its elements as well designed and beneficial. They endorsed the inclusion of all the elements even though they individually selected elements that best suited their personalities and/or life circumstances: “Regardless of where I was during the day, I felt like I could use Centering when I felt things getting kind of edgy and unsettled.” The overall program was described as providing useful ways of managing stress and improving their couple relationship: “… the Connecting, with thinking about what I appreciated in him, that was nothing new, but sharing it with him was a new piece and it helped me to open up more”, and “I think it's a great post-deployment type thing, because you are so separate for so long, it definitely did draw us back towards each other …” The participants strongly endorsed the program and proposed its broader availability to veterans and families: “… the guys are under a lot of stress, and we are under a lot of stress at home, even without the deployment. The military world is a different world, so anything from this aspect of empowering themselves and couples is just great, so thanks for bringing it to us.”

DISCUSSION

As noted in the section “Methods”, some dyads had data collection interrupted for emergency deployment during Hurricane Irene. Given our primary goal of evaluating feasibility of the instructional approach, we deemed delayed reporting to be an appropriate, though imperfect, solution to obtain a full 8 weeks of “normal use” data. Nine dyads were affected. These partners and some veterans were free to practice to the extent they could during nonreported weeks (though some veterans were working 18–20 hours per day). Four dyads required an additional 2 weeks, 3 an additional 4 weeks, and 2 an additional 5 to 7 weeks to achieve 8 weeks of reporting. For these 9 dyads, we cannot rule out potential historical confounds, either negative (e.g., greater stress) or positive (e.g., more practice, maturation), affecting their monthly survey data.

One of the most important findings of this pilot study concerns compliance/fidelity. We found that postdeployment National Guard veterans and their partners were able and willing to follow the recommended utilization of the proposed health promotion activities. Williams et al, in a review of CAM therapies that they conducted for the VA, found that the studies they reviewed often reported high rates of dropout. From this, they concluded that adherence to meditation may be problematic in a clinical setting. Although our methods do not allow a direct comparison to these studies, it appears that our adherence may have been higher, perhaps because of the support of the partner relationship.

This also contrasts with the often-lamented avoidance of help seeking or self-help commonly attributed to the military population. We observed during recruitment that most dyads entering the study were led by the partner initiating the contact (e.g., bringing the soldier to our table at a Yellow Ribbon event or telling their soldier “we need this” in response to a newsletter announcement). This affirms the viability, indeed the importance, of leveraging an existing trusted relationship as a strategy for engaging the veteran in health-promoting reintegration activity. Also, although we offered the project to veteran/partner dyads of all kinds, including parent/adult, child, sibling or friend, only one dyad entered the study that was not a spouse/life partner relationship. It appears that inclusion of massage, although deemed very helpful by those who participated in Mission Reconnect, calls for a level of intimacy that may not be seen as suitable by this population for other types of relationships. A somewhat different approach needs to be explored for nonpartnered veterans.

The data on massage for veterans suggest that partners may achieve significant acute effects for veterans' stress-related symptoms with minimal instruction in very basic massage techniques. Perhaps, more striking was the finding that presession levels of most symptoms declined over time,

suggesting declining background levels of most symptoms over the intervention period for veterans. Although postmassage ratings can be attributed to the massage, change in premassage ratings over time cannot be attributed to a single source with confidence. Participants reported during focus groups that they felt the whole program was beneficial in symptom reduction and relationship strengthening, but with no comparison group, we cannot be certain how much of their increased comfort is program effect or simply a matter of time and settling in, so to speak. This will be tested in phase II.

Although data were not collected on effects of veteran-delivered massage on partners in follow-up focus groups, there was consensus that partners wanted and appreciated receiving massage and that veterans found satisfaction in providing it. This was an unanticipated finding that we will explore further in phase II as potentially supportive of reintegration and relationship quality.

The survey data suggest that the intervention approach may yield significant reductions during the reintegration process, for both veterans and their partners, in measures of PTSD, stress, depression, and self-compassion. Depression scores (BDI-II) for both veterans and partners dropped from the mild range to the minimal range during intervention. Mean PTSD scores were below the threshold for the clinical diagnosis (50) from baseline onward, though a substantial range in scores was seen. The change in self-compassion scores is of particular interest in light of the concept of “moral injury” as related to PTSD in OIF/OEF veterans. The absence of significant change on the Compassionate Love Scale may be because of a ceiling effect, given that baseline scores were relatively close to the maximum possible score (105). The lack of significant effects on the QoLI may be a function of insufficient sensitivity of the instrument or too small a sample.

Finally, we recognize that reintegration and resilience are multifaceted constructs. In this feasibility study, we sought to assess potential for impact of the intervention on some variables that theoretically contribute to those broad constructs. In phase II, with feasibility established, we will focus more directly on measures of both reintegration and resilience, as well as sleep and relationship quality, in a four-armed randomized controlled trial. We plan to refine the intervention approach based on phase I data; use web-based delivery to computers and mobile devices so that it can be a fully autonomous, self-directed intervention; and then compare outcomes to a standard of care in-person program currently being used in the military to promote reintegration and resilience.

CONCLUSIONS

Veterans and their partners in this sample showed willingness to engage and use the mind/body practices and massage methods offered in Mission Reconnect and appeared to benefit from them. This study suggests that leveraging a trusted relationship may offer a viable approach to implementing self-directed interventions such as this for promoting well-being during postdeployment reintegration. Given that members of this branch of military are at particular risk for being underserved, in both short-term and long-term mental health service needs, autonomous and self-directed interventions may play an increasingly important role over time.

These pilot data encourage further development of the approach followed by testing with a larger and more diverse sample as is planned for phase II. Questions remaining to be answered include optimal duration of intervention period, longevity of effects, usability of the intervention by more ethnically diverse populations, and effects for veterans from various branches of the military.

BACK TO TOP

Anxiety, Social Support, and Physical Health in a Sample of Spouses of OEF/OIF Service Members

Military Medicine
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ABSTRACT

The goal of this study was to examine the relationships between heightened anxiety, social support, and physical health in a sample of spouses of returning Iraq and Afghanistan service members. 86 spouses were recruited nationally as part of a pilot trial of a military spouse telephone support group. Participants completed measures of physical and mental health via telephone including a screening tool for generalized anxiety disorder (GAD). Scores for social support and health outcomes were compared across two groups (positive vs. negative screens for GAD) using one-way analysis of variance analysis procedures. Path analytic techniques were used to evaluate the relative effects of anxiety and perceived social support on overall health and physical health comorbidities. A total of 38 participants screened positive for GAD. Participants with probable GAD reported having less social support than those screening negative for GAD. GAD participants also reported poorer overall health and more physical health comorbidities than their GAD-negative counterparts. Path analysis indicated that heightened anxiety is associated with worse overall health and social support does not buffer this interaction. The results suggest that anxiety-related health is a critical factor to be addressed in spouses of service members.

INTRODUCTION

Military spouses are at risk for experiencing high levels of stress, both while their significant other is deployed and upon return. Children, finances, and worry about the deployed are just a few of the stressors spouses often face. The current military conflicts are resulting in a high rate of redeployment, the likes of which have not been seen since World War II. Additionally, service members are being subjected to deployments as long as 15 months in length. This is highly stressful for service members whose rates of developing psychological disorders like post-traumatic stress disorder are positively correlated with length of deployment and number of deployments. Postdeployment can be a time fraught with considerable stress, where reunion functions as a stressor in its own right. Readjustment can be a taxing process and 22% of spouses of Operation Enduring Freedom and Operation Iraqi Freedom (OEF/OIF) veterans report reunion to be “difficult” or “very difficult.” Similar to research with service members, deployment and the length of deployments have been associated with worse mental health in spouses. Mansfield et al found that prolonged deployment was associated with more mental health diagnoses postdeployment among army wives, including anxiety

disorders, depressive disorders, sleep disorders, acute stress disorders, and adjustment disorders. A study of U.S. soldiers and marines found that postdeployment, military spouses experienced similar rates of major depressive disorder and generalized anxiety disorder (GAD) to married service members, although spouses were more likely to report that emotional problems and stress were having a significant impact on their lives. High prevalence of psychopathology in spouses is particularly important because of the emerging research on comorbidity with medical conditions.

Research has shown high rates of medical illness in psychiatric populations, particularly in depressed individuals. More recently there has been an increased focus on the relationship between anxiety and physical health. The presence of anxiety disorders has been associated with higher prevalence of physiological comorbidities when compared to healthy controls. Harter et al found that, even after controlling for gender, comorbid substance use disorders, and depression, individuals with anxiety disorders were more likely to report cardiac disorders, hypertension, gastrointestinal problems, genitourinary disorders, and migraine. Another study found that anxiety disorders were not only associated with a number of medical illnesses, but also significantly associated with poorer health-related quality of life and disability. Therefore, the stress of military deployments puts spouses at risk for negative mental and physical health outcomes.

One of the most natural protective structures in a spouse's world is likely to be the local community. This social support structure may serve as a buffer against the stress of the deployment cycle. Evidence for the buffering hypothesis of social support has been inconsistent, but Rosen and Moghadam found that, of several sources of perceived social support, only perceived support from wives of service members from the same unit served as a buffer against a service member's absence. More recent research on social support has indicated that certain forms of social support may be more effective than others. Moelker et al found that support from family, friends, and neighbors was deemed to be more useful than family support rendered by the army.

The purpose of this article was to explore the roles of social support and elevated anxiety in relation to physical health in a sample of spouses of OEF/OIF service members. The stressful circumstances of separation and reunion can have negative effects on the marriage, family, and especially the spouse's psychological and physical health. Prior research has focused either on the prevalence of psychiatric diagnoses or the role of social support in the lives of military spouses. This article emphasizes the intersection between anxiety and the potential buffering effects of social support for spouses of returning service members and seeks to extend the research on the negative effects of deployment on the mental health of military spouses by incorporating measures of perceived social support and physical health outcomes.

METHODS

The sample comprised 86 spouses of returning OEF/OIF service members. Participants in this article were recruited nationally for a pilot trial of a military spouse postdeployment telephone support group. Eligible participants were married to a service member, or living as married, for at least 1 year. They were spouses of service members who had been home for at least 1 month. Eligible spouses were in a committed relationship with the service member throughout his deployment and had telephone access. Individuals were excluded from this study if they had any auditory impairment that precluded telephone use or if assent for spouse's participation was not given by the service member. Spouses of returning service members were recruited through multiple avenues (Welcome home events, Veterans Affairs Medical Centers, The Wounded Warrior Project,

military bases, online, etc.). The majority of participants contacted the study through e-mail. Potential participants were sent informational materials. We screened interested individuals by telephone and obtained their consent for study participation. Data were also collected by telephone.

Measures

The Generalized Anxiety Disorder-7 (GAD-7) is a 7-item screening measure for anxiety disorders, with a focus on the symptoms of GAD based on Diagnostic and Statistical Manual of Mental Disorders-IV-TR diagnostic criteria. Participants rate the frequency of distress because of anxiety symptoms over the past 2 weeks on a scale ranging from (0) “Not at All” to (3) “Nearly Every Day.” The GAD-7 has shown good internal consistency reliability at 0.92. Scores on the GAD-7 range from 0 to 21 and a cut point of 10 has demonstrated good sensitivity (0.89) and specificity (0.82) in the detection of GAD.

Social Support Index

The Social Support Index (SSI) is a 17-item measure assessing the degree to which the family sees the community as a form of support as well as the level of integration of a family into their local community. The SSI was developed for the assessment of support-related resilience in military families. Participants rate their level of agreement with statements concerning their community. Items like “People can depend on each other in this community” are rated on a scale ranging from (0) “Strongly Disagree” to (4) “Strongly Agree, ” with total social support scores ranging from 0 to 68. The SSI has shown good internal consistency reliability at 0.82. The SSI has also shown good test–retest reliability at 0.83.

Self-Perceived Health

Self-perceived health was evaluated by a single item addressing general health. This item is from the general health subscale of the Short Form-36. Participants rated their general health on a 5-point Likert scale with anchor points of (0) “Excellent,” (1) “Very good,” (2) “Good,” (3) “Fair,” and (4) “Poor.” This is a simple, yet well-studied measure of overall health, which has been predictive of health-related events in several studies. The Short Form-36 has shown good internal consistency reliability in diverse populations, ranging from 0.65 to 0.94 with a median of 0.85.

Physical Health Comorbidities

These physical problems were assessed by summing the scores (“Yes”—1, “No”—0) in response to 2 questions, “Do you have, or has a doctor told you that you currently have, any of the following health problems (high blood pressure, stomach ulcers, irritable bowel syndrome, or any other serious problems with your stomach or bowels)?” These items were drawn from the Asset and Health Dynamics Among the Oldest-Old study, which adapted items from existing instruments, and have been used in national studies of stress associated with caregiving. The physical health comorbidities included were chosen because of characteristic patterns or preventability and health service needs. These physical health comorbidities are commonly associated with high levels of stress.

Data Analysis Plan

For the purposes of group comparisons, analysis of variance tests were conducted to assess group differences between GAD (GAD-7 score > 10) and non-GAD participants on social support, overall self-perceived health, and prevalence of physical health comorbidities. One-way analysis of variances were run to assess for differences between GAD and non-GAD participants on social support, overall self-perceived health, and prevalence of physical health comorbidities. We estimated path analyses to associations between social support and anxiety in relation to physical health using social support (SSI) and anxiety (GAD-7) as the independent variables regressed simultaneously on spouse health variables. Tests of moderation/buffering were run in accordance with Baron and Kenny's recommendations. We ran hierarchical regressions in which anxiety, social support, and an interaction term of anxiety and social support were entered into models predicting spouse health variables.

RESULTS

The sample was predominantly Caucasian (*N* = 73; 84.9%), all participants were female and the mean age of participants was 37.4 (SD = 8.97) years. On average, spouses had been married to their significant other for 10.4 (SD = 8.17) years. The number of service member deployments ranged from 1 to 20 (*M* = 2.55, SD = 2.77). The majority of service members were noncommissioned officers (*N* = 61.6%). The greater part of service members were enlisted personnel (*N* = 81.4%) with a remaining 18.6% who were commissioned and warrant officers, which is similar to the composition of current active-duty military personnel. Service members were largely Army (83%: active duty, reserve, national guard) with representatives from the Marines (8%), Air Force (3%: active duty, reserve, national guard), and Navy (6%). The mean GAD-7 score was 8.94 (SD = 5.70). The sample had a mean SSI score of 44.00 (SD = 8.63), a mean self-perceived health score of 1.92 (SD = 0.99), and a mean physical health comorbidities score of 0.51 (SD = 0.68).

Using the GAD-7 cut point score of 10, 44.2% (*N* = 38) of participants screened positive for GAD. The groups (GAD-positive and GAD-negative screens) did not differ on any demographic variables reported. Significant group differences emerged between the GAD (*M* = 40.95, SD = 8.59) and non-GAD (*M* = 46.42, SD = 7.95) groups on social support ($F(1, 84) = 9.34$, $p = 0.003$). Differences were also found between the GAD (*M* = 2.39, SD = 0.72) and non-GAD (*M* = 1.54, SD = 1.01) groups on the spouse's self-perceived health ($F(1, 84) = 19.35$, $p < 0.001$). Significant differences also emerged between the GAD (*M* = 0.74, SD = 0.76) and non-GAD (*M* = 0.32, SD = 0.56) groups on physical health comorbidities ($F(1, 83) = 8.55$, $p = 0.004$).

Correlation and path analyses to examine the relationship between heightened anxiety, social support, and physical health were conducted using Predictive Analytic Software 18. The path analysis model estimated with anxiety and social support predicting perception of the spouses' overall health accounted for approximately 23% of the variance in the perception of health outcome variable ($F(2, 83) = 12.14$, $p < 0.001$). The path coefficient from anxiety was significant and positive (0.44), whereas the path coefficient of social support was nonsignificant and negative (0.08).

The next path analysis model with physical health comorbidities regressed on anxiety and social support was also statistically significant but only accounted for approximately 8% of the variance in the outcome variable ($F(2, 82) = 3.49$, $p = 0.035$). Both independent variables contributed nonsignificantly to the model, with anxiety contributing a positive path coefficient (0.17), and social support a negative path coefficient (0.16).

The guidelines detailed by Baron and Kenny were followed to test if social support had a moderating effect on anxiety. Guidelines assert that the moderator hypothesis is supported if the interaction between anxiety and social support significantly predicts spouse health outcomes. However, because the interaction term did not contribute further significant variance to either model, the moderation hypothesis was not supported by the data.

DISCUSSION

To our knowledge this is the first investigation examining the relationship between heightened anxiety, social support, and physical health in spouses of service members. Psychological disorders, in particular anxiety disorders, have been associated with poor health outcomes. Social support may function as a buffer to the stressors experienced by spouses of returning service members during and after deployment.

In this sample, all predictor and outcome variables were correlated. As expected, the non-GAD group reported higher levels of social support than the GAD group. Conversely, the GAD group was more likely to endorse having poor health and physical health comorbidities than the non-GAD group. These findings are consistent with prior research, indicating that social support may serve as a protective factor for psychological health and that heightened levels of anxiety are associated with poor health and health-related quality of life.

With respect to path analysis, our first model, explaining self-perceived health, showed GAD-7 anxiety scores to have a relationship four times stronger with perception of health than social support. Twenty-three percent of self-perceived health variance was explained by anxiety and social support together. Individuals with higher anxiety scores had worse perception of their overall health, as expected.

In our second path analysis model explaining physical health comorbidities, neither anxiety nor social support yielded statistically significant path coefficients, and together they explained 8% of the variance in comorbidities. Interestingly, despite heightened anxiety differentiating between groups in terms of physical health comorbidities, no significant associations were evidenced for either predictor when the other was statistically controlled.

These findings highlight the importance of the relationship between anxiety and self-perceived physical health. The weak relationship between social support and self-perceived health in the first model is consistent with previous research, which has shown inconsistent support for the stress-buffering hypothesis of social support. The results suggest that moderation/buffering is not present in our data, because of the lack of a significant relationship between the interaction term of anxiety and social support and health outcome variables.

Despite the differences shown in the amounts of perceived social support between the GAD and non-GAD group, the evidence suggests that heightened levels of anxiety are an important factor to be addressed. This does not preclude the potential importance of social support for spouses. Measures of perceived social support, like the one employed in this study, are likely to be influenced by maladaptive cognitions that tend to accompany anxiety disorders and may not reflect the actual levels of social support available and provided to the spouse. Instead, it indicates the importance of further research on the benefits of specific dimensions of social support provided and received (e.g., emotional, tangible, advice) for spouses of service members at various points in the deployment cycle.

The cross-sectional nature of this study limits causal interpretations. Additionally, the small sample size and all female cohorts are limitations of this study. Although the study was open to men and women, no male spouses volunteered. The absence of a diagnostic, interview-based, measure of anxiety is a limitation although the GAD-7 is a recognized clinical screening instrument. Other limitations include the select number of comorbidities assessed and the absence of objective information on health functioning such as chart diagnoses and test results. Despite the select number of comorbidities, the physical health comorbidities assessed in this study are among the most common pathologies reported in individuals with heightened anxiety.

In conclusion, given that research has shown spouses of service members to be at high risk for developing psychological disorders like GAD and the high rates of somaticizing within this population, it is essential for primary care physicians to be adept at identifying anxiety symptoms in military or veteran spouses presenting with medical illnesses. Spouses presenting for services in primary care clinics should be screened for anxiety disorders, and the presence of an anxiety disorder should be factored in when addressing physical health complaints. This indicates the importance of psychiatric consultation in primary care clinics. The complex and reciprocal interactions between physical and mental illnesses point to the need for more research on the relationship between mental and physical health comorbidities.

The relatively frequent presentation of spouses of deployed service members for mental health services in primary care clinics also points to the need for adequate and appropriate treatment options available once a diagnosis has been made. Additionally, this highlights the importance of communication between physicians and mental health professionals and ultimately the integration of mental health and medical care. Finally, treatment providers should take care to be aware of, and to treat, the physical and mental health needs of spouses of service members presenting for services.

BACK TO TOP

Mammography Screening by Race/Ethnicity Among U.S. Servicewomen, 2009–2010

Military Medicine
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Abstract

Background: Mammography screening has been shown to vary by race/ethnicity and is often thought to result from variations in access to health care. The objective of this study was to compare the prevalence of recent mammography screening among U.S. active duty servicewomen by race/ethnicity using administrative claim data from the Military Health System, which provides beneficiaries with equal access to medical care. Methods: Mammography screening use during fiscal years 2009–2010 among non-Hispanic white, non-Hispanic black, Asian/Pacific Islander, and

Hispanic servicewomen was analyzed using logistic regression. Results: Overall, the prevalence of mammography screening during the study period was 61%. In comparison to non-Hispanic white servicewomen, Asian/Pacific Islander (OR [odds ratio] = 1.08; 95% CI [confidence interval] = 0.94–1.23) and Hispanic servicewomen (OR = 0.97; 95% CI = 0.85–1.11) were as likely and non-Hispanic black servicewomen were more likely to have a screening mammogram (OR = 1.09; 95% CI = 1.01–1.18). Screening mammography also increased with age, was highest in the Navy, was higher among officers than enlisted personnel, and did not differ by marital status. Conclusion: Although screening was slightly higher for non-Hispanic blacks than that for non-Hispanic whites, in general, racial/ethnic differences in mammography screening were not substantial in an equal access system.

Introduction

Breast cancer is the most common cancer among U.S. women and the second most common cause of death from cancer.1 However, breast cancer statistics vary by race/ethnicity. Although overall age-adjusted incidence rates are higher among white women than those among black women, mortality rates are higher among black women.1 In addition, although breast cancer incidence rates are higher among non-Hispanic white women than those among Hispanic women,2 5-year survival rates are worse among Hispanic women.3 Breast cancer incidence and mortality rates are lower among Asian/Pacific Islander (API) women than those among white women.2 The reason for the racial/ethnic variations in breast cancer outcomes is likely multifactorial and related to differences in cancer incidence, treatment, and disease presentation. For example, later-stage disease at diagnosis is more common among black and Hispanic women than among non-Hispanic white women.2,4

In comparison to white women, national survey data over the past 2 decades have tended to find comparable usage of mammography, which is an effective breast cancer screening tool,5 among black women and lower usage among Hispanic and API women.6–8 However, survey data, which rely on participants' self-report, tend to overestimate true usage and the resulting misclassification has been shown to be more extreme among black and Hispanic women than that among white women.9 After accounting for this differential misclassification, black women have been observed to have significantly lower mammography usage than white women.9,10 To our knowledge, the level of misclassification among API women has not been calculated, but if it is also assumed to be greater than among white women, then it is likely that the true disparities in mammography usage in the general population between white women and Hispanic women or API women are even greater than survey data indicate.

Variation in health care access likely accounts for much of the racial/ethnic disparities in mammography use. Racial/ethnic minority groups tend to have lower health care access, which has been shown to be inversely associated with mammography usage.11 National survey data have indicated that racial/ethnic disparities were attenuated or reversed after adjusting for health care coverage,6 which suggests that other factors may also influence mammography usage. However, as discussed above, survey data are susceptible to differential misclassification by race/ethnicity; therefore, the true association between race/ethnicity and mammography usage after controlling for health care assess is uncertain.

The Department of Defense (DoD) Military Healthcare System (MHS) provides universal health care regardless of race/ethnicity and thus offers a unique opportunity to conduct disparities research. The MHS medical claims data can be used to assess mammography usage to avoid the self-reporting misclassification described earlier. Although a previous medical chart review among DoD beneficiaries tended to observe higher mammography usage among racial/ethnic minority groups than among white women, this study included participants from a clinical trial at five national military medical centers and did not adjust for potential confounders.12 Therefore, it was unclear if these results could be generalized to non-volunteer DoD beneficiaries or if covariate adjustment would affect the results.

The objective of this study was to investigate if mammography screening among active duty servicewomen varied by race/ethnicity after adjustment for covariates using DoD-wide medical claims data. It was hypothesized that race/ethnicity would not be associated with mammography usage in this equal access health care system.

Methods

Data Source

This study assessed screening mammography usage by race/ethnicity during fiscal years 2009–2010 based on data from the DoD's MHS Management Analysis and Reporting Tool (M2). M2 encompasses multiple databases that include detailed demographics and medical claims information (diagnoses and medical procedures) on inpatient and outpatient care at military treatment facilities (direct care) or at non–military treatment facilities paid for by the DoD (indirect care). Clinical diagnoses of all medical conditions were coded using the International Classification of Diseases–Ninth Revision (ICD-9), and procedures were coded using ICD-9, Current Procedural Terminology, and Healthcare Common Procedure Coding System codes.

Study Subjects

All active duty servicewomen ages 40 to 62 years, who were non-Hispanic white, non-Hispanic black, API, or Hispanic (not exclusive of race), and did not have a history of breast cancer, were eligible for this study. The classification of a mammogram as screening (see below) required knowledge of prior medical diagnoses and procedures in the preceding 2 years; therefore, servicewomen were eligible only if they were continuously enrolled as active duty during fiscal years 2007–2010. Demographic information is automatically collected on active duty service members and was available in the Defense Enrollment Eligibility Reporting System, which is included in M2.

Servicewomen between ages 40 and 62 years at the beginning of fiscal year 2009 were selected for the study. Although there is some debate on the optimal age to start mammography screening, younger servicewomen were not included because no guidelines recommend routine screening before age 40 years. The American Cancer Society recommends annual screenings beginning at age 40 years13, whereas the U.S. Preventive Services Task Force recommends biennial screening beginning at age 50 years.14 Servicewomen 63 years or older at the beginning of fiscal year 2009 were not included because they would have become eligible for Medicare during the assessment period (2009–2010); therefore, their medical data in M2 may have been incomplete. There are also very few active duty servicewomen in this age range.

Exclusions were also made for race/ethnicity, history of breast cancer, and military branch. Racial/ethnic groups other than non-Hispanic white, non-Hispanic black, API, or Hispanic (not exclusive of race) were not included because of small sample sizes. Servicewomen were excluded from the analyses if records indicated that they had a recorded history of breast cancer during the 2 preceding years (n = 120) because subsequent mammograms are considered surveillance mammograms rather than screening mammograms. Finally, servicewomen were excluded if their branch of service was listed as other (i.e., Coast Guard or Commissioned Corps of the Public Health Service; n = 2,041) because mammography usage may be affected by service branch, which was adjusted for and assessed as a potential effect modifier.

Assessment of Screening Mammography

To allow for adherence to the least restrictive biennial guidelines, for this study a servicewomen was considered to have had a screening mammography during fiscal years 2009–2010, if there was a recorded mammography procedure code (Current Procedural Terminology : 76091, 76092, 77056, 77057, 76083, 76085, 77052; Healthcare Common Procedure Coding System: G0202, G0203, G0204; ICD-9: V76.11, V72.12) and if there were no new diagnoses of breast cancer (ICD-9: V103, 174.xx, 233.0), breast masses (ICD-9: 611.72), or breast surgeries (mastectomy or breast conserving surgery) before the date of mammography.15 In addition, the identified mammogram had to be conducted more than 11 months after a previous mammogram15 to further decrease the likelihood of including diagnostic mammograms.

Statistical Analyses

The distributions of age, service branch, rank, and marital status were compared across the four racial/ethnic groups using the $\chi 2$ test. To determine whether mammography usage varied by race/ethnicity, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using multivariate logistic regression, adjusting for age, service branch, military rank, and marital status. Effect modification between indicator variables that represented race/ethnicity and the covariates was assessed by including two-way interaction terms in the regression models. All statistical analyses were performed using SAS (version 9.3; SAS Institute Inc, Cary, NC) and the two-sided significance level was set at $p < 0.05$.

Results

A total of 15,667 eligible active duty servicewomen were included in this study. The distributions of basic demographics were observed to vary by race/ethnicity. Non-Hispanic white servicewomen tended to be older and were more likely to be officers than were servicewomen in the other racial/ethnic groups. The Army was the most common service branch, except among non-Hispanic white servicewomen who were more likely to be Air Force personnel. Non-Hispanic black servicewomen were more likely to be single than married, in contrast to servicewomen in the other racial/ethnic groups.

Overall, 61% of the study population had a screening mammogram during fiscal years 2009–2010. Univariate analyses indicated that the percentage of servicewomen who had a screening mammogram did not vary significantly by race/ethnicity (range: 59–62%, $p = 0.46$). Marital status also did not appear to be related to screening mammography ($p = 0.35$). However, the percentage of servicewomen with a screening mammography did vary significantly by age, service branch, and military rank ($p < 0.01$).

In multivariate logistic regression analysis, there was no indication of effect modification between race/ethnicity and any of the covariates ($p > 0.05$). Compared to non-Hispanic white servicewomen, mammography screening was not significantly different among API servicewomen (OR = 1.08; 95% CI = 0.94–1.23) and Hispanic servicewomen (OR = 0.97; 95% CI = 0.85–1.11). However, mammography screening was higher among non-Hispanic black servicewomen than that among non-Hispanic white servicewomen (OR = 1.09; 95% CI = 1.01–1.18). There were indications that screening mammography use increased with age and varied by service branch and military rank. In comparison to the usage among Army servicewomen, screening mammography use was similar among Air Force servicewomen (OR = 1.05; 95% CI = 0.98–1.14) and higher among Navy servicewomen (OR = 1.23; 95% CI = 1.13–1.35). Screening mammography use was also more likely among officers than enlisted personnel (OR = 1.15; 95% CI = 1.07–1.23). There was no indication that screening mammography usage varied by marital status (OR = 1.03; 95% CI = 0.96–1.10).

Discussion

In this equal access health care system, mammography screening was underutilized. In comparison to non-Hispanic white servicewomen, mammography screening usage was similar among API and Hispanic servicewomen and slightly higher among non-Hispanic black servicewomen. In addition, mammography screening was shown to increase with age and vary by service branch and military rank.

In agreement with our findings, after adjusting for type of insurance and other covariates, the 2008 National Health Interview Survey (NHIS) results indicated that use of mammography screening, in comparison to non-Hispanic white women, was similar among non-Hispanic Asian and Hispanic women but was more common among non-Hispanic black women.16 Comparisons of our findings to these national survey results, however, should be made cautiously because the mammography ascertainment differed. In the NHIS, recent mammography (in the past 2 years) was defined according to participants' self-report but has been shown to differentially overestimate true usage by race/ethnicity.9,10 It is uncertain if the same racial/ethnic variations would have been observed if the NHIS results were corrected for differential misclassification. Comparisons to other

national survey data10 among whites and blacks that have been corrected for differential misclassification are also difficult because calendar years included varied and because the survey data include all mammograms, whereas only screening mammography was included in this study. Similarly, although the overall prevalence of screening mammography (61%) in this study was lower than a previous estimate12 among active duty women (71%), many aspects of the studies differed, including the calendar years, assessment period, and definition of an eligible mammography. Therefore, it is difficult to know the true level of agreement between our findings and previous findings, both in the general population and among active duty servicewomen.

It was also unclear why differences in mammography screening were observed between non-Hispanic white and non-Hispanic black active duty servicewomen. Mammography compliance is not strictly enforced but periodic physical examinations are, and mammograms are provided free of charge to all servicewomen older than 40 years.12,17–20 Therefore, although possible, it seems unlikely that servicewomen would seek mammography screening outside of the DoD MHS (paid for either entirely out of pocket or through other health insurance). Therefore, mammography screening outside the MHS is unlikely to account for the observed racial/ethnic differences. Adjustment for continuous age provided similar results (data not shown); therefore, residual confounding by age also does not appear to be a valid explanation for the results. Other factors, such as marital status, education, and income that have previously been shown to be independently associated with mammography screening,16 were adjusted for either directly or indirectly during the multivariate analysis. Military rank was used as a proxy for education and income. Therefore, there is the possibility of residual confounding to the extent that rank may not adequately represent education and/or income, but this may only be a concern if the resulting misclassification was differential by race/ethnicity.

Although experts continue to debate the merits of mammography screening among women aged 40 to 49 years, guidelines are more consistent for women aged 50 years or older. It is, therefore, understandable that mammography screening was highest among servicewomen older than 49 years. Variation by service branch is likely because of differences in medical examination policies. During this study period, all three service branches recommended mammography screening beginning at age 40 years, but the recommended screening frequency varied; the Navy recommended annual screenings,19,20 the Army recommended screenings every 1 to 2 years,18 and the Air Force left frequency decisions to the primary care provider and patient.17 In addition, although we are unaware of official differences in enforcement of the mammography screening, in practice, enforcement may vary by service. In contrast to covariate-adjusted national survey results where single women were less likely to have mammograms,16 our results indicated that marital status was not associated with mammography among servicewomen. However, in agreement with national survey data that indicate a positive association between education/income and mammography screening use,16 officers were observed to have higher mammography screening use than enlisted women.

The main strength of this study was the use of data from a health care system based on equal access, which provided a unique opportunity to investigate racial/ethnic disparities in mammography screening that was not dependent on participant recall. It is not clear why mammography screening was higher among non-Hispanic black servicewomen than that among their non-Hispanic white counterparts. Although the clinical relevance of the difference (OR = 1.09) is unclear, the finding was, nonetheless, statistically significant and thus indicates that factors other than medical care access might have influenced mammography screening utilization. In addition, conducting multivariate analyses provided the ability to simultaneously adjust for multiple potential confounders (i.e., military service branch and rank) to better assess the association between race/ethnicity and screening mammography usage in the DoD MHS. Study limitations include those inherent to using medical administrative

databases, such as the possibility of incomplete data, coding inaccuracies, and errors. However, the possibility of incomplete data should have been minimized because the analyses were restricted to active duty servicewomen who are unlikely to seek health care that is not provided by the DoD. It is also unlikely that any incompleteness or inaccuracy in the data would be either differential by race/ethnicity or substantial enough to account for the findings; thus, these factors are not likely explanations for the observed variations. However, because there was no information in the administrative data, we were unable to account for other possible confounders such as family history of breast cancer, which may be related to both race/ethnicity and mammography screening. Finally, these findings should not be generalized to all similar-aged, non–active duty female DoD beneficiaries. Although it may have been more informative to include these latter beneficiaries who also benefit from equal health care access and are likely to be more comparable to the general population, we did not include them in the study because of a high proportion of missing information on race/ethnicity.

In conclusion, Hispanic and API servicewomen were as likely and non-Hispanic black servicewomen were more likely than non-Hispanic white servicewomen to have mammography screening, thus indicating that equal health care access can minimize health disparities observed in the general population. These findings also indicated that even though mammography is an effective breast cancer screening tool and a covered health care benefit, there is uniform underusage. Studies that identify the driving factors behind this underutilization are warranted.

BACK TO TOP

Prevalence of and Risk Factors for Autopsy-Determined Atherosclerosis Among US Service Members, 2001-2011

The Journal of the American Medical Association
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Abstract

Context Autopsies of US service members killed in the Korean and Vietnam wars demonstrated that atherosclerotic changes in the coronary arteries can appear early in the second and third decades of life, long before ischemic heart disease becomes clinically apparent.

Objective To estimate the current prevalence of coronary and aortic atherosclerosis in the US armed forces.

Design, Setting, and Participants Cross-sectional study of all US service members who died of combat or unintentional injuries in support of Operations Enduring Freedom and Iraqi Freedom/New Dawn between October 2001 and August 2011 and whose cardiovascular autopsy reports were available at the time of data collection in January 2012. Prevalence of atherosclerosis was analyzed by various demographic characteristics and medical history. Classifications of coronary atherosclerosis severity were determined prior to data analysis and designed to provide consistency with previous military studies: minimal (fatty streaking only), moderate (10%-49% luminal narrowing of ≥1 vessel), and severe (≥50% narrowing of ≥1 vessel).

Main Outcome Measures Prevalence of coronary and aortic atherosclerosis in the US armed forces and by age, sex, self-reported race/ethnicity, education, occupation, service branch and component, military rank, body mass index at military entrance, and International Classification of Diseases, Ninth Revision, Clinical Modification, diagnoses of cardiovascular risk factors.

Results Of the 3832 service members included in the analysis, the mean age was 25.9 years (range, 18-59 years) and 98.3% were male. The prevalence of any coronary atherosclerosis was 8.5% (95% CI, 7.6%-9.4%); severe coronary atherosclerosis was present in 2.3% (95% CI, 1.8%-2.7%), moderate in 4.7% (95% CI, 4.0%-5.3%), and minimal in 1.5% (95% CI, 1.1%-1.9%). Service members with atherosclerosis were significantly older (mean [SD] age, 30.5 [8.1] years) than those without (mean [SD] age, 25.3 [5.6] years; P < .001). Comparing atherosclerosis prevalence among with those with no cardiovascular risk factor diagnoses (11.1% [95% CI, 10.1%-12.1%]), there was a greater prevalence among those with a diagnosis of dyslipidemia (50.0% [95% CI, 30.3%-69.7%]; age-adjusted prevalence ratio [PR], 2.09 [95% CI, 1.43-3.06]), hypertension (43.6% [95% CI, 27.3%-59.9%]; age-adjusted PR, 1.88 [95% CI, 1.34-2.65]), or obesity (22.3% [95% CI, 15.9%-28.7%]; age-adjusted PR, 1.47 [95% CI, 1.10-1.96]), but smoking (14.1% [95% CI, 8.0%-20.2%]) was not significantly associated with a higher prevalence of atherosclerosis (age-adjusted PR, 1.12 [95% CI, 0.73-1.74]).

Conclusion Among deployed US service members who died of combat or unintentional injuries and received autopsies, the prevalence of atherosclerosis varied by age and cardiovascular risk factors.

Age-adjusted ischemic heart disease mortality rates in the United States have declined by 72% since their peak in 19681- 2—a phenomenon attributed about equally to reduction in risk factors and expansion of therapies.3- 4 These preventive and therapeutic advancements derive from an improved elucidation of the disease process. An early breakthrough in the understanding of the natural history of atherosclerotic heart disease was achieved in 1953, when Enos and colleagues5 at the Armed Forces Institute of Pathology reported a 77% prevalence of coronary atherosclerosis among US soldiers killed in the Korean War. By demonstrating anatomically that atherosclerosis affected a large proportion of young individuals without clinical evidence of heart disease, their study revolutionized the understanding of the onset and progression of cardiovascular disease.6 A follow-up report in the Vietnam War era,7 along with a number of autopsy studies in the civilian population,8- 14 provided additional evidence that the onset of atherosclerosis may occur at an early age.

Since the publication of these studies, health policies for children and young adults in the general population15- 16 as well as the military population17- 18 of the United States have been implemented to reduce the risk of cardiovascular disease associated with risk factors such as hypertension, diabetes, cholesterol, and smoking. We conducted a cross-sectional study to assess the current prevalence of autopsy-determined atherosclerosis among US service members who died in support of combat operations.

Methods

Every US service member who died in support of Operations Enduring Freedom (OEF) or Iraqi Freedom/New Dawn (OIF/OND) between October 2001 and August 2011 (OIF began in March 2003 and was renamed OND in September 2010) was included in this cross-sectional study. To maintain continuity with previous military studies, those with a manner of death labeled as “suicide,” “natural,” or “undetermined” were excluded. Active duty service members and activated reservists of all service branches (ie, Air Force, Army, Coast Guard, Marine Corps, and Navy) were eligible for entry. This study was approved by the Office of Research at the Uniformed Services University of the Health Sciences; as deceased persons research, it did not require institutional review board approval.

Autopsy, Demographic, and Diagnostic Data Sources

We obtained autopsy reports from the Armed Forces Medical Examiner Tracking System (AFMETS) and demographic and medical encounter data from the Defense Medical Surveillance System (DMSS). AFMETS, managed by the Mortality Surveillance Division of the Armed Forces Medical Examiner System, Dover, Delaware, is the central registry for US military fatalities.19 DMSS, managed by the Armed Forces Health Surveillance Center, Silver Spring, Maryland, is the central repository for medical surveillance data for the armed forces, which contains longitudinal data on service members, including almost complete ascertainment of all medical encounters since 1990, as well as demographic and deployment data.20

Demographic data included age, sex, race/ethnicity, highest education level achieved before death, occupation, service branch, active or reserve component, and military rank. On entering the military, service members self-select their race/ethnicity from a list of fixed categories; race/ethnicity was reported because of a known association with atherosclerosis.8- 9,13 Medical encounter data included body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) at military entrance and history of atherosclerosis, ischemic heart disease, and major cardiovascular risk factors (ie, hypertension, dyslipidemia, obesity, diabetes mellitus, impaired fasting glucose, and smoking) based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), codes. Service members were considered to have a

history of any of these diseases or risk factors if they had at least 1 inpatient encounter or 2 outpatient encounters within 180 days with a defining diagnosis in any diagnostic position. All risk factor data were recorded prior to death.

Evaluation of Atherosclerotic Lesions

All US military deaths associated with combat or unintentional injuries in support of OEF or OIF/OND—whether the service member died in theater or after evacuation—required a comprehensive autopsy performed by a board-certified pathologist. For those who died in theater, autopsies were conducted at Dover Port Mortuary, Dover Air Force Base, Delaware, and were typically completed within 72 hours of death. For those who were wounded, medically evacuated, and subsequently died of wounds, autopsies were often conducted at the local military treatment facility, including National Naval Medical Center, Bethesda, Maryland (n = 32); Brooke Army Medical Center, Fort Sam Houston, Texas (n = 28); and Walter Reed Army Medical Center, Washington, DC (n = 20). Early in OEF, some autopsies were conducted at Landstuhl Regional Medical Center, Germany (n = 68).

All autopsies included an examination of the cardiovascular system. After removal of the heart from the pericardial sac and anterior chest chamber, the major coronary arteries (ie, left main, left anterior descending, circumflex, and right coronary) were inspected in the fresh state. The inferior portions of the ventricles were then sectioned and the valves opened according to the physiologic sequence of blood flow. The aorta was opened longitudinally, beginning typically at the aortic valve and carried distally through the bifurcation and into both common iliac arteries. The pathologist documented the location and degree of all atherosclerotic lesions based on gross examination.

To provide consistency with previous military studies, we determined the following classifications of coronary atherosclerosis severity prior to data analysis: minimal (fatty streaking only), moderate (10%-49% luminal narrowing of ≥1 vessel), and severe (≥50% narrowing of ≥1 vessel). We also documented the presence of aortic atherosclerosis.

Statistical Analyses

We used summary statistics to describe the population. We evaluated the prevalence of atherosclerosis by various demographic characteristics and diagnostic histories and reported unadjusted and Mantel-Haenszel age-adjusted prevalence ratios (PRs) with 95% confidence intervals. We used logistic regression to evaluate risk factor combinations and to assess for effect modification, reporting odds ratios (ORs). To compare included and excluded participants, we used $\chi 2$ and Fisher exact tests of homogeneity (for categorical variables) and unpaired t tests (for continuous variables).

All analyses were performed with Stata/IC version 11.2 (StataCorp). P values less than .05 were considered statistically significant; all P values were based on 2-sided tests.

Results

Of the 6191 fatalities in the case identification period, 4143 cases were identified by the Armed Forces Medical Examiner System (532 were initially excluded because the manner of death was other than combat or unintentional injury and 1516 because of injury to the cardiovascular system precluding complete autopsy). On review of the reports, we excluded an additional 311 cases (235 with no autopsy on file, 69 with damage preventing coronary examination, and 7 indicating organ donation). Included in the analysis were 3832 service members aged 18 to 59 years, of whom 98.3% were male.

Included and excluded participants were mostly homogenous demographically, although the excluded were younger (mean [SD] ages, 25.9 [6.2] vs 27.0 [6.6], respectively; P = .002) and had a smaller proportion of college graduates (10.0% vs 14.8%; P = .008); the groups had similar mean (SD) entrance BMIs (included, 24.3 [3.6] vs excluded, 24.4 [3.2]; P = .85) and similar proportions with 1 or more cardiovascular risk factor diagnoses (included, 8.5% vs excluded, 10.9%; P = .14).

Atherosclerosis Prevalence

The overall prevalence of coronary or aortic atherosclerosis was 12.1% (95% CI, 11.1%-13.1%). The prevalence of coronary and aortic atherosclerosis was 2.1% (95% CI, 1.7%-2.6%). The prevalence of any coronary atherosclerosis was 8.5% (95% CI, 7.6%-9.4%); severe coronary atherosclerosis was present in 2.3% (95% CI, 1.8%-2.7%), moderate in 4.7% (95% CI, 4.0%-5.3%), and minimal in 1.5% (95% CI, 1.1%-1.9%). The prevalence of any aortic atherosclerosis was 5.7% (95% CI, 5.0%-6.5%).

Factors Associated With Prevalent Atherosclerosis

Age consistently produced the strongest association with prevalent atherosclerosis. Service members with atherosclerosis (mean [SD] age, 30.5 [8.1] years) were approximately 5 years older than those without (mean [SD] age, 25.3 [5.6] years; P < .001); those aged 40 years and older had about 7 times the prevalence of disease as compared with those aged 24 years and younger (45.9% vs 6.6%; unadjusted PR, 6.95; 95% CI, 5.49-8.80) (Table 1).

Lower education level and higher military entrance BMI were significantly associated with prevalent atherosclerosis, after adjusting for age. As compared with those who completed high school or less, those who completed at least some college had lower prevalence of disease (11.2% vs 13.8%; age-adjusted PR, 0.65; 95% CI, 0.45-0.92); this association did not extend to college or higher-level graduates. As compared with those with a normal BMI (18.5-24.9) on military entrance, those with a BMI in the overweight (25.0-29.9) or obese (≥30.0) range had a significantly

higher prevalence of atherosclerosis (overweight: 12.7% vs 7.6%; age-adjusted PR, 1.39; 95% CI, 1.10-1.75; obese: 15.8% vs 7.6%; age-adjusted PR, 1.87; 95% CI, 1.35-2.60). Age-adjusted PRs by sex, race/ethnicity, occupation, service branch, active/reserve component, and military rank were not significant (Table 1).

Age-adjusted atherosclerosis prevalence was associated with several diagnoses (Table 2). As compared with those with no major cardiovascular risk factor diagnoses, those with a diagnosis of dyslipidemia (50.0% vs 11.1%; age-adjusted PR, 2.09; 95% CI, 1.43-3.06), hypertension (43.6% vs 11.1%, age-adjusted PR, 1.88; 95% CI, 1.34-2.65), or obesity (22.3% vs 11.1%; age-adjusted PR, 1.47; 95% CI, 1.10-1.96) had a significantly higher prevalence of atherosclerosis. Of all risk factor combinations, only obesity and hypertension (n = 8) resulted in a statistically significant association after adjusting for age (50.0% vs 11.1%; age-adjusted OR, 3.14; 95% CI, 1.54-6.44).

Comment

The prevalence of autopsy-determined coronary atherosclerosis among US service members was 8.5% in our study population. Older age; lower educational level; higher BMI at military entrance; and prior diagnoses of dyslipidemia, hypertension, and obesity were associated with a higher prevalence of atherosclerosis.

This prevalence demonstrates a steep decline from the rates of 77% noted in the Korean War5 and 45% in the Vietnam War7 (Table 3)—a decline that can be explained by either real or artifactual phenomena. Within the latter category are several methodological discrepancies among the 3 studies. First, while the Vietnam study employed angiography on perfusion-fixed coronary arteries, the Korean and current studies relied on macroscopic visualization, which is likely less sensitive to detect the earliest atherosclerotic changes. Second, the Korean study grouped fibrous thickening with fatty streaking as atherosclerosis, but it is now understood that intimal thickening may occur physiologically as a nonatherosclerotic adaptation.23 Third, while the Vietnam study used an absolute scale for grading plaque size, the present study enlisted the percentage-obstructed method used in the Korean study. Fourth, the autopsies in the earlier studies were conducted for scientific purposes, such as the study of wound ballistics, but the autopsies reviewed for this study were ordered to be conducted routinely rather than selected by specific patterns of injury; our method is therefore likely to have minimized expectation bias.24

Selection biases may also attenuate direct comparisons of these studies. In light of the possibility that recent military volunteers have healthier cardiovascular profiles than their conscripted counterparts in the Korean and Vietnam wars, the potential emerges for a self-selection or “healthy warrior” bias when juxtaposing studies conducted during and after the draft era. In addition, advancements in battlefield medicine and technology may have saved the lives of wounded soldiers with atherosclerosis, who, by virtue of compromised perfusion, would have died in earlier conflicts; the prevalence of atherosclerosis at autopsy, in other words, may appear higher in the Korean and Vietnam wars because of unequal combat casualty care. Demographic and socioeconomic changes in the military population over this period may also account for the decline in atherosclerosis; because these data are unavailable for the Korean and Vietnam war studies, comparisons should be made cautiously. Finally, the

smaller proportion of combat fatalities autopsied in the Korean and Vietnam war studies—less than 1% in both cases, as compared with more than 60% in the current study—may have resulted in less representative samples.

In light of historic epidemiology, these artifactual explanations are matched by compelling factual alternatives. Autopsies conducted for general aviation mishaps over the past 5 decades have generally demonstrated declines in any and severe coronary atherosclerosis, although shifting demographics complicate interpretation of these findings. Less subjectively, prevalence of cardiovascular risk factors in the general US population, with the exceptions of obesity and diabetes, are trending down. Although similar trend data are not available in the military, a recent study of more than 280 000 Air Force members found lower prevalences of hypertension, dyslipidemia, and diabetes as compared with the general US population. It is not unreasonable to assume that the prevalence of these risk factors among deployed US troops has declined since Korea and Vietnam. Smoking rates have also decreased in the military, often surpassing absolute rate reductions in the civilian population. The majority (51%) of service members smoked cigarettes in 1980, but by 1998 this figure had decreased to 30%. This 40% reduction in smoking prevalence within the military since the end of the Vietnam War likely contributed to our results.

Although the military culture tolerated or even promoted tobacco use in earlier eras, more recent Department of Defense (DoD) policy initiatives have aimed to reduce smoking. These have included discontinuation of cigarettes in K- and C-rations, efforts to deglamorize tobacco, and making Navy ships smoke-free.37 Current DoD Instructions seek to bring cigarette prices on military installations to within 5% of the local economy and to make DoD facilities smoke-free. Service-specific implementation of these policies have led to such initiatives as banning cigarettes from Air Force medical campuses and prohibiting smoking on submarines. Despite these policy initiatives and improvements, current military smoking rates (30.5%)36 continue to exceed civilian rates among similar age groups (21.4% in 18- to 24-year-olds and 23.7% in 25- to 44-year-olds).

The findings of this study should be interpreted cautiously in light of its other limitations. Because autopsies were performed by multiple pathologists over the span of a decade, interobserver and intersession variation may exist. Studies by the World Health Organization, however, have demonstrated high reproducibility of coronary and aortic atherosclerotic grading among medical examiners and over time. Based on the 2008 DoD health-related behavior survey, we also suspect that ICD-9-CM diagnoses failed to capture many cardiovascular risk factor exposures. In this survey of more than 28 000 active duty personnel, 30.5% had smoked cigarettes in the previous 30 days and 12.6% were classified as obese based on BMI.36 The degree of undercapture of these and other cardiovascular risk factors would likely not vary by the presence or absence of atherosclerosis, however, resulting in a nondifferential misclassification that would bias our results toward the null.

Our findings suggest that the prevalence of atherosclerosis has declined among deployed US service members since the Korean and Vietnam wars, and the work of Ford and associates3- 4 indicates that the prevalence of ischemic heart disease in the general population of US adults has declined over a similar time period. However, targets for further improvement remain. The 2008 DoD health-related behavior survey identifies smoking, obesity, diet, and physical activity as prime targets for public health intervention within the military community, and data from the National Health and Nutrition Examination Survey indicate that only 1.2% of US adults achieve the lifestyle metrics correlated with a stepwise reduction in all-cause and cardiovascular mortality. To help “identify those personnel with a potential high risk for cardiovascular disease,”17 the DoD should

consider automatic coding within their electronic health record for diagnoses such as obesity and smoking that are objectively measured during health care visits. Military and civilian health care systems should continue to help patients reduce their cardiovascular risk factors, beginning in childhood and continuing throughout adult life. Despite remarkable progress in prevention and treatment, cardiovascular disease remains the leading cause of death in the United States and other developed nations, and even small improvements in the prevalence of smoking and other risk factors may reduce death rates further and prolong healthy lives.

BACK TO TOP