

Research News

Disparities, Variability Found in Methadone Maintenance Dosing Patterns

Methadone maintenance therapy has been the primary treatment for heroin abuse in the United States for over 30 years. Methadone treatment prevents users from experiencing the “high” associated with opiate abuse, eliminates withdrawal symptoms, and reduces the craving for heroin. Recent studies have shown that both higher doses and longer duration of methadone therapy are associated with more successful treatment. To measure the extent to which methadone maintenance clinics in the United States meet the current recommended treatment standards (doses at or above 80 milligrams [mg] of methadone per day), researchers funded by NIDA analyzed data from the National Drug Abuse Treatment System Survey (NDATSS), conducted in 1988, 1990, 1995, 2000, and 2005. The researchers explored whether characteristics of the clinics’ patients and staff, clinic ownership and payment arrangements, and clinic management’s attitudes and beliefs about drug treatment and HIV prevention influenced the quality of treatment received by the patients. The study found that the proportion of patients who received methadone doses below 60 mg/day declined from 79.5 percent in 1988 to 34.4 percent in 2005; the proportion of patients receiving doses below 40 mg/day also declined substantially during the same period. Of concern to the researchers was that clinics that treated higher percentages of African-American or Hispanic patients, those with managed care arrangements (such as an association with an HMO) that required patients to have preauthorization for treatment services, and those that advocated a drug-free approach were less likely to provide the higher recommended methadone dose levels to their patients. Clinics that supported or provided HIV prevention services were more likely to provide higher doses. Overall, although the number of clinics that underdosed patients declined substantially between 1988 and 2005, only 44 percent of patients were receiving at least 80 mg of methadone per day by the end of the time period. “Units that provide low doses may lack human and financial resources or management systems that contribute to their inability to meet care standards,” conclude the authors.

Pollack HA, D’Aunno T. Dosage patterns in methadone treatment: Results from a national survey, 1988–2005. *Health Serv Res.* 2008;43(6):2143–2163.

Brain Receptors Underlie Sex Differences Observed in Morphine Analgesia

Opioid-based narcotics such as morphine are some of the most widely prescribed medications for human pain management. Research suggests, however, that morphine may be less effective in reducing pain in women compared with men. Because men and women appear to have similar levels of morphine in the blood and brain after morphine administration and also process and eliminate the drug from the body at comparable rates, scientists have proposed that differences in the receptors in the brain that bind morphine may underlie sex differences observed in morphine-induced analgesia (pain relief). To test this hypothesis, researchers funded by NIDA examined whether sex differences in the amount of a type of receptor in the brain called the μ -opioid receptor affects morphine-induced analgesia. The researchers focused specifically on μ -opioid receptors in an area of the brain called the periaqueductal gray (PAG), which is thought to play an essential role in morphine’s effects on the brain. Overall, female rats had significantly fewer μ -opioid receptors in the PAG, although these levels fluctuated heavily during the reproductive cycle—females in the stage of their cycle where levels of estrogen and progesterone were lowest had μ -opioid receptor levels similar to male rats. Morphine was significantly more effective in reducing pain in male rats compared with females, though females with the lowest levels of estrogen and progesterone were more sensitive to the painkilling effects of morphine than females with higher levels of the hormones. Blocking the μ -opioid receptors in the PAG reduced the painkilling effects of morphine in male rats but not in females, indicating that the PAG may not be the primary area of the brain regulating morphine analgesia in females. The authors suggest that

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future studies should explore the effects of the steroid hormones produced by the body (such as estrogen) on μ -opioid receptor expression in the brain. Because of these differences, additional studies are also needed to identify more effective treatments for persistent pain in women.

Lloyd DR, Wang X, Murphy AZ. Sex differences in micro-opioid receptor expression in the rat midbrain periaqueductal gray are essential for eliciting sex differences in morphine analgesia. *J Neurosci*. 2008;28(52):14007–14017.

Marijuana Prevention Campaigns May Have Undesired Effects on Marijuana Use

Marijuana use prevention campaigns targeting adolescents often stress severe harms that can result from the initiation and continued use of marijuana. Some researchers have expressed concern with this approach, suggesting that if the expected or anticipated harms associated with marijuana use do not match what adolescents experience if they try the drug, the resulting “expectancy change” may actually lead them to be more willing to try marijuana again in the future than if they had not been exposed to such a campaign. To test this theory, researchers funded by NIDA surveyed a nationally representative sample of adolescents aged 12 to 18 to assess the National Youth Anti-Drug Media Campaign, one of the Nation’s largest drug-prevention messaging campaigns directed to teens. Participants were interviewed twice, with about 1 year between interviews. For the purpose of this study, only adolescents who had not tried marijuana at the time of the first interview were included. During the first interview, adolescents were asked about their expectations of the physical, social, and cognitive harms associated with marijuana use and whether they believed marijuana use would damage their performance in school. Their responses were compared to the harms perceived in the second interview. By the second interview, 14.5 percent of the adolescents remaining in the study had tried marijuana. Overall, the researchers found strong relationships between expectancy changes and changes in intent to use marijuana in the future—adolescents who found that the experienced harms of marijuana use failed to live up to their expectations were more likely to say that they planned to try the drug again in the future. The researchers also found that expectancy changes were more likely to occur as a result of use (direct experience) and not of indirect experience (such as observing a friend’s experience with marijuana). “Our results suggest that if adolescents choose to initiate marijuana use, the likelihood of continuance may be affected by the extent to which their expectancies have been violated...At a minimum, these results warn against overstating marijuana harms in prevention,” conclude the authors.

Skenderian JJ, Siegel JT, Crano WD, Alvaro EE, Lac A. Expectancy change and adolescents’ intentions to use marijuana. *Psychol Addict Behav*. 2008;22(4):563–569.

Crack Cocaine Use Hastens Progression of HIV Infection to AIDS

Substance abusers have a high risk of HIV infection, due to factors including sharing contaminated needles and high-risk sexual behaviors. Research has suggested that continued drug abuse may lead to the rapid progression of HIV infection to AIDS, both by reduced adherence to antiretroviral (ARV) medication regimens and by potential direct effects of the drug on the HIV virus. To better understand the relationship between specific drugs of abuse and HIV progression, researchers funded by NIDA followed 222 HIV-positive drug abusers for 30 months. The most commonly abused drugs were alcohol, marijuana, powder cocaine, and crack cocaine. Participants were contacted monthly and assessed every 6 months for ARV prescriptions, drug use, and HIV progression. The researchers analyzed 130 of the participants who had white blood cell counts above the level considered diagnostic for AIDS at the beginning of the study. Participants who abused crack cocaine had significantly increased viral loads (the amount of the virus found in the blood) and were more than twice as likely to have their disease progress to AIDS during the study as participants who abused other drugs. Although reduced adherence to ARV medications likely contributed to some participants’ HIV progression, crack cocaine abusers who were not prescribed any ARV medications also had greater risk for HIV progression than participants who abused other drugs, indicating that the drug itself may directly affect HIV progression. The authors conclude that this study highlights a strong need for interventions to reduce crack cocaine abuse in people infected with HIV.

Baum MK, Rafie C, Lai S, Sales S, Page B, Campa A. Crack-cocaine use accelerates HIV disease progression in a cohort of HIV-positive drug users. *J Acquir Immune Defic Syndr*. 2009;50(1):93–99.

Few U.S. High Schools Use Evidence-Based Drug Prevention Curricula

Initiation of drug use increases rapidly through the middle school to high school years, making that period a critical time for substance abuse prevention. And while many high schools provide some substance abuse education, most are not using evidence-based programs. Researchers funded by NIDA estimated the proportion of school districts in the United States that had at least one high school teaching an evidence-based (i.e., having demonstrated evidence of effectiveness) universal substance abuse prevention curriculum during the 2004–2005 school year. For the purpose of this study, six universal prevention curricula were identified based on the following criteria: (1) they target substance use; (2) they are intended for all students regardless of their risk for initiating drug use; (3) they are designed for use in high school; and (4) they are classified as effective by either the Substance Abuse and Mental Health Services Administration or the Center for the Study and Prevention of Violence at the University of Colorado. Out of 1,392 nationally representative school districts participating in the survey, only 56.5 percent taught any kind of substance use prevention programming, and only 10.3 percent used one of the six evidence-based curricula. In particular, large school districts and districts with a majority of African-American students generally were more likely to use any substance abuse prevention programs as well as evidence-based prevention programs. The authors challenge schools and school districts, with help from the Office of Safe and Drug-Free Schools, to make use of the availability of evidence-based substance abuse prevention curricula targeting this age group, although they recognize the difficulties schools face in fitting drug prevention curricula into an already crowded academic schedule.

Ringwalt C, Hanley S, Vincus AA, Ennett ST, Rohrbach LA, Bowling JM. The prevalence of effective substance use prevention curricula in the nation's high schools. *J Prim Prev.* 2008;29(6):479–488.

Gene Changes Linked to Nicotine Dependence and Success With Smoking Cessation

Many studies suggest that genetic factors play a role in an individual's likelihood of becoming dependent on an addictive substance such as nicotine, as well as in the level of difficulty he or she faces in quitting: scientists have reported that changes in single units of DNA, called single-nucleotide polymorphisms (SNPs), may contribute to the genetic variation observed in vulnerability to nicotine dependence. However, these studies used patients enrolled in clinical trials of smoking cessation, which have very strict entrance criteria. Therefore, individuals enrolled in these trials may not be representative of the population as a whole. To look for overlap between these studies and the general population, researchers in NIDA's Intramural Research Program performed genome-wide association studies to look for SNPs from 480 European-American participants from a community-based study of personality and behaviors associated with cancer risk. Participants were categorized as those who never smoked extensively, those who reported lifetime nicotine dependence and who currently smoked, and those who had been dependent on nicotine but quit. Out of 289 genes with SNPs that varied significantly between current smokers and people who had never been dependent on nicotine, 30 overlapped with those identified in previous studies; out of 67 genes with SNPs that varied significantly between current smokers and people who had quit, 5 overlapped with those identified in previous studies. Many of the genes identified across studies are involved in the establishment and plasticity of neuronal connections. Some of these genes may contribute to the role memory plays in addiction, and may be potential targets for the development of new antismoking drugs.

Drgon T, Montoya I, Johnson C, Liu QR, Walther D, Hamer D, Uhl GR. Genome-wide association for nicotine dependence and smoking cessation success in NIH research volunteers. *Mol Med.* 2009;15(1-2):21–27.

Electronic Diary Captures Moods and Cues Leading to Heroin and Cocaine Use

A technique called ecological momentary assessment (EMA) uses handheld data collection devices such as personal digital assistants (PDAs) or cellular phones to report, in real time, on the activities, moods, and cravings experienced by people attempting to quit the use of an addictive drug. EMA has been used most often in studies of smoking cessation, but it is used rarely with people attempting to quit the use of illicit drugs. To assess the feasibility of using EMA to study the moods and cues that may lead to relapse to illicit drug use, investigators at the NIDA Intramural Research Program studied 102 cocaine- and heroin-dependent individuals undergoing methadone outpatient treatment. Each participant was loaned a PDA for the course of the study. Special software delivered five random prompts per day for 5 weeks, then two random prompts per day for 20 weeks. The prompts asked the participants whether they had experienced commonly accepted triggers of craving and relapse, including certain moods and environmental exposures (such as seeing the drug or handling cash) within the past hour. Participants were also asked to make a voice recording on their PDA whenever they experienced a craving or used cocaine or heroin. The rate of PDA loss during the study was very small, and participants

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answered a mean of 75 percent of the random prompts. Interestingly, the responses recorded differed between the two drugs—the triggers reported by the random prompts significantly increased before cocaine use but not before cocaine craving, whereas for heroin abusers they increased before heroin craving but not before heroin use. One explanation for these findings was that the methadone treatment may have helped participants avoid using heroin after experiencing a craving. “These findings offer an unprecedented glimpse into the buildup of mood changes and cue exposure in the hours before cocaine and heroin use or craving during outpatient treatment,” state the authors. They recommend that further studies should use EMA to study how participants’ physical locations, companions, or activities impact craving and use, to help in the development of effective therapies to prevent relapse to illicit drug use.

Epstein DH, Willner-Reid J, Vahabzadeh M, Mezghanni M, Lin JL, Preston KL. Real-time electronic diary reports of cue exposure and mood in the hours before cocaine and heroin craving and use. *Arch Gen Psychiatry*. 2009;66(1):88–94.

Aging Population of Steroid Abusers May Face Underrecognized Health Problems

Beginning in the late 1970s and early 1980s, the illicit use of anabolic-androgenic steroids (AAS) moved out of the exclusive realm of elite competitive athletics and into the general population. By 1989, the ongoing NIDA-sponsored Monitoring the Future study reported that 3 percent of 12th-grade students had abused AAS in their lifetime. The National Household Survey on Drug Abuse (administered by the Substance Abuse and Mental Health Services Administration) estimated that by 1991, nearly 1 million men aged 12 and older in the United States had abused AAS. The first large wave of these AAS abusers will soon pass the age of 45 and may face underrecognized long-term medical and psychiatric consequences due to their AAS abuse. Investigators funded by NIDA report in a new review article that the potential physical damages from AAS abuse that may be seen in an aging population include cardiovascular effects such as hardening of the arteries and weakening of the heart muscle, infertility, and, possibly, permanent damage to the brain. Psychological effects may include depression associated with disruption of the body’s hormone systems, which in turn can lead to resumed AAS abuse and dependence, as abusers repetitively return to AAS use in an attempt to counteract the symptoms they experience due to hormone disruption. Steroid abusers may also have a high risk for abuse or dependence on opioids as well as other illicit drugs. In a recent study of male weightlifters, 35 percent of those abusing AAS met the criteria for lifetime history of abuse of or dependence on an illicit drug, compared with 2 percent of non-AAS-abusing weightlifters. Currently, little is known about the lifetime prevalence of these and other potential health problems related to past or continued AAS abuse. “As this wave of aging abusers approaches, it is imperative to initiate larger and more systematic studies of the long-term effects of AAS,” conclude the authors.

Kanayama G, Hudson JI, Pope HG Jr. Long-term psychiatric and medical consequences of anabolic-androgenic steroid abuse: A looming public health concern? *Drug Alcohol Depend*. 2008;98(1-2):1–12.

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The National Institute on Drug Abuse (NIDA) is a component of the National Institutes of Health, U.S. Department of Health and Human Services. NIDA supports most of the world’s research on the health aspects of drug abuse and addiction. The Institute carries out a large variety of programs to ensure the rapid dissemination of research information and its implementation in policy and practice. Fact sheets on the health effects of drugs of abuse and other topics are available in English and Spanish. These fact sheets and further information on NIDA research and other activities can be found on the NIDA home page at www.drugabuse.gov. To order publications in English or Spanish, call NIDA’s new *DrugPubs* Research Dissemination center at 1-877-NIDA-NIH (1-877-643-2644) or 240-645-0228 (TDD), or fax or e-mail requests to 240-645-0227 or drugpubs@nida.nih.gov.