

Research News

Increase in Heart Infections Caused by Injection Drug Use Observed

Injection drug use (IDU) can contribute to an increased risk of infective endocarditis (IE)—inflammation of the lining of the heart caused by an infectious agent. Investigators funded by NIDA calculated that the number of IDU-related hospitalizations for IE increased substantially between 2000-2001 and 2002-2003, while the population of injecting drug users remained stable. Using data from the CDC's National Hospital Discharge Survey database collected between 1996 and 2003, the investigators identified cases of IDU-related IE using two algorithms: one designed to be specific (only identifying cases that are definitely IDU-related IE, at the risk of excluding some cases), and one designed to be sensitive (identifying more cases of IDU-related IE, at the risk of including some false-positive results). These algorithms indicated that the number of IDU-related hospitalizations for IE increased between 38 and 66 percent from 2000-2001 to 2002-2003. An exception was IDU-related IE among people living with HIV or AIDS, which declined during the entire study period. The investigators hypothesize that increasing methamphetamine use and increasing injection frequency among heroin abusers may be the mechanisms driving the increase in IDU-related IE. "Research into whether the two mechanisms proposed...or other mechanisms (acting alone or in combination) have produced the observed increase in IDU-related IE is needed" to develop effective interventions to stem IDU-related IE, state the authors.

Cooper HL, Brady JE, Ciccarone D, Tempalski B, Gostnell K, Friedman SR. Nationwide increase in the number of hospitalizations for illicit injection drug use-related infective endocarditis. *Clin Infect Dis.* 2007;45(9):1200-1203.

Positive Emotions Linked to Smoking May Contribute to Difficulty Quitting in Dual-Smoker Couples

In couples where both partners smoke, smoking, although a problematic behavior, may actually support positive social interactions within the couple, contributing to failure of quit attempts. To test this hypothesis, investigators funded by NIDA recruited dual-smoker couples and couples in which only one partner smoked. More than half of the smokers, but none of their partners, had a diagnosed heart or lung problem aggravated by smoking. The participants were asked to discuss health-related disagreements during a videotaped session; 5 minutes into the session, a cue signaled the smokers to light up, and the conversation continued for another 5 minutes. Immediately afterward, the participants watched their interactions on videotape and used an electronic joystick to continuously report recalled changes in their emotional experiences. The partners in dual-smoker couples reported an increase in positive emotion when smoking together compared to the beginning of the session. In contrast, couples with only one smoker reported a decrease in positive emotion—including the participants who smoked. Individual characteristics such as gender or level of psychological distress did not appear to contribute to the changes in emotional experience. "This kind of dyad-level emotion regulation through smoking could help to explain why smokers whose spouse or partner also smokes have more trouble quitting and staying quit," state the authors. "Clinicians can usefully intervene by helping couples realign their relationship in ways not organized around tobacco use."

Shoham V, Butler EA, Rohrbaugh MJ, Trost SE. Symptom-system fit in couples: Emotion regulation when one or both partners smoke. *J Abnorm Psychol.* 2007;116(4):848-853.

Hemopressin Binds to Cannabinoid Receptor and Reduces Perception of Pain

The psychoactive compound in marijuana that alters brain functioning can bind to at least two receptors found in the cells of the body, called cannabinoid receptors CB₁ and CB₂. Together, CB₁, CB₂, and the molecules produced by the body that normally bind to these two receptors (endocannabinoids) are called the endocannabinoid system. Studies have shown that the endocannabinoid system plays a role in inflammation, nerve pain, and disorders including Alzheimer's disease, and would potentially make a good target for new treatments of these conditions. Researchers funded in part by NIDA have identified a peptide called hemopressin that binds to CB₁ receptors and, when given to mice either by direct injection or orally, reduced the perception of pain without sedative effects or impairment of motor activity. The researchers caution that further studies are needed to understand what functions hemopressin may normally have in the body. However, they conclude, hemopressin has potential to serve as a template for the development of a novel pain therapy in the future.

Heimann AS, Gomes I, Dale CS, Pagano RL, Gupta A, de Souza LL, Luchessi AD, Castro LM, Giorgi R, Rioli V, Ferro ES, Devi LA. Hemopressin is an inverse agonist of CB₁ cannabinoid receptors. *Proc Natl Acad Sci USA*. 2007;104(51):20588–20593.

Anti-Inhalant Messages Targeting Young Adolescents Vary in Ability to Influence Future Use

Use of inhalant drugs, including solvents, aerosols, gases, and nitrites, usually begins in early adolescence. To test factors that might improve adolescents' responsiveness to anti-inhalant messages, researchers funded by NIDA recruited 894 sixth- and seventh-graders to view various anti-inhalant commercials that were embedded within an anti-bullying video. The commercials featured either a doctor (adult) or peer as the message source, presented either potential physical or social harms of inhalant use, and targeted either the student (direct message) or a parent (indirect message), for a total of eight different messages. Students were randomly chosen to view one of the eight messages. Before viewing the video, the students filled out a pretest questionnaire, which included questions about current substance use. Based on the answers to the pretest, the researchers classified children as resolute inhalant nonusers, vulnerable nonusers (those at risk for trying inhalants), and users. After the video, the students completed a posttest that included questions about their impression of the commercial and their intentions to use inhalants in the future. While vulnerable nonusers were significantly more persuaded by the peer source, users tended to be more influenced by the adult. Vulnerable nonusers' responses did not differ by suggested harm, but users evaluated the commercials that suggested social harm more favorably. Both users and vulnerable nonusers evaluated the indirect message more favorably. Overall, more favorable responses to the message viewed were significantly associated with lower intentions to use inhalants in the future.

Crano WD, Siegel JT, Alvaro EM, Patel NM. Overcoming adolescents' resistance to anti-inhalant appeals. *Psychol Addict Behav*. 2007;21(4):516–524.

Therapeutic Playgroup May Help Foster Children with School Success Skills

Young children who do not possess the social and academic skills to succeed in elementary school are at risk of increasing academic failure and behavioral problems as they progress in school. Foster children often fall into this at-risk category. Researchers funded in part by NIDA designed a small pilot evaluation of a therapeutic playgroup to improve foster children's success in early school grades. The researchers invited all foster children in Lane County, Oregon, entering kindergarten through second grade in the fall of 2002 to participate. Of 24 children (80 percent of those eligible) whose foster caregivers consented to participate, 11 were randomly assigned to the therapeutic playgroup intervention and 13 to regular foster care services. The therapeutic playgroup met for 2 hours twice weekly for 7 weeks during the summer and included activities targeting social competence (such as sharing and cooperating with peers) and emotional and behavioral self-regulation (such as managing negative emotions). The foster parents and laboratory assessors completed questionnaires assessing the children's behavior before and after the intervention, and during the same time periods for the children in the control group. Children in the playgroup showed increased social competence and decreased lability (poorly regulated emotional expression) after the intervention, while children in regular foster care showed a slight decrease in social competence and an increase in lability. "The intervention appeared to help stabilize children's behavior, whereas the behavior of children in the comparison group deteriorated," conclude the authors. The playgroup intervention is currently being tested in a larger NIDA/NICHD co-funded randomized trial of 200 kindergarten-aged foster children.

Pears KC, Fisher PA, Bronz KD. An intervention to promote social emotional school readiness in foster children: Preliminary outcomes from a pilot study. *School Psych Rev*. 2007;36(4):665–673.

Motivational Interviewing Reduces Marijuana Use in At-Risk Adolescents

The majority of high-school aged youth who abuse alcohol and drugs are not likely to seek help for their substance use. Investigators funded by NIDA performed a pilot study of a brief motivational interviewing intervention for substance use designed for the primary care setting—a setting that has the potential to reach many adolescents. The investigators screened youths aged 12 to 18 at a free community-based primary care clinic. Participating adolescents deemed at high risk of substance abuse based on a screening questionnaire called the CRAFFT—which asks about drug- and alcohol-related behaviors including driving while under the influence, using alcohol or drugs while alone, and getting into trouble while using alcohol or drugs—were randomly assigned to receive either the intervention, called Project CHAT, or usual care. Project CHAT is a 15- to 20-minute session that focuses on assessing the adolescent’s motivation to change their substance use, enhancing motivation for change, and making a plan for change. A booster phone call to review goals was scheduled one month later. Out of 64 adolescents enrolled, 42 completed the study. Three months after study assignment, adolescents who participated in Project CHAT—whether or not they could be reached for the booster call—reported less marijuana use, lower intentions to use marijuana, and lower estimates of use by friends than adolescents who received usual care. A larger test of Project CHAT in other primary care settings is planned and will include more patients and examine longer-term outcomes.

D’Amico EJ, Miles JN, Stern SA, Meredith LS. Brief motivational interviewing for teens at risk of substance use consequences: A randomized pilot study in a primary care clinic. *J Subst Abuse Treat.* 2007;35(1):53–61.

Pain Management with Virtual Reality—Exploring the Underlying Neurobiology

Virtual reality (VR) has been used successfully to manage acute pain in patients undergoing invasive or uncomfortable procedures including burn care, lumbar puncture, and outpatient chemotherapy. By diverting a patient’s attention from an unpleasant medical procedure and engaging their higher cognitive and emotional functions in an immersive environment, VR can reduce a patient’s subjective (perceived) experience of pain. However, the neurobiological mechanisms driving the efficacy of VR in pain management have not been thoroughly investigated. In a review article, researchers including a NIDA staff scientist suggest that an area of the brain called the anterior cingulate cortex (ACC) may have particular importance in the mediation of pain perception by VR. The ACC has two distinct regions: one that is activated during demanding cognitive tasks, and another that mediates attention and emotional reactions to pain. The authors hypothesize that during exposure to VR, the ACC exerts effects on other neural structures known to modulate pain, including the periaqueductal gray area of the midbrain. Neural connections between these two areas of the brain and the amygdala may also play a role in the emotional modulation of pain perception during VR. The authors encourage that “future research in this new but rapidly growing field should strive to clarify the neurobiological means by which VR modulates pain perception...and understand how the specific features of a VR environment affect the pain outcome.” Such information may help researchers tailor a VR environment to the characteristics of individual patients, which in turn could increase its efficacy.

Gold JI, Belmont KA, Thomas DA. The neurobiology of virtual reality pain attenuation. *Cyberpsychol Behav.* 2007;10(4):536–544.

Chaperone Protein Sig-1R Helps Cells Regulate Calcium Levels Under Stress

Chaperone proteins—proteins found in the endoplasmic reticulum (ER) of cells that help other proteins fold into the correct configurations—also play a role in helping cells maintain the correct levels of calcium, which is needed for signaling to drive many critical cellular functions. A receptor called sigma-1 (Sig-1R) is known to help regulate functions in the nervous system including those involved in memory and drug addiction. However, the molecular action of Sig-1R has not been understood. In a new set of studies, researchers from NIDA’s Intramural Research Program show that Sig-1R is a chaperone protein that helps regulate calcium signaling at the junction of the ER and the mitochondria, the internal energy sources of cells. The researchers found that Sig-1R normally forms a complex with another chaperone called BiP; when the ER experiences stress resulting in alterations in calcium levels, the complex dissociates, and Sig-1R binds to and chaperones another type of protein, called the inositol 1,4,5-triphosphate receptor 3 (IP3R3). The dissociation of Sig-1R and BiP can also be caused by agonists (molecules that activate a receptor) independent of ER stress and, in some cases, can prolong the association of Sig-1Rs with IP3R3 during ER stress. Chronic stress to the ER appears to increase the number of Sig-1Rs and alter their distributions within the cell. Previous laboratory studies have shown that molecules that

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bind to Sig-1R may have therapeutic effects in cancer, drug seeking, depression, and other diseases and disorders. "Our present results suggest that Sig-1R agonists may exert their effects by freeing Sig-1R chaperones from BiP, thereby increasing bioenergetics in mitochondria. On the contrary, Sig-1R antagonists do the reverse by blocking the action of agonists," conclude the authors.

Hayashi T, Su TP. Sigma-1 receptor chaperones at the ER-mitochondrion interface regulate Ca(2+) signaling and cell survival. *Cell*. 2007;131(3):596-610.

Gene Variations Increase a Teenager's Risk of Lifetime Nicotine Addiction

The nicotine found in tobacco products is one of the most addictive drugs, legal or illegal. Since genes are known to contribute significantly to addiction risk, genomic research is critical for the identification of both the genes involved in the process of nicotine addiction and those individuals that may be most vulnerable to nicotine's addictive properties. A NIDA-funded gene screening study, published in the July 2008 issue of *PLoS Genetics*, found that Americans of European descent who carry a specific combination of genetic variations have a 1.6- to almost 5-fold increased risk of becoming addicted to nicotine as adults, but *only* if they began smoking before age 17. The researchers were able to zero in on closely linked variations within the gene cluster that contains the $\alpha 5$, $\alpha 3$, and $\beta 4$ components of the nicotine binding receptor. Interestingly, the study also uncovered a different gene variation that actually reduces the risk of adult nicotine dependence for people who began smoking in their youth. According to the study's lead author, "Because disease risk from the adverse health effects of tobacco smoke is related to lifetime tobacco exposure, the finding that an age-dependent effect of these [gene variations] has a strong influence on lifetime smoking behavior reinforces the public health significance of delaying smoking onset."

Weiss RB, Baker TB, Cannon DS, von Niederhausern A, Dunn DM, Matsunami N, Singh NA, Baird L, Coon H, McMahon WM, Piper ME, Fiore MC, Scholand MB, Connett JE, Kanner RE, Gahring LC, Rogers SW, Hoidal JR, Leppert MF. A candidate gene approach identifies the CHRNA5-A3-B4 region as a risk factor for age-dependent nicotine addiction. *PLoS Genet*. 2008 Jul 11; [Epub ahead of print].

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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 <http://www.drugabuse.gov>.

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