



MEDTOX® Journal

Public Safety Substance Abuse Newsletter

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In This Issue

Announcements

Is there an Early Warning Genetic Marker for Future Acts of Criminal Behavior?

Can Provigil Help Cocaine Addicts Stay Clean?

Georgia Survey on Teenage Alcohol Use Sheds Light on Underage Drinking

News in Treating Heroin Addiction: Implantable Naltrexone Is Gauged a Success

March Name that Drug: The Lesser-Known Sibling

Quick Links

[Our Website](#)

[Products](#)

[Services](#)

[Contact Us](#)

[Past Issues](#)

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Announcements

Analysis of 7-Aminoclonazepam at MEDTOX



Clonazepam (Klonopin) is a benzodiazepine derivative initially approved for use in the United States as an anticonvulsant. It is currently indicated for seizure disorders, anxiety and panic disorders as well as a variety of off-label uses. Benzodiazepines are widely prescribed in this country; in fact, three benzodiazepines ranked in the top 50 drugs dispensed by prescription volume in 2007. Over 20 million prescriptions for Clonazepam were filled in 2007, representing a 114% increase over the years 1998 - 2007. After taking a dose, Clonazepam undergoes extensive metabolism, primarily to 7-aminoclonazepam. While the parent compound is present in low levels, 7-aminoclonazepam is the primary analyte detectable in urine of individuals taking Clonazepam.

When the expanded benzodiazepine assay was initially developed at MEDTOX, there were no commercially-available standards for the metabolite, so detection of Clonazepam was limited to identification of the parent drug. Now that synthetic standards for the 7-amino metabolite are available, MEDTOX has replaced the parent drug Clonazepam with 7-aminoclonazepam to significantly improve overall detection of this drug. MEDTOX currently performs confirmation testing for the Clonazepam metabolite and other significant benzodiazepine drugs by state-of-the-art HPLC-MS-MS technology (high performance liquid chromatography with tandem mass spectrometry).

Is there an Early Warning Genetic Marker for Future Acts of Criminal Behavior?

Starting in 2005, the MEDTOX DAR program has offered customers an advanced training course titled,



"*Understanding the Criminal Mind.*" This special seminar focuses on the neurobiological, psychological, and environmental components thought to be contributive of criminal behavior. The premise of the seminar is that for many career criminals there appears to be a combustible package of social and physiological factors that collide to precipitate serial criminality. Those sorts of hypotheses however come with social and political implications, so careful analysis of the putative science is vital towards an effective understanding of what is going on in the minds of career criminals. Violent serial criminals are those who

society fears the most and who the criminal justice system has the hardest time figuring out. A better understanding of the factors that may contribute to the development of such a criminal might help develop responses that can be applied early in life before a criminal lifestyle has taken root.

By scanning the biographies of serial criminals, a reader can quickly come to identify the early interpersonal and family experiences that suborn adolescent and adult criminality, especially violent criminal behavior. Abusive or absent fathers, disinterested and non-nurturing mothers, mean neighborhood streets, and empty checkbooks are all factors that are frequently attributed in the case histories of serial criminals. But in many cases, some quite notorious, serial criminals have been the end products of elite upbringing, doting parents, affluence, and the best of schools. In late 2009, there was a great debate amongst academics and politicians about why many big American cities were experiencing precipitous declines in violent crime in the face of economic catastrophe. The current recession has spurred unemployment rates to levels not seen since the Great Depression, families are losing their homes, and whole neighborhoods in some cities have been wiped out by foreclosure. These sorts of conditions have been the fodder for many sociologists who argue that criminals are bred by the forces of economic and social struggle. But during the withering experience of the current recession, many large cities have become livable again due to reductions in the rates of violent crime. Even during the Great Depression, crime rates for serious offenses were at some of the lowest levels in history. So the debate rages on. Is criminality biological? Is it environmental? Is it both? If it is both biological and environmental, what are the exact contributions?

A recent study of *fear conditioning* and the role it plays later in life as a precursor of criminality was recently published in the *American Journal of Psychiatry*.^[1] Fear conditioning is a learned response where subjects learn

to fear new stimuli (i.e. loud noise, skin prick, etc.) and to associate that fear with a context that existed at the time of its experience (i.e. living room, automobile, etc.). In a clinical or experimental environment, fear conditioning can be accomplished by pairing a noxious or aversive stimulus with another benign or neutral one. Repeated skin pricks experienced in the kitchen will eventually lead to a condition where entering the kitchen (a neutral stimulus) ultimately triggers a fear response. The operating thesis for neuroscience researchers has been that misfiring in the front temporal regions of the brain may underlie poor fear response conditioning. As to how delicate aspects of the limbic system go awry in this way leads to the debate about the contributions of biological and environmental factors in criminal behavior. Invariably, these discussions stray into debate about the force that genetic expression plays in the determination of some biological factors. But in this case, the instant study examined a population of 1795 children from Mauritius and ascertained their fear-conditioned response at age three. Twenty years later, they researched and ascertained the criminal status of the now adult children. The research indicated that those children who failed to respond to fear conditioning stimulation at the age of three, some 20 years later, largely made up and represented the criminal offender group. In many cases, the subjects in the "offender" group failed to demonstrate any conditioning at all. So at least as far as this research goes, poor fear conditioning is a phenomenon associated with criminal behavior. There is still much more to be learned about this relationship and that additional research is forthcoming.

Does this research add much more to the discussion over the neurobiological basis of crime? This debate has been on going for over 20 years. The contributions of computers, MRI, and other imaging techniques have brought focus and scientific veracity to the discussions. The brain and its responses to stimuli can be studied in real time nowadays. Expect that research will continue to burrow deeper into the brain for clues in understanding the criminal mind.

(More information about the Understanding the Criminal Mind seminar can be obtained by contacting a regional MEDTOX government sales representative or by emailing DARSProgram@mac.com)

[1] Gao Y et al. Association of poor childhood fear conditioning and adult crime. Am J Psychiatry 2010 Jan; 167:56

Can Provigil Help Cocaine Addicts Stay Clean?



Several volumes ago, the MEDTOX Journal Newsletter extensively evaluated the arrival of Provigil to the prescription drug scene. In a tongue-in-cheek poke, the Newsletter described Provigil as "brain speed." To some extent, the name is fitting. Provigil is much more than just a caffeine jolt to the brain's engine. The drug appears to be establishing as a unique therapy for unusual diagnosis. Provigil is a brand name for modafinil. The drug is manufactured by Cephalon, Inc. Cephalon is also the manufacturer of the fentanyl lollipop *Actiq*, the dissolvable fentanyl lozenge *Fentora*, and also *Vivitrol*, a naltrexone product that is primarily used to treat cravings in alcoholism. Cephalon recently released to the market an iteration of modafinil, an isomer called armodafinil. The drug's brand name is *Nuvigil*. Recently, researchers set about to evaluate claims that modafinil helps abstinent cocaine addicts attain and sustain successful, restful sleep. Disruptions of sleep cycles are just one set of factors that conspire to stress recovering cocaine addicts to relapse.

Both modafinil and armodafinil are Schedule IV drugs. Both drugs cause a release of an increase in availability for norepinephrine and dopamine. The latest research tends to support the belief that these drugs interact with dopamine and norepinephrine transporters in the brain, and that those actions increase the overall levels of

dopamine and norepinephrine activity. Both of these neurotransmitters are critical components of the sympathetic nervous system and the sympathomimetic response in humans. Concurrent to the drugs effects on dopamine and norepinephrine neurons, the drugs increase the levels of histamine, a neurotransmitter associated with, among other things, "wakefulness." Most readers can identify with the effects of *antihistamines* on wakefulness. Nearly all antihistamines are drugs that cause drowsiness. Antihistamines are the principal component of over-the-counter sleep aids. Although not a member of the amphetamine family of stimulants, both drugs have similar pharmacologic actions. Quite obviously though, central nervous system stimulants like methamphetamine and cocaine trigger profoundly stimulative actions in the brain. And although modafinil and armodafinil impact the levels of dopamine and norepinephrine, their underlying mechanisms and potency are drastically different and much more sublime.

Because of modafinil's pharmacological profile, researchers have experimented with it in off-label utilizations. A recently concluded study of modafinil and its impact on the sleeping patterns of recovering cocaine addicts was published in the *American Journal of Psychiatry*^[1].

The objective of the study was to assess the impact of morning utilization of Provigil on recurring daytime sleepiness and in the stabilization of nighttime sleeping rhythms.

For recovering cocaine addicts, nearly all aspects of sleep worsen as time goes by in recovery. Sleep irritation and deprivation are not helpful in managing the stress associated with abstinence. Modafinil was administered to a cohort of recovering cocaine addicts, while an analogous cohort was administered placebo. The effects were obvious and they built up over time during recovery. Modafinil was identified with longer total sleep time and faster transitions to REM (rapid eye movement) sleep. Subjects receiving modafinil reported significantly less daytime sleepiness as well.

For the recovering cocaine addict, reduction of sleep related stress is an important component towards maintaining sobriety. It appears that modafinil (Provigil) possesses significant effects in stabilizing nocturnal sleep and reducing the weariness of daytime sleepiness for recovering cocaine addicts.

[1] Dackis, C. O'Brien, C. Normalizing effects of modafinil on cocaine-induced sleep abnormalities. *Am J Psychiatry* 2010 167:248-249.

Georgia Survey on Teenage Alcohol Use Sheds Light on Underage Drinking

It is reported that 20% of all alcohol in the United States is consumed by underage youths between 12-20 years of



age.^[1] This number is startling to parents, but if kids are asked about it they will probably tell you that the number does not surprise them. In California, MEDTOX is involved with a special pilot drug-testing program for the Hart Union School District (<http://www.hartdistrict.org>). This first of a kind program involves voluntary random drug testing of students in grades 7-12. To enroll in the program, students and parents must sign an authorization form that consents to the testing. Nearly one year into the program, MEDTOX technicians and program managers still continue to be surprised by the comments made by student participants about alcohol. Although the students acknowledge the

presence of hardcore drugs in the community and in and around the schools, they point out that alcohol abuse is at the core of adolescent drug abuse. Alcohol is easy to get. Parental wine lockers and bars are easy pickings when alcohol is needed for a party. According to a report published not long ago in the Center for Disease Control's *Morbidity and Mortality Weekly Report (MMWR)*, alcohol use by teenagers in Georgia is a significant problem^[2]. Parents and officials living in other states and cities should take the survey and trend information from this report and apply it to the situations they face in their own communities. With some fluctuations, the data gathered from this Georgia report resembles prior Monitoring the Future survey results from states like Arkansas, Nebraska, and

Wyoming.

The MMWR report evaluated a high school student survey that was undertaken by the Georgia Department of Public Health in 2007. The student response rate in the survey was 89%. Of the 89% that participated in the survey, 38% of them reported current alcohol use and 19% reported binge drinking in the last 30 days. Binge drinking was defined in the survey as having five or more drinks of alcohol in a row (i.e. within a few hours of one another) on at least one day sometime within 30 days prior to taking the survey. Binge drinking is exceedingly dangerous, especially when it involves teenagers who are unfamiliar with alcohol. Of those students who reported current alcohol use, 44% reported drinking hard liquor, such as scotch, vodka, or whiskey. Liquor was the most common alcoholic beverage consumed by survey participants. Those who identified as having been involved with binge drinking in the survey were significantly more likely to have been drinking hard liquor. Beer was the second most popular alcoholic beverage and it was more likely to be the second alcoholic beverage choice for males. Females, on the other hand, identified malt liquor beverages as their second choice beverage. Nearly 37% of the "current drinkers" obtained the alcohol from friends and 58% said that they usually consumed the alcohol at someone else's home. For ninth graders who acknowledged drinking, home was identified as the location where most alcohol was consumed. Twelfth graders reported that they did most of their drinking outside the home. As to how the participants in the survey got their alcohol, 25% said that "I gave someone else money to buy it for me" while 20% said, "I got it some other way." Twelfth graders were more likely than ninth graders to have had someone else buy alcohol for them. Female respondents were more likely to report that they had been given the alcohol. Most non-binge drinkers also reported being provided with alcohol.

This report from Georgia corroborates and builds on other national surveys, such as the 2002-2006 National Surveys on Drug Use and Health. The tendencies as to how alcohol is obtained and where it is consumed are remarkably similar in each of the related research instruments. Future research is likely to focus on some of the characteristics of people and places that are alluded to by participating students. In those instances where alcohol is provided to a student, who is that person and what relationship is the person to the respondent? And how does a student arrange to have alcohol purchased? Is it a stranger in a liquor store parking lot or is it someone who has fake identification? And why exactly is hard liquor preferred by students over beer or wine? Is it a case of potency, a quicker means of getting high perhaps? All of these questions would help parents, educators, law enforcement, and others craft more effective prevention and enforcement campaigns.

(Readers who would like more information on the Hart Union School District Voluntary Drug Testing Program (<http://www.hartdistrict.org>) can obtain the information by emailing MEDTOX at DARSProgram@mac.com)

[1] MMWR Weekly, Centers for Disease Control (CDC), August 2009: 58:885-890

[2] Ibid

News in Treating Heroin Addiction: Implantable Naltrexone Is Gauged a Success

For generations, treatment professionals have known that utilization of the opiate antagonist naltrexone is an effective treatment for maintaining sobriety in recovering heroin addicts. But the real-life usefulness of naltrexone is hampered by the tendency for patients to skip or miss doses and/or in many cases, just stop taking the drug.



Naltrexone has been around for several decades now. In a formula called *Vivitrol*, naltrexone is an effective therapy for reducing cravings in alcohol dependency. *Vivitrol* is a once-a-month injection that is administered in a doctor's office. In a recently published study conducted in Australia,

researchers evaluated a cohort of recovering heroin addicts to determine whether or not naltrexone worked more effectively in tablet or surgical implant form.

The six-month study evaluated 129 heroin dependent patients seeking treatment for their opiate addiction. Following an outpatient detoxification program, the population was randomized into two groups: one group received naltrexone tablets and placebo implants while the other group received placebo tablets with naltrexone implants.^[1] The results were striking. The patients who received implanted naltrexone remained opiate-abstinent at rates that were much higher than those assigned to taking naltrexone tablets. The implant patients maintained therapeutic levels of naltrexone in their systems for much longer periods of time than did the tablet-taking patients. Return to regular heroin use took significantly more time for the implant patients than it did for the tablet takers (158 vs. 115). By all measurements, the implant form of naltrexone brought about better results than did the tablet. Patient compliance with medication regimens is a difficult thing to manage and maintain in treating substance abuse disorders. It is clear in this case that removing the choice and daily burden of having to take medication can serve to benefit overall potential for rehabilitation and recovery.

An interesting side to this study was a finding related to abuse of other dangerous drugs by the patients of these two cohorts. Although naltrexone interferes with access to opiate receptors by narcotics (i.e. *heroin, oxycodone, hydrocodone, and fentanyl*), it does not block receptors associated with neurotransmitter systems for other classes of drugs, such as *amphetamines, benzodiazepines, and marijuana*. And despite naltrexone's ability to reduce alcohol cravings in recovering alcoholics, it does not block the neurochemical actions of alcohol. In evaluating the data from the study, the use of illicit, non-opioid drugs was the same for both groups. So although abstinence from heroin was attained and sustained through the action of naltrexone, complete sobriety remained elusive. Such is the challenge in treating substance abuse disorders. There is no silver bullet in treatment. Clinicians are challenged to come up with multifaceted therapies that take a holistic approach towards recovery. And as successful as the implantable naltrexone product was in this study of heroin addicts, long-term sobriety from all drugs of abuse is the goal for both doctor and patient.

[1] Hulse GK et al. Improving clinical outcomes in treating heroin dependence: Randomized, controlled trial of oral or implant naltrexone. Arch Gen Psychiatry 2009 Oct; 66:1108.

March Name that Drug: The Lesser-Known Sibling

This month's mystery drug is a prescription medication that is widely used in a variety of medical and clinical settings. It also has great value as a street drug. The drug is frequently diverted to addicts who may be "strung out" or in some phase of drug withdrawal. Despite widespread utilization of this month's drug in the large marketplace of drug abuse, the drug is rarely identified as a drug of abuse. This month's drug exists in two principle formulas: the name brand drug and the generic format. On the street, this drug is most commonly found in the generic form and ranges in concentrations from 0.125 mg up to 2.0 mg. The brand name version has a very distinct "stamp," a physical appearance that is highlighted by bright colorization.



This month's drug is a member of a very large and familiar chemical family of substances. This drug is a relatively modern iteration of a parent drug, a prescription drug that spawned a very long and distinguished bloodline of medications spanning 50 years of pharmaceutical success. This month's drug came to market in the brand form in the 1970s. It was not until the late 1980s however that it gained traction with physicians. Generic forms of the drug became available shortly thereafter. Brought to market by F. Hoffmann-La Roche Ltd., this drug shares the broad chemical characteristics of a family of sibling drugs in that it exerted significant influence as a central nervous system *inhibitory* drug. Considered a long acting variant of its siblings, this drug experienced immediate success as a treatment for generalized anxiety disorder and epilepsy. At the time of its emergence into the market, phenobarbital and other *barbituric acid* compounds were the only real pharmaceutical options for physicians and their patients in the treatment of epilepsy. But as therapeutic agents, barbiturates had significant drawbacks because of their great potential for abuse and addiction. This month's drug represented a notable advance in potency and safety in the treatment of epilepsy and other seizure disorders. In recent years, the drug has been combined with the *SSRI* (selective serotonin reuptake inhibitor) class of antidepressants to treat vexing forms of treatment resistant depression. This combining therapy has proven to be quite effective. In some parts of the country, this drug is a component of a prescription drug cocktail used to treat chronic pain. It is a federally controlled substance under Schedule IV. Patients can obtain multiple refill authorizations for this drug. As per the terms of Schedule IV, physicians can prescribe this drug over the telephone if the need should arise.

This month's drug is a swift acting derivative of the parent chemical that launched it and all of its siblings. This drug quickly traverses the blood-brain barrier and exerts its effects on the central nervous system. A significant clue to this drug's identity lies in the fact that it quickly binds to receptors that regulates GABA actions. GABA activity is enhanced when this drug binds to those receptors. In a related action, the drug also appears to reduce the rate of acetylcholine release and seems to inhibit central activity involving serotonin. In sum, via its GABA enhancing effects, the drug reduces the overall level of electrical firing of neurons in the central nervous systems and brings about a modicum of sedation. Unlike most of its sibling drugs, this drug metabolizes into an inactive substance that is then eliminated from the body.

Although this drug lacks the lore and drama of other substances highlighted before in this column, it is nonetheless a major cog in the wheel of street drugs and in illicit markets. This drug almost always tops the product menus for Internet drug marts. On the street, the drug is valued most in its role as a drug that is mixed with a primary drug of abuse to bring about a unique enhanced euphoria that could not be achieved by using either drug alone. In places such as New York City and Los Angeles, this drug is a frequent "combo" partner to methadone and oxycodone. In such a role, this drug enhances the core effects of narcotics to create a unique high that is qualitatively better than the highs obtained were those narcotics were taken alone. Ironically, this drug also seems to fulfill the role of "rescue" drug, a medication that can be taken should an addict begin to experience withdrawals from some other drug of choice. The drug can help mitigate the pains of alcohol and opiate withdrawal. Patients suffering from dual diagnosis disorders understand the value of this drug as a "psych-med." In the generic format, this drug is inexpensive. As a result, the drug is regularly used in public mental health programs. On the street in the illicit drug market, this month's drug services many different needs.

Because of its widespread utilization, it has a predictable presence in many American medicine cabinets. Adolescents will often bring the drug to locker parties (gatherings of adolescents that skim drugs from their home medicine cabinets) and combine the drug with other potentially dangerous drugs.

Chronic use of this drug can provoke physical dependency and a very unpleasant withdrawal. For those who have been taking chronic doses of the drug over an extended period of time, withdrawals will likely lead to a trip to a local emergency room. Should a long-term user of this drug want to stop taking the drug, a patient and doctor would have to work out a tapering program that weans the drug from the body over an extended period of time. The direct "high" or euphoria from this drug is noticeably less powerful than it is for other drugs in its class, but it attracts a substantial number of users. Because this drug has calming effects that are not overwhelming or anesthetizing, it creates fans that are loyal and consistent.

This month's drug belongs in the class of benzodiazepines. The chemical parent to the drug is diazepam (Valium). This month's drug has dozens of siblings that include notables such as Xanax (alprazolam), Ativan (lorazepam), and Versed (midazolam).

This month's drug: Klonopin (clonazepam)



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