Update on Methamphetamine Treatment: Toward a New Pharmacotherapy
Walter Ling, MD, Mark Stanford, PhD

Worldwide, approximately 37 million people use amphetamine and prescription stimulants in one form or another; it is the most commonly used and misused drug second only to cannabis (UNODC, 2017). In California, 20 to 29 year olds comprised 34% of all individuals admitted to treatment for primary methamphetamine use, and is the primary drug responsible for 26% of all admissions (SAMHSA, 2014.)

A little historical reflection helps to understand how we got here. The psychostimulant properties of amphetamine were discovered by a graduate student at UCLA in the 1920s during an effort to synthesize ephedrine, then widely used for treatment of asthma. During World War II, both sides gave their soldiers methamphetamine to keep up their vigilance and extend endurance, while the medical profession advocated its use for all sorts of ailments, including seizures and psychosis.

The first amphetamine epidemic appeared in Japan right after the War. America's first epidemic emerged in 1966 during the Summer of Love in San Francisco, California, which contributed to the founding of the Haight-Ashbury Free Clinic and gave birth to slogans like "speed freaks" and "speed kills." The 1980s brought a smokable form of methamphetamine termed "ice" and "crystal" and other names, and by the late 1990s, methamphetamine use spread from Western states into the Midwest and South, with increases seen in the Northeast in the past decade.

What crack did for cocaine, ice and crystal did for methamphetamine, altering use patterns, attracting new user populations, and enhancing its addictive potential. Smoked and injected methamphetamine gets into the brain in seconds instead of minutes from snorting and even longer for ingestion (10-30 minutes). Moreover, the effects of methamphetamine last many hours, more than 10 times longer than the effects of cocaine. Being something that hits your brain in seconds after smoking or injecting, makes you feel on top of the world, and keeps you there for hours to days is why methamphetamine is so addictive and so much more destructive.

Unlike cocaine, which acts outside the nerve cell to block the reuptake of dopamine, methamphetamine gets inside the cell body where it interferes with the storage of dopamine and causes its further release. This difference in their mechanisms of action explains why methamphetamine, compared to cocaine, is so much more toxic and why its effects last so much longer.

The immediate effects of methamphetamine, from its powerful stimulant effects on the central nervous system—via release of dopamine—and on the cardiovascular systems—via release of norepinephrine—include increased blood pressure, breathing rate and heart rate, often with irregularity, making heart attack and stroke the most serious medical emergencies among methamphetamine users. Elevated temperature is also common.
Other acute effects include increase in pupil size, sensory acuity and energy and decrease in appetite, sleep, and reaction time. Psychological effects include euphoria, increased confidence, alertness, mood, and sex drive and decrease in boredom, loneliness, and timidity. Because tolerance to the euphoric effects develops quickly while the physical effects last much longer, some users continue to use every few hours to sustain the high—binging—to the point of physical exhaustion while the levels of methamphetamine build up, leading to more severe psychotic symptoms such as paranoia, hallucinations, delusions, mood disturbance, formication, teeth grinding and other repetitive, purposeless activities—tweaking—and sometimes violence that brings users to medical attention.

The chronic physical effects of methamphetamine include weight loss, weakness, “meth mouth” (e.g., dry mouth, broken teeth, oral infection, cavities, and burned lips), tremor, cough, headaches, anorexia, and general deterioration of health; the chronic psychological effects include confusion, irritability, poor concentration, paranoia, hallucinations, anxiety, panic reactions, depression, violence, insomnia, and memory loss.

Treatment of the direct medical consequences is straightforward and mostly a matter of medical management. Acute agitation does not always require medication—a calm environment and reassurance that the condition will pass in time—talking down—may suffice. In cases requiring medication, one or two doses of a benzodiazepine alone, or a high-potency antipsychotic (5mg haloperidol or 2mg risperidol), orally or parenterally in combination with 1-2mg of lorazepam and 1mg of the anticholinergic cogentin, usually are adequate. Antidepressants and anxiolytics may be used to counter early-abstinence symptoms of depression and anxiety, respectively, though of limited, short-term benefit according to recent work (Shoptaw et al., 2009).

Methamphetamine-induced psychotic symptoms, clinically indistinguishable from acute schizophrenia, can persist as a chronic methamphetamine psychosis and may require treatment with neuroleptics. However, the long term effects and side effects of such treatments remain uncertain, raising serious concerns given the increasing number of young users. (Leelahanaj et al., 2005).

Getting off methamphetamine is more complicated than getting off heroin because users are often confused and can’t cooperate in treatment; many users don’t know they need help. No medications directly correct the acute clinical manifestations that bring methamphetamine users to medical attention.

Staying off methamphetamine is also more complicated. Becoming addicted is a matter of drug effects but staying addicted is a matter of memory. We become addicted from what drugs do to our brain but we stay addicted because we remember the experience. To stay off drugs—relapse prevention—we have to erase the drug memory.

Still, many medications have been tried to promote cessation of drug use and to prevent relapse based on targets involving various mechanisms: direct manipulation of the dopamine system, indirect modulation of dopamine via the opioid and via the GABA inhibitory system, and cognitive enhancement of the cortico-limbic reward circuitry, among others. So far the results have been disappointing.

Briefly, bupropion (Wellbutrin) (Elkashef et al., 2008; McCann, 2011) has shown tentative results, but selegilene (Eldepryl), sertraline (Zoloft), gabapentin (Neurontin), rivastigmine (Exelon), risperidone (Risperdal), ondansetron (Zofran) (Ling, Rawson, & Shoptaw, 2006), baclofen (Heinzerling et al., 2006), and modafinil (Heinzerling et al., 2010) have no or negligible results. Methylphenidate (Concerta) examined in a European study did show some efficacy in reducing relapse (Tiihonen, 2007). Our own recently completed trial of methylphenidate vs placebo showed no significant differences between the groups in a preliminary analysis of the data (unpublished). A recently completed Icelandic trial of depot naltrexone (by monthly injection), reported at this year’s annual meeting of the College on Problems of Drug Dependence, failed to replicate earlier positive results in the Jayaram-Lindstrom study of oral naltrexone. A two-stage design trial testing the combination of depot naltrexone and oral bupropion vs placebo will begin this fall in line with recent interest in testing combination of medications acting additively or synergistically on different mechanisms.
Dextroamphetamine and other similar drugs have been tried in small studies as replacement medications, but the idea is politically incorrect in the United States and many other countries. Non-euphoric analogues also have been considered and tried elsewhere but without much success.

N-acetylcysteine (aiming at glutamatergic modulation), and mirtazapine (a α2-adrenergic receptor antagonist), are being explored for their new and different mechanisms of action, as are several D3 antagonists and partial agonists, based on preclinical work in animal models. Vaccine/antibody research continues after more than a decade of slow progress, and it may hold promise reducing methampheta-mine binding in the bloodstream and thus limiting its penetration into the central nervous system.

Considering the large numbers of medications and hypothesized mechanisms so far examined and the singular lack of any success, it is perhaps time to rethink new approaches. Here data are sparse and one can only speculate. The major barrier to overcoming methamphetamine dependence is relapse prevention, which is a matter of memory—without drug memory there is no relapse. Thus, it is literally accurate to say “relapse prevention, forget it.” Extinction strategies, with and without medications such as d-cycloserine (antagonist of N-methyl-D-aspartate receptor), are being explored for treatment of PTSD and other mental disorders and may help facilitate elimination of drug memories, so could be an area of fruitful research. Meanwhile, perhaps patients can be instructed on forgetting by doing non-drug activities to create non-drug memories to replace the old ones. In the end, doing things differently is the way to have life turn out different.

ABOUT THE AUTHOR
Walter Ling, M.D., is Professor of Psychiatry and Director of the Integrated Substance Abuse Programs (ISAP) at UCLA, one of the foremost substance abuse research groups in the United States and worldwide.” Dr. Ling’s research in pharmacotherapy for opioid addiction provided pivotal information for the approval of LAAM, naltrexone (in oral and extended-release depot forms), and buprenorphine. His current research includes opioid use disorders, treatment of pain in opioid-maintained patients, and examination of methylphenidate for methamphetamine dependence. Under Dr. Ling’s leadership, ISAP’s research includes the development of pharmacotherapies and behavioral therapies for the treatment of substance use disorders involving opioids, cocaine, methamphetamine-mine, alcohol, and nicotine. Dr. Ling has extended ISAP’s research beyond the United States to Asia and the Middle East, and he has led or participated in international training efforts in 15 countries to advance addiction medicine and addiction research.

EDITOR’S NOTE: Potentially effective treatment for methamphetamine addiction identified
Last year, the first study of naltrexone’s effect on methamphetamine users has found that this medication, approved by the US Food and Drug Administration for the treatment of alcoholism, is potentially a very promising treatment for methamphetamine addiction. Published in the journal Neuropsychopharmacology, the study, was the first to evaluate naltrexone for treating methamphetamine addiction. Researchers analyzed 22 men and eight women who use methamphetamine an average of three to four days a week. During a four-day hospital stay, each person was each given either Naltrexone -- 25 milligrams the first two days, 50 milligrams on days three and four -- or a placebo daily. Ten days later, the subjects were readmitted to the hospital for four more days; those who had taken naltrexone earlier were given placebos, and vice versa. On the last day of each hospital visit, all participants were given intravenous doses of methamphetamine. Three hours later, the researchers asked how they felt and how much they wanted more of the drug.

It was found that naltrexone significantly reduced the subjects’ craving for methamphetamine, and that it made them less aroused by methamphetamine: Subjects’ heart rates and pulse readings both were significantly higher when they were given the placebo than when they took naltrexone. In addition, participants taking Naltrexone had lower heart rates and pulses when they were presented with their drug paraphernalia than those who were given placebos. The results indicated that naltrexone reduced the rewarding effects of the drug -- those taking naltrexone did not find methamphetamine to be as pleasurable and were much less likely to want more of it.

Naltrexone was well tolerated and had very minimal side effects. The researchers found that men and women both were helped by taking Naltrexone, although the positive effect on men was slightly smaller. It made no difference whether the participants were given naltrexone during their first hospital stay or their second. Naltrexone works by blocking opioid receptors in the brain.
Research continues to study the causes of drug and alcohol addiction and possible treatments including plans to examine whether naltrexone would be more effective in combination with other medicines and at different doses. This current project funded by the National Institute on Drug Abuse and UCLA’s Clinical and Translational Science Institute.

Methamphetamine use disorder is a serious psychiatric condition that can cause psychosis and brain damage, and for which no FDA-approved medication exists. An estimated 12 million Americans have used methamphetamine, nearly 400,000 of whom are addicted to it, according to recent estimates. Although the new study is promising, it needs to be backed up by clinical trials. The next step in evaluating naltrexone’s effectiveness for treating people addicted to methamphetamine is underway: the National Institute on Drug Abuse is sponsoring clinical trials.


Methamphetamine Use Disorders in Patients of Methadone Maintenance Treatment

Methamphetamine abuse continues to be a concern for many patients in methadone maintenance treatment (MMT). Of course, naltrexone is contraindicated in patients receiving opioid agonist treatment for opioid use disorder. For an MMT cohort population, one of the most effective non-medication treatment for methamphetamine addiction is behavioral therapies, such as cognitive-behavioral and contingency-management interventions.

Contingency management interventions, which provide tangible incentives in exchange for engaging in treatment and maintaining abstinence, have been shown to be effective. Motivational Incentives for Enhancing Drug Abuse Recovery (MIEDAR), an incentive based method for promoting cocaine and methamphetamine abstinence, has demonstrated efficacy in methamphetamine abusers through NIDA’s National Drug Abuse Clinical Trials Network. Stimulant abuse was targeted in the research because it remains one of the most treatment-resistant problems in the methadone-maintained population. Furthermore, because there is a well-established association between stimulant and alcohol use, alcohol abstinence was simultaneously targeted for reinforcement. To further encourage abstinence from multiple substances, additional reinforcement was provided when participants demonstrated abstinence from opioids.

The primary hypotheses were that participants in the abstinence incentive condition would submit more stimulant and alcohol-negative samples and sustain longer durations of abstinence from these drugs than usual care participants. Secondary hypotheses were that participants in the incentive condition would attend more counseling sessions and submit more opioid-negative urine samples than participants in the usual care condition. Differences in retention were not anticipated, because usual care retention rates are generally high for methadone maintenance patients who are stabilized and receiving an adequate dose.

The results of this National Drug Abuse Treatment CTN study clearly demonstrate the effectiveness of motivational incentives targeted to drug abstinence when implemented in community methadone maintenance treatment programs. Specifically, the relatively low-cost tangible incentives offered in this study doubled the likelihood that participants would provide stimulant- and alcohol negative samples at any given visit. The intervention also increased by more than 2-fold the percentage of participants submitting negative samples during 10 to 12 weeks of the study and increased by 3-fold or more the percentage of participants who achieved 4 weeks or more of stimulant abstinence. This effect was primarily due to reductions in stimulant use. Thus, drug use outcomes were improved in the total number of drug-free samples provided and in a longer duration of continuous abstinence. In this study, an abstinence incentive approach that paid $120 in prizes per participant effectively increased stimulant abstinence in community-based methadone maintenance treatment clinics. SOURCE: Arch Gen Psychiatry. 2006;63:201-208

Get access to previous issues of the Grand Rounds newsletter!

For comments or feedback about substance use prevention and treatment, or about training services for your clinic or agency, contact Rudy Escalante, Janus CEO: Rudy_Escalante@janussc.org For comments or questions about this or other newsletters, or if you have ideas for future newsletter topics, contact Mark Stanford, Ph.D., Editor of the Grand Rounds newsletter and Director of the Janus Medication—Assisted Treatment Programs. Mark_Stanford@janussc.org