CSAM NEWS

Newsletter of the California Society of Addiction Medicine / Summer 1993, Vol. 20, No. 2

INSIDE

NEWS is published three times a year by the California Society of Addiction Medicine, a nonprofit professional organization in the state of California with offices at 3803 Broadway, Oakland, CA 94611; (510) 428-9091.

Subscription rate is $25 per year.

The California Society is a specialty society of physicians founded in 1973. Since 1989, it has been a State Chapter of the American Society of Addiction Medicine.

MDMA UPDATE: THE SCIENCE AND POLITICS OF ECSTASY

Steve Heilig, MPH

The history to date of MDMA in America resembles nothing so much as a kind of "acid flashback," in that it follows the pattern of activity surrounding lysergic acid diethylamide, this time a quarter century after LSD itself burst upon the national drug scene. Consider that MDMA, like LSD, was "discovered" by scientists, languished in oblivion for decades until it began to be researched and advocated as a psychotherapeutic drug, was utilized in secret government experiments on human subjects, received increasing media attention as the public learned of its psychoactive properties, became subject to legal sanctions as recreational use spread, and slowly but surely became a widespread street drug with often exaggerated claims and rumors of both its benefits and hazards.

In 1985, MDMA (3,4-methylenedioxymethamphetamine) was classified by the Drug Enforcement Agency as a Schedule I drug with no medical use and high abuse potential, based upon fears of widespread use and studies in rats indicating the potential of irreversible brain damage associated with MDA, a related compound. This decision by the DEA was hotly contested by many researchers and psychotherapists who felt MDMA had potential as a psychotherapeutic medication. The political and scientific status of the drug was reviewed in this publication at that time (Smith, Wesson, Buffum, 1985).

MDMA remains on Schedule I, but scientific research—limited almost exclusively to animal studies—has continued, and illicit recreational street use has virtually exploded in the years since then. The actual extent of use remains unknown, but sales of over 100,000 doses per month nationwide were estimated by the end of the 1980s, and a 1987 random anonymous survey of 369 Stanford undergraduate students showed that 39% of those students had taken MDMA at least once (Peroutka, 1987). In recent years, the increasing size and frequency of the "rave" gatherings where MDMA is extensively used would support suspicions of even more widespread use, and an estimate of six million doses a year now being manufactured has been given. Given the magnitude of use of this drug, an overview and update of current knowledge is appropriate.

Basic Science: Still in the Animal State

MDMA was first synthesized as a modified amphetamine in Germany in 1914, and resurfaced among psychedelic chemists and psychotherapists in the 1970s. The burst of media and regulatory attention came in the mid-1980s. Hundreds of publications focusing on MDMA have appeared in the scientific literature since that time. The bulk of these report on animal studies researching suspected effects of MDMA on brain physiology and function, with a far lesser number of reports on humans.

Studies of MDMA neurotoxicity in rats have shown degeneration of serotonergic axonal terminals, and this effect is currently being intensively researched with evidence mounting that MDMA can have marked serotonergic impact. A 1990 NIDA report on MDMA suggested that studies in rats are at least partially generalizable to primates, and another study indicated that serotonin damage is permanent in monkeys (Scazello et al., 1993).

While this kind of research continues, the general consensus is still that little solid data exists on long term effects of MDMA neurotoxicity. Studies of MDMA's impact on serotonin function in humans have been assessed as being flawed for a number of reasons, especially the doses given to animals as compared to those taken by humans (Grob, Bravo, Walsh, 1990). In addition, the jury is still out on the animal studies; one recent study suggests effects on serotonin are temporary and insufficient to produce marked and lasting behavioral effects (Robinson et al., 1993). However, concern continues that alterations in brain chemistry could produce negative physiological and psychological results. Some evidence purporting to support those fears has appeared in the literature in the past few years.

The Ecstacies and Agonies of Ecstasy: Clinical Reports

Formal research with human subjects on the psychotherapeutic properties of MDMA was largely derailed by the DEA's action in 1985, but informal investigation and recreational use has continued and expanded widely. The original incentives for researching MDMA as a psychotherapeutic drug centered around its potential as a tool in forming a beneficial therapeutic relationship and hastening progress in therapy and self-actualization. Regarding reasons for recreational use, a survey of 100 self-identified street users of MDMA in Australia confirmed the commonly perceived benefits of MDMA, including a positive mood state, feelings of closeness and intimacy with others, increased energy, and increased insights and perceptual and sensual enhancement (Solowij, Hall, Lee, 1992). With increased dosage MDMA has been reported as hallucinogenic (Siegal, 1986). A widespread perception that MDMA has aphrodisiacal effects has not generally been supported by the limited studies. The only reported negative impacts in the Australian study were an increase in tolerance with continued use and increased physical discomforts or "hangovers."

Interestingly enough, a study of 29 subjects referred by psychotherapists largely confirmed the previously posited beneficial psychotherapeutic effects, and downplayed potential abuse concerns, noting tolerance and toxicity factors which might limit recreational use (Greer and Tolbert, 1986). A survey of 20 psychiatrists with personal experience ingesting MDMA again confirmed perceptions of both personal and potential psychotherapeutic benefits in this sophisticated study group (Liester et al., 1992). Especially interesting in this research is an associated decrease in use of other psychoactive substances. Those positive potentials have led some authors to propose classifying MDMA as an "empathogen" or "entactogen," based primarily upon increased empathy and communication associated with its use. In more common parlance, MDMA has been termed a "heart" or "hug drug."

As such pleasurable and potentially beneficial effects of MDMA have become widely known, an entire subculture gradually formed around the drug, with extended and massive "rave" dance gatherings featuring widespread MDMA use first observed in Europe in the late 1980s. The common street dose is in the range of 80-120 milligrams, with a minimum of approximately 50 mg. required for any perceived effect. Effects are usually felt within 30 minutes, with the "trip" lasting a few hours. There are many street names for MDMA, with the most common being "ecstacy," "XTC," "X," "Adam," or "rave." MDMA is not a cheap drug on the street; a single dose commonly sells for $20 or even more.

Massive "rave" dance gatherings featuring widespread MDMA use were first observed in Europe in the late 1980s.

MDMA was (and is) widely perceived to be relatively or completely harmless by users, and the limited studies of one-time or short-term use undertaken prior to DEA involvement generally supported the relative safety of the drug (Downing, 1986). However, reports of untoward effects began appearing in the medical literature soon after the widespread "raving" began.

Many such reports are primarily of psychological sequelae, including both acute and chronic paranoid psychosis and panic disorders (McCann, Ricaurte, 1992; Pallanti, Mazzi, 1992; McGuire, Fahy, 1991;

William, Meagher, Galligan, 1993; Whitaker-Azmitia, 1989; Winstock, 1991). Three cases of MDMA "flashbacks" requiring prolonged intervention were reported in Britain (Creigton, Black, Hyde, 1992). Two patients with long-term functional impairment were also reported (McCann, Ricaurte, 1991).

The various potential physiologic risks of MDMA use began to be identified simultaneously, and case reports appeared in California in the mid-1980s (Hayner, McKinney, 1986). More recently, medical consequences of MDMA use led to a number of reports and at least seven reported fatalities in Britain in 1990-91, with a pattern of toxicity noticed featuring fulminant hyperthermia, convulsions, disseminated intravascular coagulation, and acute renal failure (Brown, 1987; Chadwick et al., 1991; Dowling, McDonough, Bost, 1987; Henry, Jeffreys, Dawling, 1992). This pattern has been generalized as a hypermetabolic reaction by some clinicians, and may be related to more than MDMA by itself. These reactions may be related to dehydration resulting from the prolonged and vigorous dancing which commonly accompanies its use (Campkin, Davies, 1992).

Researchers in Europe have also reported adverse impacts from chemical contaminants in street doses of MDMA, and from combinations of MDMA with other drugs such as amphetamine, LSD, or unknown substances, where none of the single doses are at toxic levels but the cumulative dosage may be (Barrett and Taylor, 1993). Anecdotal reports from hospital emergency rooms in this country have linked MDMA use with meningitis. Seven cases of hepatotoxicity were also reported and such cases are suspected to be increasing, although this may be related more to contaminants in the street drug doses than to MDMA itself. On a related public health note, at least five instances of serious automobile accidents related to MDMA use while driving have been reported in Britain.

Treatment and Prevention Considerations

What might all this mean for the clinician who may encounter MDMA users in practice? First, the applicability of all of the foregoing research and reports is limited by a number of factors, including methodological limitations or flaws, variation in dosage and possible impurity of putative MDMA doses, varying combinations of MDMA with other drugs, and perhaps observer bias. Further complicating the picture is the fact that there is no solid epidemiological data on how much MDMA is being taken by how many people. But assuming that recreational use is relatively widespread, a few things should be kept in mind about MDMA.

First, the serious adverse reactions increasingly being reported are relatively very rare when the probable extent of use is considered. "We don't have anything close to a denominator to estimate how many people are taking MDMA," says epidemiologist John Newmeyer, PhD, of the Haight Ashbury Free Medical Clinics. Newmeyer is in the very early stages of collaborating on an epidemiological study of MDMA use, but feels that at this point, "It's a problem of more smoke than fire. MDMA is not very hazardous, so looking for adverse MDMA reactions is like fishing for a very rare fish." The Clinic's Director of Detox Programs, Darryl Inaba, PharmD, confirms that, "We don't see many people reporting problems with MDMA compared to the number of people taking it. We've seen maybe one or two people a month, with depression, psychotic reactions, or just concerns about rumors of dangers they've heard."

Alexander Shulgin, PhD, the chemist who first reported data on human studies of MDMA in the 1970s, agrees and is even more skeptical of the mounting fears about MDMA's threats. "The solid data to date is still exclusively animal, and the amounts of drug given are finally coming down to the levels used by humans," he says. "At realistic doses – say in the 100-120 mg range – the serotonin changes seen are shrinking and disappearing. There has been no demonstration in humans that would reflect dumping of serotonin. But such positive studies don't get published while the negatives are published – in order to get government research funds you have to pursue only the risks of the drug." Shulgin is also skeptical about the reports of serious reactions and deaths. "You have to look at those reports very carefully. Either MDMA is not shown to be truly present, or there are other drugs more likely to be causing the problems. Almost every one of the 15-20 difficulties have been due to hyperthermia. The people putting on the raves are often irresponsible and don't have fluids available for people. So, while there have been some deaths associated with MDMA, the causality is very thin."

David Smith, MD, medical director of the Haight Clinics, says that MDMA use has now been common in the San Francisco Bay Area for some time, and notes that "MDMA is definitely part of the reincarnation of the psychedelic phenomenon." He has seen some serious cases, primarily at the Clinics' Rock Medicine section which sets up medical tents at major rock music

"If malignant hyperthermia is present, you have to get them to a hospital."

shows, and has been involved in the treatment of two patients with prolonged psychotic reactions after ingestion of MDMA at raves. Smith says he is aware of at least two deaths attributed partially to

MDMA seizures and toxicity in the San Francisco area, but agrees these are relatively rare reactions. Clinicians who have seen some adverse reactions suspect that other psychoactive drugs commonly mixed with street doses of MDMA, especially amphetamine, LSD, and more recently heroin, are contributory or even primary precipitators of the reactions, including the common and benign nystagmus and jaw tension seen in these patients. The practice of mixing such drugs with MDMA is often referred to as "candy-flipping" among users, especially with regard to LSD and MDMA combinations.

Reports of severe psychological reactions related to MDMA may also be due to other factors, notes Charles Grob, MD, Director of Child and Adolescent Psychiatry at Harbor-UCLA Medical Center and the only American researcher to receive FDA approval for human trials of MDMA. "Most of the reports I've seen ignore set and setting—in one report the setting was the New York subway system, where even I have paranoid reactions!" Other patients have had serious psychiatric problems which may have predisposed them to react adversely, but these histories have been downplayed or not reported, he says.

When they do occur, adverse MDMA reactions may be acute and related to the single dose and timing. For such suspected MDMA reactions, the Clinic staff uses the same "talk-down" approach taken with other psychedelic or amphetamine cases, with half-doses of lorazepam (Ativan) administered when the person is extremely agitated, in order to help facilitate communication. But, Smith warns, "if malignant hyperthermia is present, you have to get them to a hospital."

British clinicians have recommended early and aggressive treatment of "MDMA morbidity" with gastric lavage, adrenergic blockage, intravenous fluids and passive cooling, and admission to intensive care in cases where close monitoring of complications is required (Barrett, Taylor, 1993). The British Poisons Information Service advocates early use of dantrolene (Dantrium), a change from the earlier recommendation of chlorpromazine (Thorazine), which may lower the convulsive threshold and therefore is counterindicated. Other British authors, considering the potential but unproven effects of MDMA on liver function, have recommended that, "A history of MDMA misuse should be sought in young people with unexplained jaundice or hepatomegaly" (Henry, Jeffreys, Dawling 1992).

Due primarily to the temporary rise in blood pressure associated with larger doses, a number of counterindications to MDMA use have been suggested, including any history of hypertension, cardiac conditions, use of MAO inhibitors, epilepsy, or current pregnancy. Pioneering MDMA researcher and psychiatrist Claudio Naranjo, MD, has suggested that a very small percentage of people are very sensitive to modified amphetamine such as MDMA and will react with the severe hypertension and sweating seen in many of the reported adverse reactions (Stafford, 1992). This reinforces the growing consensus that host susceptibility is a primary consideration in MDMA reactions, with an unknown but apparently small percentage of people at risk for adverse reactions at common street dose levels.

Dr. Grob reiterates that "I don't think the evidence for common clinical sequelae has much validity at this point. But I do have real concerns about indiscriminate use, such as when young people mix MDMA with other drugs and pay no attention to set and setting. I also think certain people shouldn't be taking MDMA in any case, such as those with brittle psychological function and without impulse control, and certainly those with cardiac disease."

Longer-term reactions associated with MDMA are even more rare, but Smith and his colleagues at the Haight Clinic have begun to develop a categorization of such reactions, noting that chronic toxicity can prolong toxicity reactions and bring about a range of symptomology ranging from mild dysphoria to frank psychosis. An MDMA-induced anxiety syndrome has also been posited, perhaps resulting from the host of previously unconscious material brought to the surface by MDMA but remaining unresolved. Depression may also result in such cases. Again, however, with good human research prohibited, such reports remain anecdotal.

"I don't think the evidence for common clinical sequelae has much validity at this point. But I do have real concerns when young people mix this with other drugs and pay no attention to set and setting. I also think certain people shouldn't be taking MDMA in any case, such as those with brittle psychological function and without impulse control, and certainly those with cardiac disease."

While aware of these medical consequences and controversies, Smith

feels that the addictive potential of MDMA also does not appear to be high. "This is not a drug that lends itself to addiction. You'd get toxic effects long before you were addicted, and tolerance builds up rapidly. There may be some definite medical consequences which may or may not be dose-related, and there is a large population exposure, but hypermetabolic or other adverse reactions are quite rare. It's not a major addiction issue at this time, but a growing and potentially serious medical, psychological, epidemiological and social one."

Dr. Grob recently received FDA approval for the first Phase I trial of MDMA to assess its potential for alleviation of physical pain and psychological distress in end-stage cancer patients.

On the preventive public health front, the Haight Ashbury Clinics and San Francisco AIDS Foundation have joined in a public education effort, utilizing the format of the colorful cardboard fliers used to advertise rave events. The "X" fliers provide warnings about unknown impurities in street doses, dehydration, alcohol use, and HIV prevention, and an "ecstacy and safe sex" telephone information line. "We're trying to reach the broader population who probably won't go near a doctor or clinic," says Barry Lawlor of the Haight Clinic. "Ours is a non-judgmental approach. We've had some controversy with those who think we might be encouraging use of MDMA, but the model here is the same as in the risk reduction campaigns used for needles and HIV. Our message is that it's better to be in recovery, but if you're going to use, do it less dangerously. These cards are like a paper equivalent of bleach or clean needles."

Conclusion: MDMA – Back to the Future

What may lie in the future regarding MDMA? Regarding licit research, Dr. Grob at Harbor-UCLA recently received FDA approval for the first Phase I trial of MDMA, with the eventual aim of assessing its potential use in the alleviation of physical pain and psychological distress in end-stage cancer patients. In approving his study, he notes, "The FDA noted that MDMA does not appear to be any more dangerous than many other drugs that are the object of clinical trials, and should be subject to the same rigorous scientific standards as other researched drugs." He and other researchers see this as an encouraging sign that needed research may again be able to go forward. "People are less vulnerable to the 'war on drugs' mentality which has frozen such research," notes Grob. "Especially with drugs that are already being used out there extensively, we need to be able to investigate the effects on humans. Even NIDA has admitted that we now need to move beyond animal studies and initiate research on effects in humans."

Looking both back and forward, Grob notes that, "Psychedelic research was one of the most promising fields in the 1950s and 1960s, and now that 25 or more years have passed the hope is that this generation of researchers will be more responsible about how the studies are conducted."

As for recreational use, it's anyone's guess as to how the picture will evolve. Longtime MDMA researcher Jerome Beck, DrPH, of the Institute for Scientific Analysis in Berkeley, observes that, "It seemed like after scheduling of MDMA in 1985, supply dropped in a lot of places. But that changed with the rave scene – wherever it becomes popular, primarily in urban areas, MDMA is sure to follow. The rave scene continues to grow in the US and I suspect that use of MDMA is growing comparatively."

Writing here about MDMA in 1985, Smith, Wesson and Buffum noted presciently that, "Moving a drug to Schedule I does not stop illicit availability,...(it) does, however, have consequences. Price generally increases, the quality control of licit manufacture is destroyed, and responsible research becomes almost impossible." Until much more "responsible" research is allowed and completed, we can only attempt to assess the implications of widespread street use of MDMA. At this time, serious adverse consequences appear rare. But pharmacologist Inaba sounds one concluding cautionary note in this regard, again taking a lesson from history: "Remember that cocaine had the same reputation for safety and non-addictiveness in the early 1970s that MDMA has today, and that turned out to be very wrong. We haven't seen such problems with MDMA, and maybe we won't. But the potential is there." □

"Moving a drug to Schedule I does not stop illicit availability...(it) does, however, have consequences. Price generally increases, the quality control of licit manufacture is destroyed, and responsible research becomes almost impossible."

References

Barrett PJ, Taylor GT. 'Ecstasy' ingestion: a case report of severe complications. J Royal Soc Med 1993; 86(4):233-4.

Campkin NT, Davies UM. Another death from ecstasy. J Royal Soc Med 1992; 85(1):61.

Chadwick IS, Linsley A, Freemont AJ, et al. Ecstasy, a fatality associated with coagulopathy and hyperthermia. J Royal Society Med 1991; 84(6):371.

Creighton FJ, Black DL, Hyde CE. 'Ecstacy' psychosis and flashbacks. British J of Psychiatry 1992; 159(11):713-15.

Dowling GP, McDonough ET, Bost RO. 'Eve' and 'Ecstasy': A report of five deaths associated with the use of MDA and MDMA. JAMA 1987; 257:1615-17.

Downing J. The psychological and physiological effects of MDMA on normal volunteers. J Psychoactive Drugs 1986; 18(4):335-340.

Greer MD, Tolbert R. Subjective reports of the effects of MDMA in a clinical setting. J Psychoactive Drugs 1986; 18(4):319-328.

Grob CS, Bravo G, Walsh R. Second thoughts on 3,4-methylenedioxymethamphetamine (MDMA) toxicity. Arch Gen Psychiatry 1990; 47:288.

Grob CS, Bravo GL, Walsh RN, Liester MB. The MDMA-neurotoxicity controversy: implications for clinical research with novel psychoactive drugs. J Nervous and Mental Disease 1992; 180(6):355-6.

Hayner GN, McKinney H. MDMA: the dark side of ecstacy. J Psychoactive Drugs 1986; 18(4):341-348.

Henry JA, Jeffreys KJ, Dawling S. Toxicity and deaths from 3,4 -methylenedioxymethamphetamine. Lancet 1992; 340(8816):384-7.

Landry MJ. The Drugs of Abuse: The Processes of Addiction, Treatment, and Recovery. Washington, DC: American Psychiatric Press, 1993.

Liester MB, Grob CS, Bravo GL, Walsh RN. Phenomenology and sequelae of 3,4-methylenedioxymethamphetamine use. J Nervous and Mental Disease 1992; 180(6):345-52.

McCann WD, Ricaurte GA. Lasting neuropsychological sequelae of (+/-) methylenedioxymethamphetamine in recreational users. J of Clinical Psychopharmacology 1991; 11(5):302-5.

McCann WD, Ricaurte GA. MDMA and panic disorder: Induction by a single dose. Biological Psychiatry 1992; 32(10):950-3.

McGuire P, Fahy T. Chronic paranoid psychosis after misuse of MDMA. British Medical J 1991; 302(6778):697.

Pallanti S, Mazzi D. MDMA: precipitation of panic disorder. Biological Psychiatry 1992; 32(1):91-5.

Peroutka SJ. Incidence of recreational use of 3,4 methylenedioxymethamphetamine (MDMA, 'ecstasy') on an undergraduate campus. N Eng J Med 1987; 317(24):1542-43.

Robinson TE, Casteneda E, Whishaw IO. Effects of cortical serotonin depletion induced by 3,4-methylenedioxymethamphetamine on behavior. Neuropsychopharmacology 1993; 8(1):77-85.

Scazello, CR, et al. Serotonin recovery after +/-3,4-(methylenedioxymethamphetamine injury: observations in rats. J of Pharm and Exp Therapeutics 1993; 264(3):1484-91.

Siegal RK. MDMA: nonmedical use and intoxication. J Psychoactive Drugs 1986; 18(4):349-354.

Smith DE, Wesson DR, Buffum J. MDMA: 'Ecstacy' as an adjunct to psychotherapy and a street drug of abuse. CSAM News 1985; 12(9):1-3.

Solowij N, Hall W, Lee N. Recreational MDMA use in Sydney. British J of Addiction 1992; 87(8):11610-72.

Stafford P. Psychedelics Encyclopedia, 3rd Edition. San Francisco: Ronin Publishing, 1992.

Watson L, Beck J. New age seekers. MDMA use as an adjunct to spiritual pursuit. J of Psychoactive Drugs 1991; 23(3):261-70.

Whitaker-Azmitia PM, Aronson TA. 'Ecstacy' (MDMA)-induced panic. Am J Psychiatry 1989; 146(1):119.

Williams H, Meagher D, Galligan P. MDMA: a case of possible drug-induced psychosis. Irish J of Med Sci 1993; 162(2):43-4.

Winstock AR. Chronic paranoid psychosis after misuse of MDMA. British Medical J 1991; 302(6785):1150-1.

From the President

Gail Jara to Receive CSAM Community Service Award

Gail Jara is the Founding Executive Director of the California Society. She has been the guiding light and organizational "pilot" of CSAM since the first steering committee meetings in 1972. Her untiring efforts and dedication to the growth and well-being of the Society and to the whole field of addiction medicine have earned her a very special place in our hearts. Her efforts to advance the principles of addiction medicine, first at the CMA where she worked from 1972 to 1987, and more recently with her concurrent work for ASAM, have contributed immensely to the growth of our field. The 1993 Community Service Award is being presented to Gail to honor her as a force which has led to our "20 years of excellence."

George Lundberg, MD, to Receive the Vernelle Fox Award

George Lundberg, MD, will be honored as the 1993 recipient of the Vernelle Fox Award for his efforts to bring drug and alcohol topics into *JAMA* and into the mainstream of US medicine. Doctor Lundberg, a charter member of the California Society in 1972, was in California for 15 years. He was the second Chair of the California Society Committee on Education, from 1976 to 1980 when he left to take a short sabbatical, spending three months in Chicago as a special consultant to the American Society of Clinical Pathologists on a project to improve teaching methods in CME.

A native of Florida, Doctor Lundberg completed a clinical internship in Hawaii and a pathology residency in San Antonio. He served at Letterman Hospital in San Francisco and at William Beaumont Hospital in El Paso to complete an 11-year Army tour. Doctor Lundberg was Professor of Pathology and Associate Director of Laboratories at the LA County/USC Medical Center for 10 years. In 1977, he became Professor and Chair of Pathology at the University of California-Davis.

Doctor Lundberg has worked in tropical medicine in Central America and Forensic Medicine in New York, Sweden, and England. Since 1982, he has been at the American Medical Association where he is Editor-in-Chief of Scientific Publications with editorial responsibility for its 38 medical journals, Editor of *JAMA*, and host of the weekly television program, "*JAMA* Medical Rounds" on CNBC. Doctor Lundberg was elected to the Institute of Medicine of the National Academy of Sciences in 1992. □

— KWO

President's Column

CSAM-ASAM Joint Membership

On January 1, 1994, the California Society of Addiction Medicine will join with ASAM in requiring joint membership in both organizations. Some will ask why so formal a union is necessary. There are clear benefits of being a local chapter of a national organization – not the least of which is the strengthening of both through participation and identification with colleagues across the country.

During the past six months, the Diversion Program in California came into serious jeopardy. CSAM was a unique voice among State organizations, medical and non-medical alike, in having a large number of members who had been intimately involved with the Diversion Program in many different ways – as members of Diversion Evaluation Committees, as consultants providing evaluations of the physicians applying to Diversion, and as members of the Liaison Committee to Diversion. CSAM members were able to contribute much needed objective and pragmatic information about the Diversion Program. This wealth of expertise helped coordinate the concerns of all involved and resulted in a rational and coherent response to critics of the program. The voice of the California Society was given added weight because it was associated with the national society – ASAM.

Numerous members of the California Society, including this writer, spent days at hearings of the State Medical Board and in meetings with representatives of the Board. Although initially there were serious questions about the future of the Diversion Program, it now seems to be emerging from the process reasonably intact. There is no doubt that the eloquent and timely response of our members – coordinated and facilitated through our offices in Oakland – was invaluable in achieving this outcome. The consultative and advisory capabilities of CSAM were recognized and utilized by both the California Medical Association and the California Psychiatric Association during this crisis. It was a valuable demonstration of the importance of a strong state organization of physicians with chemical dependence treatment expertise working with sister state organizations. Many thanks to all of you who gave so freely of your time and knowledge. You have made an important difference for the future of physicians in the State of California.

It is clear to me that the stronger union of CSAM and ASAM will mark the beginning of a new era. As a result of watching our members in action during this challenge to the Diversion Program, I am confident that CSAM will continue to contribute to the practice of addiction medicine with the same effectiveness that has characterized its first 20 years. □

— Kevin W. Olden, MD

Legal Status of Prescribing Buprenorphine

by H. Westley Clark, MD, JD, MPH; Lawrence Nelson, JD, PhD; Douglas L. Bovee, MD

Editors' Note: Although several published studies suggest that buprenorphine is a promising new treatment for heroin dependency (maintenance or detoxification), the FDA has not yet reviewed buprenorphine for either purpose. Although buprenorphine is approved by the FDA for the treatment of pain, and an injectable form (Buprenex) is available, the use of buprenorphine for treatment of heroin dependency is still under investigation. Because buprenorphine is classified under federal law as a Schedule V narcotic, *(emphasis added) physicians are at risk of prosecution by the DEA and administrative action by their state's medical licensing board if they prescribe it to an opiate addict solely for the purpose of treating opiate dependence or withdrawal. If buprenorphine were not a scheduled narcotic, no regulatory agency would be interested in how it is used once it has been made available for another use. However, as issues raised in the article below suggest, it is prudent for physicians to be informed about the Federal and State laws and regulations, which, in California, include a requirement for a research protocol approved by the California Research Advisory Panel.*

Ongoing research supports the efficacy of buprenorphine for the treatment of heroin dependency (CSAM *NEWS*, Winter 1992; 19(1):18-19 and Fall 1990; 17(2):8-9). Consequently, we are seeing a growing excitement among clinicians at the prospect of adding another pharmacologic agent for either detoxification or maintenance treatment. In fact, based on the promising findings reported in the literature, some physicians have already begun using buprenorphine for this purpose. One detailed a protocol for withdrawal in a letter to the editors of this newsletter (CSAM *NEWS*, Spring 1993; 20(1):8).

Normally, rapid diffusion of information about evolving treatments is welcome; it permits a possible benefit to reach a larger number of patients. Furthermore, the adoption and modification of new treatments by clinicians provides information to researchers about side effects and new treatment issues. Clonidine, for example—an antihypertensive agent which is used either orally or by transdermal patch in the treatment of narcotic withdrawal—moved quickly from research to general practice. Although clonidine is not approved by the FDA for treatment of opioid withdrawal, it is widely used for this purpose and described in both the textbooks and periodic literature. However, not all drugs can be so easily shifted from research to practice. Buprenorphine, for example, cannot because it is a narcotic.

Federal laws and regulations

Buprenorphine is a opiate agonist/antagonist. In the Federal Controlled Substances Act, it is classified under Schedule V where it is specifically labeled as a narcotic.

The classification of buprenorphine as a "Schedule V narcotic" is not simply a tautology. It invokes a body of laws and regulations which govern narcotics, but not other classes of drugs. The Controlled Substances Act of 1984 has defined "narcotic" as a class of drugs containing opioids and cocaine (See Section 21 USC 802(17)).

At this point, the only narcotic approved for treatment of narcotic addiction, either detoxification or maintenance, is methadone. *Prescribers* are constrained by Federal regulations from using any narcotic other than methadone for detoxification or maintenance treatment of narcotic addiction. See Title 21 of the Code of Federal Regulations, Section 291.505. Outside of research, buprenorphine cannot be used for those purposes. Only approved narcotic treatment *programs* may undertake maintenance treatment for opioid addiction, and they may use only methadone (and soon LAAM; see the article on page 10).

That said, we should note the exceptions. A hospital may maintain a patient who is an opioid addict on a narcotic such as buprenorphine if that patient is admitted for treatment of medical conditions other than addiction and requires temporary maintenance during the hospital stay (21 CFR 291.505 (f)(2)).

Federal regulations do permit a licensed physician functioning outside an approved narcotic treatment program to administer (but not to prescribe) narcotic drugs to a person but only for the purpose of relieving acute withdrawal symptoms if that is necessary while arrangements are being made for referral for treatment. This is considered emergency care. In such a case, not more than one day's medication may be administered at one time, and

not for more than three days; this schedule cannot be renewed or extended (21 CFR 1306.07(b)).

State laws and regulations

In addition to Federal regulations, state law governs the prescribing of controlled substances. Most jurisdictions, including California, follow the Uniform Controlled Substances Act, with minor modifications. California law classifies the following as a "non-prescription," in other words, an act outside the authority given to a physician, or a violation of the law:

> An order for an addict or habitual user of controlled substances, which is issued not in the course of professional treatment or as part of an authorized methadone maintenance program, for the purpose of providing the user with controlled substances, sufficient to keep him or her comfortable by maintaining customary use (California Health and Safety Code 11153(a)(2)).

It is not clear how "in the course of professional treatment" in this context may be interpreted in the future—for example, whether a prescription for buprenorphine by an addiction medicine specialist would come to be interpreted by regulatory agencies as within "the course of professional treatment" — but for the present we know that whatever is considered outside the law is considered outside the course of professional treatment.

California law says that the primary treatment of an addict for addiction to a narcotic drug can be conducted only in state approved facilities (California Health and Safety Code 11217). In 1972, a modification was made to that restriction when the leaders of what became the California Society sponsored a bill specifying that a physician may administer, in his or her office or other medical facility, medications that are medically necessary, except for narcotic drugs (California Health and Safety Code 11217.5). For example, a physician, in any setting, may use non-narcotic medications to relieve the symptoms of opioid withdrawal—such as ibuprofen for muscle aches, and temazepam (Restoril) for sleep.

In an apparent contraction, a 1982 California Attorney General's Opinion permits the administering of propoxyphene (Darvon) and propoxyphene napsylate (Darvon N) for the relief of pain experienced in heroin withdrawal to a patient under his/her direct care (65 Opinions of the Attorney General (California) 293 (1982)). If the patient receiving Darvon or Darvon N resides in a registered and approved "recovery house," the physician may also prescribe or furnish the medication.

Discussion

It is important for the physician to recognize that buprenorphine is an abusable drug. There is a growing literature on its abuse. A liberal policy of using buprenorphine in the treatment of opioid addiction may contribute to creation of a street market for this drug. Once a drug has a significant street value, it invariably will come to the attention of the Federal Drug Enforcement Agency and its state counterpart, perhaps motivating those agencies to seek a more restrictive scheduling. If that happened, it would reduce the chances that buprenorphine will become available for use by addiction medicine specialists outside of research protocols conducted in clinics specially licensed for the treatment of opiate addiction.

Thus, before physicians choose to use buprenorphine for a patient for narcotic detoxification, they should inform themselves of the Federal and State laws and regulations which govern its use for that purpose. It may be advisable for physicians to avoid using buprenorphine outside approved research protocols until its status as an agent for detoxification and maintenance has been clarified. □

H. Westley Clark, MD, JD, MPH, is Chief, Associated Substance Abuse Programs for the San Francisco Veterans Affairs Medical Center.

Lawrence Nelson, JD, PhD, is a Policy Analyst in the Treatment Research Unit of San Francisco Veterans Affairs Medical Center, UCSF.

Douglas L. Bovee, MD, is in the private practice of addiction medicine in Eugene, Oregon.

The preparation of this article was supported, in part, by NIDA grant R18-DA06097.

Definitions

Prescribe: In the context of this article, to prescribe means to write an order for medication which is subsequently dispensed to the ultimate user. This does not include an order written in a patient chart for medication to be administered to a patient in hospital.

Dispense: To dispense means to give a medication to the ultimate user for subsequent consumption. In dispensing medication, the pharmacist or physician labels the container as required, with directions for use, etc.

Administer: To administer means to give a medication directly to the ultimate user for immediate consumption, usually under observation.

(21 CFR 1306.02 (f) and 21 CFR 1306.07)

FDA Advisory Panel Recommends Approval of LAAM

Walter Ling, MD; Donald Wesson, MD; Richard Rawson, PhD; Sandy Dow

The FDA's Drug Abuse Advisory Committee met on June 7-8 in Rockville, Maryland, and voted unanimously to recommend approval of LAAM for treatment of opioid dependence. The medication should be available to clinics later this year according to Alex Bradford, former Chairman and President of Biometric Research Institute (BRI) and now Chairman and CEO of Biodevelopment Corporation, the company that will manufacture and distribute LAAM under the trade name of LAAM. The approval of LAAM came after several years of intense effort from NIDA's Medications Development Division, under the leadership of Charlie Grudzinskas, PhD, Division Chief (now Acting Deputy Director of NIDA), Frank Vocci, PhD, LAAM Project Director (now Acting Chief of the Division), and BRI, NIDA's contractor for LAAM development.

LAAM (levo-alpha-acetylmethadol) is a congener of methadone, but it is not, as it is often misunderstood, simply a long-acting methadone. LAAM's clinical characteristics are different from those of methadone and these differences account for its potential clinical advantage.

Well absorbed after oral administration, LAAM, a pro-drug, is metabolized in the liver to nor-LAAM and dinor-LAAM which are more potent and have longer half-lives than the parent drug. As a result, the onset of opioid effects after oral LAAM administration is slower than methadone and the clinical effects are more prolonged. LAAM can thus be administered three times a week at the clinic, eliminating the need for daily dosing and take-home medication (the major source of street methadone diversion). Its slow onset of action should make it less subject to abuse by addicts seeking an immediate "high." Moreover, because LAAM requires biotransformation in the liver to exert its full clinical effects, it acts more quickly when taken by mouth than when injected, which should reduce its potential for intravenous abuse.

Clinical interest in LAAM dates back more than 25 years and some of the pivotal work on its safety and efficacy was completed in the 70s, before the HIV and current cocaine epidemics, at a time when few female addicts were in treatment and fewer still were available for research participation. NIDA and BRI, therefore, undertook additional studies with cohorts of contemporary male and female opioid addicts, including a usage study in which clinicals were guided almost solely by the information contained in the proposed package insert. Results of these studies confirm previously available information attesting to LAAM's clinical safety and efficacy, allowing the Advisory Committee to go forward with its recommendation for FDA approval.

LAAM, a pro-drug, is metabolized in the liver to nor-LAAM and dinor-LAAM which are more potent and have longer half-lives than the parent drug.

With the Advisory Committee's affirmative recommendation, FDA is expected to formally approve LAAM momentarily. Meanwhile, the DEA has taken steps to reschedule LAAM from Schedule I to Schedule II to allow for its clinical use. Biodevelopment Corporation, on its part, plans to have a series of regional informational and educational meetings later this fall for physicians and other clinic personnel as it begins to make LAAM available to the clinics.

The package insert and FDA regulations for use of LAAM will be similar to those for methadone except that take-home doses of LAAM will not be allowed. This prohibition will probably be temporary, until the addicts and the treatment community become familiar with the properties of LAAM. From the perspective of public health and policy, LAAM should be safer and therefore more desirable take-home medication than methadone because of its lower potential for diversion to the street.

LAAM should add significantly to the armamentarium available to clinicians caring for patients with opioid dependence. □

Status Note

Treatment Outcome Project

This CSAM project will gain consensus among providers, managed care companies, and researchers on core data elements so that better data will be available to support policy decisions about how to structure coverage for addiction treatment. (*NEWS, Summer 1992; 19:2(3-8).*)This project is under the direction of a steering committee chaired by P. Joseph Frawley, MD. Members are Norman Hoffmann, PhD, New Standards/ CATOR, Inc; John Montgomery, MD, Human Affairs International/ Aetna; John Bartlett, MD, MCC Companies, Inc., and Martin Doot, MD, Parkside Medical Services. "We will agree on recommendations to the different data banks which are currently in use or in development," said Frawley. □

NEWS ABOUT MEMBERS

Art Bolter's practice continues in his office in Castro Valley after the close of the John Muir Adolescent Treatment Center in San Ramon where he was Medical Director since 1989.

Karen Sees has begun her term of office as President of the American Osteopathic Academy of Addictionologists.

Lyman Boynton is Medical Director of Kaiser Permanente's Chemical Dependency Recovery Program in San Francisco which expanded and moved into new quarters in April.

Bill Brostoff was appointed to the Professional Conduct Committee (well-being committee) of St. Mary's Hospital in San Francisco.

Kevin Olden received the Outstanding Teacher of the Year Award from the graduating house staff in medicine at St. Mary's Hospital in San Francisco. □

APPLICANTS FOR MEMBERSHIP

The names of applicants are published and sufficient time is allowed for comments from the members before the Executive Council acts to accept them as members. If you have comments to bring to the attention of the Executive Council, please contact Kevin Olden, MD, at (415) 668-1001, or write to him in care of the California Society office.

Charles P. Connor, MD, is a board-certified psychiatrist at the San Francisco VA Medical Center. He graduated from the Medical College of Wisconsin in 1985 and completed a three-year residency at the University of Chicago in 1989.

Charles L. Dorsey, MD, a board-certified pediatrician, is Chief of the Department of Addiction Medicine at Napa State Hospital. He graduated from Duke University's School of Medicine. He completed a three-year residency at Tulane Charity Hospital in New Orleans.

Stuart D. Klein, MD, a board-certified internist, is the Medical Director of Sunrise Center at Pomerado Hospital in Poway. He attended Howard University Medical School, interned at UCLA Harbor General Hospital in Torrance, and did a two-year residency at Mercy Hospital in San Diego.

Ernest M. Thomas, Jr, MD, is a family practitioner in Los Gatos. He graduated from Meharry Medical College in 1960. He did one year of internal medicine at San Diego County Hospital in 1962. He is Clinical Assistant Professor of Family Medicine at Stanford University, and Instructor in Family Medicine at USC and UCD. □

Clarification/Correction

In the article, "Naltrexone treatment of alcohol dependence," in the last issue, Doctors Wesson, Smith and Ling reported on public interest stimulated by newspaper articles describing two studies in the *Archives of General Psychiatry*. In fact, in addition to the November 13-14, 1992 newspaper articles based on Associated Press News Releases by A. J. Hostetler, titled "Drug appears to prevent relapse of alcoholism," there was also TV coverage (Dan Rather, CBS Evening News, December 16, 1992). The references to this coverage and its timing were omitted from the article, along with the authors' comment that "as is common now, the newspaper accounts appeared several days before most of us on the West Coast received our copy of the journal." The result was that a point important to the overall commentary intended for the article was lost to the reader. □

CONTINUING MEDICAL EDUCATION

ASAM's 6th National Conference on Nicotine Dependence

November 11-14, Marriott Marquis Hotel, Atlanta
For information, contact ASAM, 5225 Wisconsin Avenue, NW, Washington, DC 20015; 202/244-8948.

State of the Art in Addiction Medicine

Sponsored by ASAM, NAADAC, and the Cambridge Institute
October 28-30, Contemporary Hotel, Disney World, Orlando
Fees: $350 for members; $425 for non-member physicians; $350 for non-physicians
Credit: 15 hours
For information, contact ASAM, 5225 Wisconsin Avenue, NW, Washington, DC 20015; 202/244-8948.

Addiction Medicine: State of the Art 1993

Sponsored by California Society of Addiction Medicine and American Society of Addiction Medicine
November 18-20, Four Seasons Hotel, Newport Beach, CA
Fees: $350 for members of CSAM/ASAM; $425 for non-member physicians; $350 for non-physicians
Credit: 19.5 hours, plus 3 hours for pre-conference master classes
For information, contact CSAM, 3803 Broadway, Oakland, CA 94611; 510/428-9091.

CSAM's 20th Annual Meeting

during the 1993 State of the Art Conference

Installation and Awards Ceremonies
Friday evening, November 19

Installation of Richard Sandor, MD, as President
Presentation of the CSAM Community Service Award to Gail Jara
Presentation of the Vernelle Fox Award to George Lundberg, MD, Editor of *JAMA*
Dinner Address by Doctor Lundberg:
"*JAMA*'s Role in Mainstreaming Alcohol and Other Drugs"

Dinner is $20 for registrants of the State of the Art Conference and $35 for others.

CSAM 20th Annual Business Meeting
at lunch on Saturday, November 20

- Reports on each CSAM committee and activity
- Election of officers and Executive Council members
- Opportunity for comment from the members.

This is an open meeting; all are welcome.
We encourage dialogue with the members regarding activities for the coming year.
Lunch is $25 per person. You do not need to purchase lunch in order to attend the meeting.

Four Seasons Hotel, Newport Beach, CA November 18-20, 1993

CSAM 1973-1993 Twenty Years of Excellence