

Naltrexone and the Treatment of Alcohol Dependence

An article in the December 13, 2001, the *New England Journal of Medicine*¹ has raised serious concerns about the efficacy of oral naltrexone in treatment of alcohol dependence. The article reports the results of the largest study of oral naltrexone ever conducted in treatment of alcohol dependence and challenges a large body of literature supporting the clinical efficacy of naltrexone in the treatment of alcohol dependence.

The study was a multicenter, double-blind, placebo-controlled evaluation of oral naltrexone (50 mg/day) as an adjunct to psychosocial treatment conducted at 15 VA centers between April 1997 and October 2000. Six-hundred twenty-seven (627) veterans (almost all men) with chronic, severe alcohol dependence were randomized to one of three medication groups: (1) 12 months of naltrexone; (2) 3 months of naltrexone followed by 9 months of placebo; (3) or placebo. Subjects were offered individual counseling, programs to improve their compliance with study medications, and encouragement to attend Alcoholics Anonymous meetings. Before randomization, subjects must have abstained from alcohol use for at least five days. Subjects were compensated twenty dollars for their participation in the monthly evaluations and fifty dollars for longer evaluations at 6, 12 and 18 months. Outcome measures included

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A REPORT TO THE LITTLE HOOVER COMMISSION Addressing Policy Barriers to Drug Abuse Treatment in California

by Gary A. Jaeger, MD, FASAM, CSAM President



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[On May 23, CSAM President, Gary Jaeger, MD, testified before California's Little Hoover Commission on the barriers to drug addiction treatment in California. The Little Hoover Commission is an independent state oversight agency that

was created in 1962 to investigate state government operations and – through reports, recommendations and legislative proposals – promote efficiency, economy and improved service. Dr. Jaeger's testimony was part of a series of hearings on Alcohol and Drug Abuse Treatment. This is an edited version of the remarks that Dr. Jaeger prepared for the Commission. Dr. Jaeger's remarks and those of other speakers are available online at <http://www.lhc.ca.gov/lhcdir/drug/drug.html>]

As President of the California Society of Addiction Medicine and a physician in the full time practice of Addiction Medicine in California, I am here to share my concerns about impediments to effective drug and alcohol treatment in California.

Misinformation and social stigmatization continue to be the foundation upon which many of our drug and alcohol policies are based. No field of medicine is more legislatively and judicially constrained than Addiction Medicine. In no field is the evidence of etiology

and treatment effectiveness more consistently ignored in the formulation of public policy.

If society is ever to be successful in minimizing the harmful effects of drug use and drug addiction, there must be a shift in the way we conceptualize these issues. As Timothy Condon, Ph.D. pointed out in testimony to the commission on April 25, 2002, "drug abuse is a preventable behavior and drug addiction is a treatable disease of the brain". Drug abuse and drug addiction together constitute this nation's most significant public health problem. While alcohol and drug use and abuse may be primarily social and legal issues with medical consequences, addiction is a medical problem with social and legal consequences. As long as we fail to differentiate use and abuse from addiction our efforts will produce limited medical and societal benefit.

Medicine has done no better than government in effectively managing the problem of alcohol and drug abuse and addiction. Alcoholics alone, excluding those addicted to other drugs, consume 15% of the health care budget nationally⁸. Thirteen per cent of breast

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Naltrexone and the Treatment of Alcohol Dependence

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number of days to relapse to heavy drinking (defined as six or more drinks/day for men and four or more drinks/day for women), the percent drinking day, and the number of drinks/drinking day.

The sites screened 3372 alcohol-dependent veterans to randomize 627 patients to the three treatment groups of 209 subjects each. Each site enrolled 30-50 subjects. Medication compliance was measured with medication bottles with electronic caps that recorded the date and time of each opening.

At 13 weeks, the mean number of days to relapse was 72.3 days in placebo and 62.4 days in the naltrexone treatment groups. The rate of relapse was 44.4 percent in the placebo group and 37.8 percent in the naltrexone groups. Percent drinking days was 14.0 ± 23 in placebo and 11.3 ± 21 in the naltrexone group. None of these was significant at the $p = 0.05$ level. The investigators concluded that the study did not support the use of oral naltrexone for the treatment of men with chronic, severe alcohol dependence.

The editorial from NIAAA in the same issue of the NEJM article discussed possible explanations for negative finding². The mean age of subjects in the VA study was about 10 years older than subjects in the previously published studies. Subjects had been drinking for longer periods of time. Alcoholics who have families and are employed have a better prognosis than those who live alone or are unemployed. One third of the veterans in the VA study were married or living with a partner, smaller than in most previous studies, and about one third were receiving disability pensions, which may have affected their motivation to stop drinking.

Commentary of Donald R. Wesson, MD³

The VA study is difficult for us to reconcile with the growing body of literature supporting the use of naltrexone in treatment of alcohol dependence. With the exception of one study (Kranzler, Modesto-Lowe & Van Kirk 2000), recently published studies support efficacy of naltrexone (Monti et al. 2001; Rubio et al. 2001). The major limitation of oral naltrexone has been lack of compliance with daily dosing. Several pharmaceutical companies are developing a depot formulation of naltrexone specifically to improve compliance in patients who were unable to maintain a regimen of taking naltrexone daily.

Compliance with taking study medication may have contributed to the negative findings in the VA study. During the first 13 weeks (presumably 91 days) the subjects took study medication an average of 73 (80%) days in the naltrexone group and 70 (77%) days in the placebo group. To judge the probable effect of compliance, the pattern of missing doses would be important. Did dropout or gaps in dosing of subjects who remained in the study influence this mean? The published article does not provide this information.

Unlike many single site controlled clinical trials of

medications for treatment of alcohol dependence, multicenter trials of medication for treatment of alcohol dependence have not yielded positive results. For example, a multicenter trial of disulfiram failed to show statistically significant benefit (Fuller et al. 1986). The reason is not understood.

Statistically, a clinical trial always has a risk of failing to show an effect even when one exists. The larger the sample size, the smaller the risk; however, the sample size is often constrained by access to subjects and the total resources available to conduct the trial. The risk of failing to detect an effect when one is present (a type II error) is larger than the converse (a type I error) declaring that an effect is present when it is not. Clinical trials conventionally have a five percent or less error of a type I error, whereas the risks of a type II error commonly 10 to 20 percent. Consequently, sometimes a negative trial is simply bad luck. Add to that the noise introduced by a multicenter trial and the notoriously unreliable self-report and limited cooperation with study procedures by an alcohol dependent population, and the chances of negative results are increased still further.

This study is impressive because of its size and the care with which it was designed and executed. Taken in context, however, it does not definitively answer the question about naltrexone's efficacy in treatment of alcohol dependence.

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FOOTNOTES

1. Krystal, J.H.; Cramer, J.A.; Krol, W.F.; Kirk, G.F. & Rosenheck, R.A. 2001. Naltrexone in the treatment of alcohol dependence. *N Engl J Med* 345(24):1734-9.
2. Fuller, R.K. & Gordis, E. *Ibid.* Naltrexone treatment for alcohol dependence.:1770-1.
3. Dr. Wesson is Vice President of Clinical Development at DrugAbuse Sciences, Inc., one of the companies developing a depot formulation of naltrexone.

IN MY OPINION

Naltrexone in the Treatment of Opiate Addiction

by John McCarthy, MD

When naltrexone was first released in the early eighties, I was eager to offer this alternative to our methadone patients. We recruited a group of about 30 patients who were interested and at a stage in their recovery where a transition to naltrexone made sense. In spite of considerable staff effort, most of the patients relapsed as they tapered their methadone dose, and the few who made it onto naltrexone stopped it after a fairly short time. Only one patient used it in a way I considered successful. He took naltrexone for 9 months, but after a couple of years of abstinence he relapsed and returned to methadone where he remains today. Numerous subsequent attempts to withdraw him from methadone lead to the same low-grade dysphoria (which was unresponsive to anti-depressants) that he blamed for his relapse when off all medications. Methadone has been effective at relieving this dysphoria and he is currently stable, working full-time, and asymptomatic.

This is the general experience in the field. There is a lore that 'motivated' professionals do well on naltrexone (e.g. Ling & Wesson 1984). I think this may not be accurate. There is no reason to think they suffer from a different illness because they are professionals, but they are often prohibited from accessing methadone by professional societies with biases against opiate agonist therapy. That some do well on naltrexone doesn't mean they might not do even better on a therapy with more proven efficacy.

I was originally interested in this medicine for its opiate blocking effect, which seemed to offer protection against relapse, and by its lack of dependence. Back then we had only theories about methadone's mechanism of action. The need for long-term maintenance was based on pragmatism: it worked reliably and nothing else did. Now we know more about the long-term brain changes and hormone dysregulation that persists after successful withdrawal from opiates, and which is ameliorated or normalized by methadone. I know of no evidence that naltrexone has any such therapeutic effect. It would be very interesting to compare physiologic functioning in patients maintained on these two medications. Theoretically, mu opiate receptor blockade should make these patients worse, since addicts appear to suffer from hypo-functioning of the endogenous opiate system. There are reports of dysphoria from naltrexone (Crowley et al. 1985).

Problems with poor compliance and loss of customary tolerance combine to make naltrexone a potentially dangerous medication. Those who stop it and relapse are at great risk of overdose death. One unpublished Australian study of naltrexone-treated patients found it

was associated with higher death rate than untreated heroin addicts. Deaths were related both to heroin overdoses after stopping naltrexone or other drug overdoses even while on naltrexone. As a solution to the compliance problem, work is underway on a depot preparation. However, prolonging the length of action doesn't resolve the underlying problem: that the drug may not address, or may worsen, the patient's biochemical deficits. Furthermore, depot naltrexone has the potential to be used coercively by criminal justice systems with ideological opposition to methadone. This worries me from a human rights perspective.

One final comment on naltrexone concerns its use as part of an ultra-rapid opiate detoxification (UROD) under anesthesia. This is another potentially dangerous use of naltrexone associated with significant morbidity and mortality, at least as currently practiced. Of the 3 patients from our program who left to undergo this procedure, one had a stroke during the procedure and all 3 eventually relapsed and returned to methadone. They all reported being given information on how painless the procedure would be. They all described painful withdrawal symptoms that they would not repeat. This procedure should be considered experimental, as there are clearly some patients for who such a drastic procedure would be contraindicated.

Whatever its putative role in alcohol treatment, naltrexone should be considered a secondary treatment for opiate addiction. While it may have a place in a small number of selected patients, we need more information on long-term physiologic function of opiate addicts using it before it can be considered an alternative to methadone.

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Anesthesia-Assisted Rapid Opioid Detoxification

by Lori Karan, MD, FASAM and Judith Martin, MD

[Note: Early this year, Blue Shield Health Plan asked the California Society of Addiction Medicine to participate in a expert advisory panel to assess the safety and efficacy of Anesthesia-Assisted Rapid Opioid Detoxification (AAROD). CSAM's Executive Council appointed two of its members Lori Karan, MD and Judith Martin, MD to represent CSAM as experts on the panel. CSAM's participation is seen as part of a larger effort to influence managed care on the appropriate treatment of addiction. This is the text of a paper prepared by Drs. Karan and Martin for their presentation to the panel.]

Thank you for the opportunity to comment upon the role of Anesthesia-Assisted Rapid Opioid Detoxification (AAROD) in addiction medicine. The mission of the California Society of Addiction Medicine is to improve the treatment of alcoholism and other addictions, educate physicians and medical students, promote research and prevention, and enlighten and inform the medical community and the public about these issues. The following opinion was developed based on comments from the Committee on the Treatment of Opioid Dependence, and the Executive Council of CSAM.

CSAM aligns itself with the NIH consensus statement of 1997, which defines heroin addiction as a chronic disease.¹ For any patient who has been addicted for at least a year, and who wishes such treatment, methadone maintenance represents the standard of care. Methadone maintenance has been shown to lower mortality, lower criminality, enhance functionality, and to reduce the incidence of seroconversion to HIV.^{2,4}

Patients who decide not to engage in maintenance pharmacotherapy face decisions on how to withdraw from the opioid to which they are addicted. Since naturally occurring withdrawal from opioids is not in itself life-threatening, some patients withdraw with no treatment at all. Other patients choose to be treated symptomatically with agents such as clonidine. When more severe symptoms are anticipated, patients may choose to undergo a gradual withdrawal in an inpatient or outpatient licensed opioid treatment program. The most common approach during medically supervised withdrawal is to utilize a progressive taper of a long acting opiate, such as methadone. Although safe, these standard forms of detoxification, even when enriched with psychosocial services, do not usually result in long-term abstinence, and relapse rates are high.^{5,6}

Kleber et al. developed rapid opioid detoxification (ROD) in the 1980's to reduce patients' length of hospitalization and to facilitate their placement upon naltrex-

one, an opioid antagonist.^{7,9} During rapid opioid detoxification without anesthesia, patients receive graduated doses of antagonist (naltrexone) to precipitate withdrawal while they are simultaneously given clonidine and other symptomatic treatments. Rapid opioid detoxification without anesthesia is more gradual and less risky than anesthesia assisted rapid opioid detoxification. Patients are awake and able to tell the treating physician what they are feeling as they undergo withdrawal. However, even though this procedure has been developed and researched, it has not received wide acceptance by addiction medicine practitioners or their patients. Although the reasons for this lack of acceptance have not been well studied, it is likely that patients do not opt for experiencing an increased intensity of symptoms during withdrawal. Rapid opioid detoxification without anesthesia has limited use with persons who are extremely motivated for abstinence, those who need to attain abstinence rapidly due to external factors, those who are not anticipating a severe withdrawal, and those who want to facilitate being placed upon a chronic antagonist, such as naltrexone.

Abruptly precipitating withdrawal produces more severe symptoms, including hypertension, tachycardia, vomiting and diarrhea.¹⁰ Anesthesia-assisted opiate detoxification (sometimes called Ultra Rapid Opioid Detoxification) uses antagonists to precipitate withdrawal, with the patient heavily sedated.¹¹ Some protocols also call for ECG monitoring and pretreatment with clonidine to control the cardiac effects of precipitated withdrawal, or post-procedure treatment with antiemetics for days to weeks.^{12,13} In addition, most protocols include ongoing antagonist after the acute procedure.

Anesthesia assisted rapid opiate detoxification appeals to patients who want a 'magic bullet' to treat their addiction. Patients do not wish to feel the pain of withdrawal. Rather they want to go to sleep and 'wake up clean.' Too often, treatment providers marketing AAROD play into their patient's unrealistic expectations. Although anesthesia may prevent a person undergoing precipitated withdrawal from being conscious of the most intense withdrawal symptoms, the duration of the withdrawal process has not been completely studied. Patients often have severe symptoms for several days after the procedure. The duration of the withdrawal is not known because patients are often given multiple medications for several weeks that mask their symptoms. Neuroscience does not support instantaneous neuroadaptation when an antagonist suddenly occupies a receptor.¹⁴ Rather, intracellular pathways and their gene regulation are affected, as well as multiple brain circuits and body systems. Thus, there is no reason to believe that a patient's withdrawal is complete when they wake up from anesthesia.^{15,16}

Anesthesia assisted rapid opiate detoxification is not a standardized procedure. Multiple variables include the timing of the last dose of opiate, the anesthetic agents utilized, the level sedation and of respiratory support, the antagonist or combinations thereof (i.e., narcan, naltrexone, and/or nalmefene), the doses and route of delivery of the antagonist(s) (NG tube versus IV), the duration of the procedure, and the intensity of monitoring thereafter.

These variables may each affect the safety and efficacy of the AAROD.

There are reasons for concern about patient safety. For instance, Keinbaum et al. noted profound epinephrine release and cardiovascular stimulation during AAROD.¹⁷ There are reports of QT prolongation,¹⁸ tachypnea,¹⁹ increased metabolism and muscle activity,²⁰ and death.¹³ Patients who undergo AAROD may need to be carefully selected to include only healthy persons without major comorbidity. As with other procedures under anesthesia, careful preoperative clearance is needed.

Anesthesia assisted rapid opiate detoxification has not been shown to be any better at preventing relapse than the already existing outpatient detoxifications that do not call for precipitated withdrawal or anesthesia.^{21, 22} Clinicians in the field comment that patients who are doing well on methadone are sometimes targeted for this procedure, and subsequently relapse, losing hard-earned clinic take-home privileges or jobs, in addition to the money for the procedure.²³

Therefore, when discussing the modalities which facilitate opiate withdrawal, we endorse a limited role for rapid opioid detoxification (without anesthesia). However, we do not support the routine use of Anesthesia Assisted Opioid Detoxification. AAROD may have a role in helping persons enter and engage into opioid antagonist maintenance, or non-opioid based treatment. However, until its safety and efficacy have been proven, and the procedure has been standardized, AAROD should only be used under research conditions with careful informed consent, monitoring, and treatment evaluation. Two components of this procedure, precipitated withdrawal and anesthesia, are known to have risks that are not present in the more commonly used detoxification and withdrawal treatments. Any benefits of the procedure have not yet been shown to be worth these added risks.

However, focusing our discussion upon facilitating alternative methods of opiate detoxification is in many ways misleading. No matter the method of detoxification, and no matter the criteria for patient selection for detoxification, poor long-term outcomes (40-60% relapse by six months, approaching 90% by 12 months) suggest a chronic disease – perhaps a long lasting abstinence syndrome – that is not being addressed by detoxification of any kind.^{5, 6, 21, 24, 25} The excellent outcomes of methadone maintenance and the poor outcomes of opiate abstinence raise questions about the role of detoxification for the treatment for opiate addicted patients. If an analogy were to be drawn with other chronic illnesses⁵, one might question supporting the withdrawal of blood pressure medications from patients who are hypertensive and the taking away insulin from patients who are diabetic.

All too often CSAM physicians see their patients work towards a false goal of medication-free abstinence that is reinforced by societal prejudice and a system of reimbursement that pays for detoxification but not maintenance. When patients risk relapse back to illicit opiates, they jeopardize relationships with the ones they love. Patients who relapse back to opiate addiction endanger their jobs, threaten their quality of life, and

most importantly, imperil their health. The risks of relapse are especially dangerous amidst the current HIV and hepatitis C epidemics.

Methadone maintenance is a treatment for opiate addiction that is safe, efficacious, and well-studied. Patients stabilized on methadone maintenance reach a new homeostatic set point that enables them to function maximally. It is the hope of members of the California Society of Addiction Medicine that Blue Shield of California and United Behavioral Health Systems will utilize their technology assessment system to review methadone maintenance and consider this important treatment for future reimbursement. Although it might seem an obvious benefit, most private insurers do not provide for methadone maintenance treatment. If Blue Shield of California takes on this examination, it will lead the country in this most important endeavor.

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Buprenorphine: When?

by Donald R. Wesson, MD



DONALD R.
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FOR ADDICTION SPECIALISTS, the burning question about buprenorphine is when will we be able to prescribe it? Buprenorphine has been a long time coming – considering that the first studies of buprenorphine for treatment of opiate dependence were conducted in the 1970s (Jasinski, Pevnick & Griffith 1978) – and it literally took an act of congress to enable us to prescribe it legally for the treatment of opiate dependence. But still

we wait. Before we can prescribe buprenorphine sublingual dosage formulations for treatment of opiate addiction the US Drug Enforcement Administration (DEA) must finalize the control schedule, the Food and Drug Administration (FDA) must approve it, the Center for Substance Abuse Treatment (CSAT) must develop a notification process, and Schering Plough Pharmaceuticals must market it. Apparently the DEA and FDA plan to act in concert, perhaps as early as August or September 2002.

Sublingual buprenorphine will be marketed in the US in two formulations, each with two milligram strengths: (1) Subutex™, buprenorphine alone (sometimes referred to as the “mono” product) containing either 2 or 8 mgs of buprenorphine, and (2) Suboxone™, buprenorphine 2 or 8 mg in combination with naloxone in a 4 to 1 ratio of buprenorphine to naloxone (the “combo” product). Suboxone will be the primary product intended for buprenorphine maintenance and detoxification treatment in the US. The addition of naloxone in Suboxone is to discourage heroin addicts from dissolving the tablets and injecting them. Taken sublingually, the naloxone in Suboxone has little effect because it is not well absorbed, and it is rapidly metabolized. The naloxone does, however, markedly attenuate the immediate opiate effects when injected (Mendelson et al. 1996) and would precipitate opiate withdrawal in dependent opiate addicts. Subutex is intended primarily for treatment of pregnant women.

The initial barrier to physicians’ prescription of buprenorphine for treatment of opiate addiction was its classification as a “narcotic.”¹ Federal law specifically prohibited physicians from prescribing a “narcotic” to addicts for purposes of treating addiction. In December of 2000, Congress passed and President Clinton later signed the Drug Addiction Treatment Act of 2000. The Act amended the Controlled Substance Act to allow “qualified” physicians, who notify the Secretary of the Department of Health and Human Services (read CSAT) to prescribe schedule III-V narcotics for treatment of opiate addiction for up to 30 patients outside the context of

clinic-based narcotic treatment programs (i.e., methadone clinics).

As early as 1999, expectations were high that FDA approval of the sublingual dosage form was imminent, and CSAM, ASAM, and the American Academy of Addiction Psychiatry (AAAP) began offering physician training for use of buprenorphine in treatment of opiate addiction. Repeated delays have prompted the ASAM Board to require that announcements for their buprenorphine training courses carry a notice that buprenorphine is not FDA-approved and that it is uncertain when it will be available for prescription.

As of July 1, FDA has not approved Subutex or Suboxone. The manufacturer, Reckitt Benckiser Pharmaceuticals,² and the Center for Substance Abuse Treatment (CSAT) predict FDA approval in the Fall of 2002. In 2000, the FDA issued a letter of approvability to the manufacturer. An approvability letter generally indicates that the studies supporting the New Drug Application are adequate to establish safety and efficacy but that the applicant must provide additional clarifying information. With buprenorphine, however, the FDA asked that new studies be conducted to determine the pharmacokinetics of buprenorphine when multiple tablets were held under the tongue.

In the March 21, 2002 *Federal Register*,³ DEA published a proposed rule to reschedule buprenorphine from a schedule V narcotic to a schedule III narcotic. The ruling would include all products containing buprenorphine including Buprenex™ (a injectable formulation of buprenorphine that has been available for many years in the US for treatment of pain), Subutex, and Suboxone. In May, after consultation with chairmen of ASAM’s Medication Development Committee and the Opioid Agonist Treatment Committee, ASAM’s president, Lawrence S. Brown, submitted a letter to DEA pointing out the lower abuse potential of the naloxone/buprenorphine combination and suggesting that differential scheduling would encourage practitioners to prescribe the naloxone-containing preparation.

Among other factors that are considered, scheduling is supposed to reflect the actual abuse and potential abuse liability of a product and its pharmacology. According to the notice in the Federal Register, the decision to move buprenorphine from schedule V to schedule III was recommended by the Surgeon General and the Department of Health and Human Services, and based on FDA’s review. However, DEA concluded:

... that the abuse potential of buprenorphine is high and closely resembles other narcotics in Schedule II. However, buprenorphine effects are less dose-dependent than pure mu agonists and a ceiling effect has been demonstrated for many of the actions of buprenorphine. This attenuation in effects at high doses may have a blunting effect on the continued escalation in dose to obtain greater reinforcing effects. ... Therefore buprenorphine appears to have somewhat less abuse potential than other schedule II narcotics.⁴

Scheduling both the mono product and the combo product into the same schedule is pharmacologically irrational. The whole point of the National Institute on Drug Abuse and Reckitt Benckiser Pharmaceuticals developing Suboxone was to reduce the intravenous abuse potential of buprenorphine. The buprenorphine/naloxone combination should have less street value and potential for diversion.

Schering Plough will market buprenorphine in the US as they already do in France and many other countries. Expectations are that when the regulatory barriers are removed, Schering Plough will move rapidly to bring the new product to pharmacy shelves.

Having physicians prescribing opiates for treatment of opiate dependence outside the structure of a methadone treatment clinic is truly what CSAM's Immediate Past President, Peter Banyas, MD is fond of referring to a "paradigm shift" in medical practice.

Buprenorphine has been a long time coming. The next article in this series will discuss some of reasons.

Acknowledgements: Thanks to Gail Jara, Walter Ling, MD and Judy Martin, MD who reviewed early drafts of this article and provided many useful suggestions.

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FOOTNOTES

1. Narcotic is a legal term, and can refer to heroin and other opiates, cocaine and sometimes even marijuana.
2. Formerly Reckitt and Colman Pharmaceuticals
3. Drug Enforcement Administration, Proposed Rules, Federal Register vol. 67, no 55, March 21, 2002, pp 13114-6.
4. Ibid pp 13114-5

THE DRUG ADDICTION TREATMENT ACT OF 2000

allows physicians to attain waivers to be able to prescribe buprenorphine for treatment of opiate dependence in an office setting when it becomes available.

The law requires that physicians who are not certified in Addiction Medicine or Addiction Psychiatry, or who do not meet other criteria must complete not less than 8 hours of training in the use of buprenorphine and the care of opiate dependent patients.

CSAM and ASAM will present a one-day workshop on "Buprenorphine in Office-Based Treatment of Opiate Dependence" on October 9, 2002 in Newport Beach as part of the Addiction Medicine Review Course. Those who attend for the full eight hours will receive a certificate of attendance suitable to send to the Secretary of Health and Human Services with your notification of your intent to prescribe buprenorphine when it becomes available.

The form to submit to the Department of Health and Human Services is available from CSAM online at www.csam-asam.org.

FDA Turns Down Acamprosate

by Donald R. Wesson, MD

On July 2, the FDA ruled that the new drug application for acamprosate was not approvable on the basis of the data submitted by the sponsor, Merck KgaA (a German pharmaceutical company unrelated to Merck and Company in the US). Acamprosate is already approved for treatment of alcohol dependence in 39 countries. It appears most effective in relapse prevention. Its mechanism of action in reducing relapse to alcohol is not clearly established.

After reviewing the major European trials used for registration in France, an FDA advisory committee, at a public hearing on May 10, 2002, voted 8 to 2 to recommend approval of acamprosate in treatment of detoxified alcoholics. Liplha Pharmaceuticals developed acamprosate and had conducted a large multicenter US trial of acamprosate in treatment of alcohol dependence. Unlike European trials used to support the registration of acamprosate in France and other countries, the US trial did not show clear evidence of acamprosate's efficacy in reducing alcohol use.

Although the FDA usually follows the recommendations of its advisory committees, it is not compelled to do so and, in this situation, did not. The FDA has requested that at least one additional U.S. clinical trial evaluating safety and efficacy be conducted as well as additional pharmacokinetic analyses and additional preclinical studies. Forest Pharmaceuticals, who market Celexa, would have marketed acamprosate in the US.

Acamprosate appears to be a promising new relapse prevention tool for detoxified alcohol dependent patients. Hopefully, the sponsor will pursue another multicenter trial in the US.

Early trials with acamprosate in treatment of alcohol dependence are reviewed in (Soyka 1996). More recent publications include a Cochrane review (Srisurapanont & Jarusuraisin 2002) and controlled clinical trials of acamprosate (Chick et al. 2000; Gual & Leherter 2001; Schadlich & Brecht 1998) in treatment of alcohol dependence. More information about the hearings is available at www.fda.gov. Search the site for "acamprosate."

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A REPORT TO THE LITTLE HOOVER COMMISSION Addressing Policy Barriers to Drug Abuse Treatment in California

Continued from page one

cancers, 40% of traumatic injuries, 41% of seizures and 72% of cases of pancreatitis are directly related to alcohol abuse⁹. Data from the Epidemiological Catchment Area study show that almost half of all alcoholics have a second psychiatric diagnosis.

The introduction to the report from the Center for Addiction and Substance Abuse summarizes the issues well: Governors and state legislatures have the largest financial, social and political interest in preventing and treating all substance abuse and addiction, whether it involves alcohol, tobacco or illegal drugs, and especially among children and teens. While the federal government has heavy responsibilities to fund biomedical research, classify and regulate chemical substances and interdict illegal drugs, the brunt of failure to prevent and treat substance abuse and the cost of coping with the wreckage of this problem falls most heavily on the backs of governors and state legislatures across America.

States that want to reduce crime, slow the rise in Medicaid spending, move more mothers and children from welfare to work and responsibility, and nurture family life must shift from shoveling up the wreckage to preventing children and teens from abusing drugs, alcohol and nicotine and treating individuals who get hooked.

Reducing Crime

The next great opportunity to reduce crime is to provide treatment and training to drug and alcohol abusing prisoners who will return to a life of criminal activity unless they leave prison substance free and, upon release, enter treatment and continuing aftercare. The remaining welfare rolls are crowded with individuals suffering from substance abuse and addiction. The biggest opportunity to cut Medicaid costs is by preventing and treating substance abuse and addiction. Governors who want to curb child abuse, teen pregnancy and domestic violence in their states must face up to this reality: unless they prevent and treat alcohol and drug abuse and addiction, their other well-intentioned efforts are doomed¹.

Success at the population level will come only when the necessary resources are integrated in effective ways. There must be integration of care within health-care systems. But this alone will not insure success. The necessary social and judicial systems must be included in an integrated manner. Appropriate courts can act as catalysts as well as conduits to needed services.

Early experiences with the voter-mandated policy changes of Proposition 36 have provided some surprises and some insights. The offenders presenting to the courts have more prevalent and more severe psychiatric illness than was anticipated. They are more often homeless, unemployed and without family support. Success with this population will require the needs in each of

these areas to be addressed. Effectively integrated services will be needed if we are to prove successful with this severely impaired population. Lessons learned here can serve us well as we look to the broader substance abuse policy issues we face.

It is reasonable to assign to the courts the additional treatment, medical and social service resources they require to effectively address the needs of this particular population. Domestic violence and child welfare courts can offer similar integrated services to additional populations with very high incidence of substance use problems. The emerging concept of therapeutic jurisprudence offers hope that such integrated systems can be effective in reducing the societal impact of substance use disorders.

Public policies to address the problems of substance abuse in California must address several key areas in a coordinated fashion:

- Prevention
- Assessment
- Treatment level determination
- Program cost data
- Program effectiveness data
- Education of providers
- Licensing issues
- Funding mechanisms, both public and private

I thank the members of the commission for the opportunity to meet with you and share my thoughts on the problems of substance abuse treatment policy in California. The 400 members of the California Society of Addiction Medicine stand ready to assist you in this undertaking.

The data suggests California can fund needed prevention and treatment initiatives and, ultimately, do so for less than we are currently spending.

Funding

There is a large body of evidence that alcohol and drug problems result in societal costs of \$400 billion per year. Much of this direct cost is already borne by employers and health plans. Workplace accidents, lost productivity, absenteeism, and the

health care costs of treating the complications of drug addiction add substantially to their financial burden. The National Center for Addiction and Substance Abuse at Columbia University estimates state governments spent \$81.3 billion in 1998 for substance abuse and addiction¹. Of every dollar spent, 96 cents went to shoveling up the wreckage of substance abuse and addiction. Only 4 cents of each dollar was used to prevent and treat the problem. In California, in 1998, state government spent \$10.942 billion on substance abuse and addiction. This amounts to \$339.63 for every person in the state¹. Only 4% of this amount was targeted to prevention and treatment.

There is currently no shortage of money being spent for substance use disorders and their social consequences.

Substance abuse treatment services can be made available to employees for \$5.11 per year, or 43 cents per month³. According to the actuarial firm of Millman and Robertson, substance abuse parity would increase premiums by under one percent or less than \$1 per family member per month⁵. The Kaiser system in California provides treatment for substance use disorders on demand and at parity with other medical illness. Residential services in a social model program are also covered benefits. Costs, in that system, are consistent with the actuarial estimates of Millman and Robertson.

There is ample evidence that treatment for substance disorders produces reductions in subsequent health care utilization and cost. Data from a study at Kaiser's Sacramento Chemical Dependence Treatment Program, funded by NIAAA and NIDA, address the issues of cost and effectiveness for substance abuse treatment. In the *Journal of Studies on Alcohol* (62:89-97,2001), S. Parthasarathy and colleagues reported on the first 18 months post-treatment follow-up of 1,011 adult patients treated in an outpatient chemical dependency recovery program. Costs for hospital inpatient care, emergency room care, and outpatient medical care were measured for 18 months prior to treatment and compared with costs in the 18 months after treatment. Costs for these same services were also determined for 4,925 matched controls.

Medical care costs for the control group remained unchanged from the first to the second 18-month period. For the treated group, costs decreased by \$31 per patient per month after treatment – a savings of \$558 per patient over the post-treatment period. The total cost of treatment was \$663 per patient for an eight-week period. During the treatment and post-treatment periods, the “net cost” (including the offset for reduced medical costs) was \$105 per treated patient. When the net treatment cost is spread across the insured population of 3 million individuals, the result is a net cost of \$2.52 per insured individual per year.

Improvement across a range of outcomes was measured at six months post-treatment with the Addiction Severity Index (ASI). Although employment-related problems showed only slight improvement, all remaining ASI scales demonstrated improvement ranging from 55 percent to 90 percent. In addition to the improvements in medical and psychiatric severity scales there were similar improvements the scales measuring family and legal problems. These translate to savings in governmental programs.

The improvement in the scale measuring severity of employment related problems lags behind the other improvements. Nevertheless, a Chevron Corporation analysis indicated that \$10 was saved for every \$1 spent on employee rehabilitation⁶.

Clearly, there are both cost and outcome benefits from treatment for chemical dependence.

Public health issues, from tuberculosis and polio to HIV and anthrax, have always been addressed by a partnership between government and private sector interests. Drug abuse and drug addiction somehow became the primary responsibility of government. We will never achieve adequate treatment access as long as we continue to assume that government alone is responsible for providing treatment. Until employers and health plans do their part in contributing to the solution of these problems, our successes will be limited.

Parity for coverage of mental health problems, including alcohol and drug problems is an essential component of the solution.

We are currently spending around \$11 billion annually in California related to substance abuse and its consequences. The Cal-Data study clearly showed public sector savings resulting from appropriate investments in treatment of substance use disorders. A seven dollar savings was realized for each one dollar spent. If California decides to move toward public policies that focus on effective prevention and treatment models, cost savings will not be immediate. However, the data suggests California can fund needed prevention and treatment initiatives and, ultimately, do so for less than we are currently spending.

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OxyContin and the Olympics: An Addiction Medicine Perspective

by David Smith, MD

Having returned from the Winter Olympics where I served as doping control officer at Soldier Hollow in Utah, I was asked to share my observations and experiences with my Addiction Medicine colleagues in CSAM. I was also asked to write some comments about the current swirl of media attention being given to OxyContin addiction. The first question of course is what does one have to do with the other except that they both start with "O". Having learned educational objectives from my esteemed colleague, Dr. John Chappel of the University of Nevada, I will try from an experiential point of view to show how the two "O's" integrate.

First, it is interesting how I even became a member of the Volunteer Olympic Medical Team. Our Haight Ashbury Free Clinics has a Rock Medicine Section, headed by Glenn Raznick or Raz, which delivers medical services to all the Bill Graham Presents rock concerts throughout the Bay Area. Raz, who was also involved in the Olympic Medical Program, asked if I wanted to be on the Olympic Medical Team as a doping control officer. Since I am an ASAM-certified Medical Review Officer and am scheduled to present on the role of the MRO to the CSAM Review Course in October, I felt that it would be a good learning experience. My motivation was enhanced when Dr. Larry Brown, ASAM's President, said that little was known about performance enhancing drugs.

When my application was accepted as a doping control officer I found that the Olympics provided no travel arrangements or housing expense reimbursement (sounds a little like volunteering for CSAM!). However, I did receive a great uniform (see picture) and I learned from Raz that physicians would volunteer long hours at Rock Medicine for a T-shirt so a uniform was a great stimulus to work. But fortunately, thanks to Gary Fischer, CEO of the Cirque Lodge, a fine drug treatment program at Sundance, I was able to stay at their extended-care studio (which was the old Osmonds recording studio), located in a beautiful, but remote area in the mountains of Utah close to Soldier Hollow.

My vision was that I would work at doping control in Soldier Hollow in the morning, ski at Sundance in the afternoon, and then take in Olympic events in Park City. This turned out to be simplistic and inaccurate vision. In fact, I got up at 4:30 a.m. every morning, drove in the dark, and passed through rigorous security before reporting to my duty station at 6:30 a.m. The Doping Control Station was very well-run technically and very tense as



◀ HAIGHT ASHBURY FREE CLINIC FOUNDER, DAVID SMITH, MD, (SECOND FROM LEFT) WITH DOPING CONTROL STAFF IN SOLDIER HOLLOW.



◀ DAVID SMITH, MD, IN HIS OLYMPIC UNIFORM.

they tested both blood and urine.

I was assigned to blood doping which is a technique used by athletes in the endurance contents. Some endurance athletes were taking a synthetic and

more powerful erythropoietin (darbepoetin, which is sold under the brand name of Aranesp) to artificially stimulate their red cell production to build up their hemoglobin and oxygen carrying capacity. This was the first Olympics for which comprehensive blood doping technology testing was available.

Before competition all athletes had their blood drawn. For females, if the reticulocytes were 2% and/or hemoglobin 16 or greater, a second blood sample was drawn and the urine was tested for darbepoetin or its derivatives at the Central Doping Control Lab in Salt Lake City. For the male the level was 2% for reticulocytes and hemoglobin was 17.5.

The greatest tension occurred when the Russian cross-country skier had a positive blood doping test and couldn't compete. Germany won the Gold Medal and Russia threatened to withdraw. I thought WWII was going to break out.

Ten days later, exhausted, but proudly wearing my Olympic uniform, I boarded a plane in Salt Lake to fly to Reno to visit and ski with John Chappel in order to work off tension and return to San Francisco with a semblance of health. During my time at the Olympics, I was so tired, I skied only one day at Sundance and watched only one Olympic event, the women's bobsled, where the U.S. won the gold medal.

As the plane took off, I noted a young woman in distress sitting next to me with a patch on her left shoulder. I asked what the patch was and she said it was a Catapres Patch for OxyContin withdrawal. I introduced myself and this started a long conversation. She was 23 and was addicted to 200 mg of OxyContin and was in acute withdrawal. She had left treatment to go to her 21-year-old cousin's funeral who had died of a OxyContin overdose. I advised her that it was mistake to leave treatment and that she was at high risk to relapse. I noticed that she had ordered two small bottles of vodka to calm her nerves. I offered her any help I could give

and she proceeded to share her OxyContin abuse story.

She indicated that she bought OxyContin for 50 cents per milligram and therefore had a \$100 per day habit. Her OxyContin came from physicians who freely prescribed it to pain patients who sold part or all of their prescription to addicts in the drug culture. She described in detail how she ground it up, solubilized it and injected the OxyContin. She showed me her tracks including an OxyContin abscess scar for which she was recently treated. Her experience was very similar to those related to me by Dr. Ken Roy, in New Orleans, including interviews with his patients as well as conversations I had with addiction medicine doctors in Florida where there is a major OxyContin abuse and diversion problem and prescription narcotic overdoses exceed heroin overdose.

In contrast to the Olympics, which were confined to Utah, the OxyContin diversion problem is nationwide. I recognize that a majority of pain patients take their narcotic pain medication in a safe and effective fashion. However, there is a significant OxyContin diversion and abuse problem that involves pharmaceutical industry clientele, physician over-prescribing, pain patient drug sales and serious addiction of young people in the drug culture. I acknowledge that the issue of pain and addiction is very complex. I feel the broader issue of OxyContin diversion and abuse needs to be responded to by our profession. I welcome CSAM membership questions and comments on both my Olympic and OxyContin experience. *You may send comments to Dr. Smith at drsmith@hafci.org.*

Eileen McGrath Named ASAM Executive VP



EILEEN McGRATH

THE AMERICAN SOCIETY of Addiction Medicine (ASAM) has announced the appointment of Eileen McGrath, J.D., to the position of Executive Vice President/Chief Executive Officer. McGrath succeeds James F. Callahan, DPA, who is retiring. McGrath officially assumed her new duties on June 24, 2002.

McGrath brings over 14 years of association leadership experience in the medical arena as Executive Director of the American Medical Women's Association, a national organization of ten thousand women physicians and medical students dedicated to advancing women physicians and promoting women's health. Her prior professional experience included direction of county alcoholism services and community alcoholism outreach in Fairfax County, Virginia, as well as substance abuse planning coordination for Northern Virginia. She was President of the Substance Abuse Program Directors of Virginia in 1978 and 1979.

Over the past 14 years, McGrath has established the American Medical Women's Association's foundation and led the successful effort to achieve the organization's AMA accreditation for Continuing Medical Education and to develop continuing medical education and grant programs for education in women's health. A significant accomplishment was her participation in achieving a more effective system of breast cancer detection in the population whose primary insurer is the Department of Defense health system.

McGrath is a graduate of the State University of New York, the University of Virginia (Masters Degree in Planning) and holds a law degree from the George Mason University School of Law. She was admitted to the Virginia State Bar in 1985 and served for three years as a law practice associate in Washington, D.C. and Virginia.

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CSAM news

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