CSAM NEWS

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CSAM Celebrates 20 Years

INSIDE

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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.

AN IDEA WHOSE TIME HAD COME

Steve Heilig, MPH

Even a cursory look back at the genesis and accomplishments of the California Society of Addiction Medicine shows that CSAM arose in response to some important needs. In the 20th year since the association's formal start, some of the pioneers dug back into their memories to recall why and how CSAM became a reality.

"There were really two ongoing forces pushing us to get organized," notes Jess Bromley, MD, of San Leandro. "One was the need to get the treatment of addiction into the medical mainstream, and the other was the need to change the outdated laws which kept us from doing that."

Bromley traces his own convictions about those needs to fallout from the drug explosion of the 1960s. "In 1969 I was Chief of Staff at San Leandro Memorial Hospital, and we were contacted by the city council and local parent-teacher association for help in dealing with the drug crisis. Heroin was beginning to appear in the suburbs and there were some overdoses in schools as well as LSD use and such. We began with meetings to start a community drug program sponsored by the Vesper Society which owned the hospital. There was a young woman named Gail Jara working for Vesper, and she seemed quite interested in this work.

"About that same time, I was elected to the California Medical Association House of Delegates and joined the CMA's Committee on Dangerous Drugs, chaired by Nick Khoury, MD, of Los Angeles. This was still during the 1960s drug era, and there seemed to be a lot of instant medical experts on drugs around. I quickly became convinced there were very few physicians really involved in drug treatment and fewer still in the CMA. And I concluded what we really needed was to get organized, and then to work towards establishing a new specialty."

Others were coming to similar conclusions. San Francisco internist Jack Gordon, MD, chaired the CMA Committee on Alcoholism in

the early 1970s. He traces the surge in interest in addiction in the Bay Area even further back. "First there was a big upswing in interest and activity in treating alcoholism. At Mount Zion Hospital in 1958, we did the first study ever on admission of alcoholic patients to a general hospital, and it was something of a classic.[1] But the basic idea was simply to treat alcoholics as human beings. Throughout the 1960s there was an effort to get more people into the field, and I think the new association was an outgrowth of that." Gordon later found himself chairing the CMA's committee, where he first encountered the core group which started what would eventually become CSAM.

"At that time, medical schools were not teaching much about substance abuse, and physicians in practice were running away from such problems. But when we put on a program for physicians, nobody would come!"

George Lundberg, MD, now editor of the *Journal of the American Medical Association*, was also involved in early efforts in California to organize addiction treatment. "I went from the Army to USC in 1967, largely because I was interested in researching adverse reactions provoked by drugs. It soon became perfectly obvious to me that the main problems were caused by the intentional recreational use of drugs, rather than adverse reactions. So I shifted my focus. And at that time, medical schools were not teaching much about substance abuse and physicians in practice were also not doing much and even running away from such problems. We started putting on programs on substance abuse for parents, employers, teachers and so on, and got a big crowd from all those groups. But when we put on programs for physicians, nobody would come!"

Yet another physician already in the field was Arthur Bolter, MD, who was running Project Eden, a drug treatment program in Hayward. Bolter, a pediatrician, also first became involved in the field in the 1960s, when kids began passing out at local schools. Fortuitously, he began discussing the problems with Bromley. "Talking things over with Jess, I also became convinced there was a real need for professionalism and organizing to upgrade treatment and to recognize people in the field," he says. "There was no place physicians could identify themselves as being interested in treating addicts. For years, the stereotype was that 'drunks were treating drunks,' with questionable means and outcomes. We thought people who were treating what others saw as a 'loathsome' problem should get some respect!"

Removing Old Restrictions

Many changes would be required for that to happen, and the one of most immediate import was legal. "At the time, the restrictions on doctors treating drug addicts were very oppressive. We needed to let doctors do what they needed to do," recalls Bolter. Bromley elaborates: "State law at that time was still a holdover from the early 1900s and the Harrison Act and Anslinger era, when policies drove almost all legitimate doctors out of the field. The AMA basically acquiesced to this purge in the 1930s, and not much had changed. At the time we were getting organized, all doctors helping opioid addicts were technically in violation of the law—its language stated that no doctor could treat addicts for addiction outside of a state or county hospital or jail.

"About this time, there was an incident which really sparked the movement to change the law," Bromley continues. "In Riverside County, two CMA members—I believe they were a psychiatrist and a general practitioner—were quietly, even surreptitiously, admitting heroin addicts to a local hospital to manage their withdrawal. Treating addicts in a community hospital was unheard of then. As we were told it, the wife of the local chief of police was admitted to that hospital for some routine surgery and became enraged that there were addicts in the same place. Her husband got involved and the docs were charged with violation of the law."

David Smith, MD, founder of the the then-new Haight Ashbury Free Medical Clinics, clearly recalls this incident as well. "I was sitting in our detox clinic when Jess Bromley called and told me two doctors had just been arrested for doing what I was doing every day. That really got my attention."

Doctor Bolter remembers another case at that time which also added momentum to the push for reform. "A physician got into trouble for blowing the whistle on the personal use of amphetamine by professional football players.[2] When he stepped in with a plan for medical management, a lot of pressure was placed on the authorities to revoke his license, and we supported him." In any event, such cases helped galvanize acceptance of the goals of a nascent organization of addiction medicine doctors within mainstream organized medicine.

"With the help of the CMA, we authored a bill in 1971 to change the restrictive state drug law in order to bring it into conformance with reasonable clinical practice," Bromley continues. "We pulled together about 20 people and drove back and

forth to Sacramento to lobby for change. Senator George Moscone became a real ally, and the CMA was on our side. We took the issue to one of the early Haight Ashbury Free Medical Clinic's conferences and got grassroots support. We got the law changed at last."[3]

Into the Medical Mainstream

In 1972, the connection with the CMA got stronger. Gail Jara joined the CMA staff after the successful lobbying partnership. She staffed several committees and one of her first efforts was to effect a merger, creating the Committee on Alcoholism and Other Drug Dependencies from what had been two separate committees. The new chairman was Stanford Rossiter, MD, from Redwood City. Says Bromley,"Through that new committee, we carried the resolution to the CMA to start a specialty society, and we were very well received. There were some visionary people there at the time who saw this as an important field needing more medical involvement. Our vision even back then was to begin in California and bring treatment of addiction into the mainstream. For a long time, while the California Society was housed within CMA, the Committee and the Society ran pretty much the same."

The fledgling group also recognized the importance of support within academic medicine, and fortunately there was someone of like mind at the University of California, San Francisco. "Here was someone who brought the imprimatur of the university, to add to the recognition that we weren't a bunch of quacks," says Doctor Gordon. "Chuck Becker did that for us. We had our first real organizing meeting at his house."

Charles Becker, MD, now emeritus professor of medicine and living in Colorado, at that time was an internist doing clinical pharmacology and toxicology at UCSF. "I recognized there was no teaching about chemical dependency in the medical school, while that was the root of so many of the problems we saw in the clinics," he recalls. "I was trying to bring my interests into the mainstream and felt that the best way to do that was with chemical dependency. I was lucky there was this very good group of practicing physicians getting organized. But I have to say that the guru was Gail Jara,

"I recognized there was no teaching about chemical dependency in the medical school, while that was the root of so many of the problems we see in the clinics. I was lucky there was this very good group of practicing physicians getting organized."

who helped us to formulate regular protocols and was an administrator of great skill and compassion. She brought practice, research and teaching all together."

Simultaneously in Southern California, Doctor Lundberg of USC and others were also starting to pull together a core group. "We started working with the Los Angeles chapter of the National Council on Alcoholism, and a few people at the county medical society got interested," he recalls. "People like Joe Takamine and Tom Ungerleider from UCLA and Joe Zuska from the Navy were key in that area, and then we hooked up with Gail Jara and the CMA recognized the obvious need." Doctor Gordon reinforces the importance of that linkage: "I absolutely guarantee you there would be no CSAM today were it not for Gail Jara."

There were other organizations in "addiction medicine" in the US which predated the formation of this new society. Noteworthy among them were the national group, the American Medical Society on Alcoholism (AMSA) founded in 1954 by Ruth Fox, MD, and the National Council on Alcoholism (NCA) founded in 1944 by Marty Mann. AMSA served as the medical component of NCA. Both of these organizations had an influence in California because the founding leaders of the California Society were members, but neither was doing what these physicians felt was needed. The Californians were focused on establishing a role in the mainstream of both organized medicine and academic medicine for the physicians who treated all drug dependence. They did not endorse the separation between alcohol and other drugs. Heroin addicts and heroin addiction got the same attention as those dependent on sedative-hypnotics or on amphetamine or on alcohol. "The shift from the focus on alcohol and alcoholism to encompass other drugs of addiction was a policy change which did not come until much later for AMSA which became AMSAODD in 1984 and NCA which became NCADD in 1988," said Max Schneider, MD.

Another charter member of the California Society whose name crops up repeatedly in these recollections is the late Vernelle Fox, MD. Doctor Schneider, a past president of both CSAM and ASAM, feels strongly that "Vikki Fox was one of our prime movers. She moved to California from Atlanta in the early 1970s, where she had established an innovative new treatment program. She was one of the outstanding clinicians and teachers and thinkers in the field. Her writings and guidance raised the level of the early organizational efforts in terms of both scientific and ethical standards. It's no accident that our annual award is named in her honor – she epitomized the best in addiction medicine." Anthony Radcliffe, MD, Chief of Addiction Medicine at Kaiser in Fontana, and also a past president of both CSAM and ASAM, credits much of his own interest and growth in the field to Doctor Fox.

"She was the second president of the California Society after Chuck Becker, and she got me involved. She always said you should teach both colleagues and patients. In Long Beach, she started the first multidisciplinary program with a treatment team of doctors, nurses, and others, showing how to detox with dignity. She said the best primary therapist for an alcoholic is an interdisciplinary team.[4] Vikki was always stretching the frontier of things – she was way ahead of her time. We're just catching up with her in the 1990s."

"Everyone was enthusiastic about forming a new society," recalls Doctor Bolter. "Many of the people involved were influential and could move things along. It wasn't a fringe group, but had some stature from the start and people were willing to join in."

Some of the organizers took a little more convincing. "I had originally been alienated from the mainstream," recalls Doctor Smith. "Looking back at history, you could see that the first incarnation of organized addiction medicine was killed in the 1930s due to lack of support from the AMA. How many lives might have been saved if medicine's response had been different? But then the San Francisco Medical Society helped our clinic get malpractice insurance back after it had been revoked, and Jess Bromley and Gail Jara convinced me we would have to work for change from within organized medicine – if only to keep from getting arrested."

Doctor Bromley chuckles as he confirms Doctor Smith's initial reluctance: "We were trying to get into the mainstream as a group, but first we had to mainstream David."

One of the primary motivations of the new group was education of other physicians. "We started by presenting programs at the CMA annual meetings, and they were very well received," says Bolter. "Then we expanded to putting on our own meetings."

Building a New Structure

As for the new organization itself, Bolter recalls that "We started out being kind of crisis reactors, until we could build proactive goals of our own. There was a lot of publicity about drugs and always an issue to react to. Doctor Gordon remembers there being lots of early meetings of the fledgling group, but also that they were enjoyable. "As an internist you had to keep very busy and see a lot of patients in those days," he recalls. "Getting together with these great folks was almost like a form of recreation, for it was fun and they were on to something very worthwhile. The biggest debates I recall in the beginning were over what to name the new group. It was born as the California Society for the Treatment of Alcoholism and Other Drug Dependencies, and everyone called it 'the California Society.'"

At the first formal meeting – on April 23, 1973, at the San Francisco Hilton, the two main topics under consideration were basic: Is treatment possible for the addict or the alcoholic? And, should there be a new professional society?

The answer to those questions was apparently yes on both counts, for at the next meeting Becker was nominated as President. Also on the slate for election to the first Executive Council were Bolter, Bromley, Gordon, Smith, Zuska, Fox, Rossiter, Schneider, as well as Basil Clyman, Sidney Cohen, David Schwartz, and Issac Slaughter. This slate was accepted, and bylaws adopted, at the first Annual Meeting of the California Society held in conjunction with the CMA annual session on March 3, 1974. The first issue of the newsletter (David Smith was the first editor) was distributed at that meeting.

A glance through the minutes and other documents from the first few meetings may bring about a feeling of deja vu because of the perennial nature of the issues: credentialing, standards for drug and alcohol treatment facilities, reimbursement for addiction treatment, legislation regarding drug law enforcement, medical school curricula, confidentiality, impaired physicians, and a hotline for physicians.

And the rest, as they say, is history. The California Society became completely independent of the CMA in 1984 and moved its headquarters out of the CMA.

The California Society served as the impetus and model for the expansion of the American Medical Society on Alcoholism into ASAM, the American Society of Addiction Medicine,[5] and continues to grow and lead. Those involved in CSAM's genesis can be justifiably proud of their early roles.

"I'm not an alcoholic or drug addict, and early on some people wouldn't listen to me because I wasn't, while others wouldn't because they thought I was! So the development of recognized expertise was reason enough to start this association."

"The greatest accomplishments have been the development of a professional society which is widely recognized, and a well-accepted certification exam," says Bolter. Doctor Smith concurs that "CSAM has been a major force in the medical education of specialists and doctors in general" and that "we were instru-

mental in the combining of alcohol with other addictions, even though many people in the alcohol field were initially resistant."

Becker agrees that one of CSAM's major contributions has been integration of previously disparate addiction interests. "There were a lot of factions early on, with the National Council on Alcoholism and AA groups wanting nothing to do with heroin addicts and vice versa. But the organizers of what was to become CSAM felt these were all part of the same problem, and they turned out to be correct." Becker also notes the improvement regarding the issue of the welfare of physicians themselves. "I'm not an alcoholic or drug addict, and early on some people wouldn't listen to me because I wasn't, while others wouldn't because they thought I was! We had many discussions about how to deal with the image problem, and with the reluctance of physicians themselves to seek treatment because they knew their colleagues wouldn't know how to help them. So the development of recognized expertise was reason enough to start this association."

Doctor Schneider also recalls some conflicts: "The funny thing is that there are always controversies around leaders, especially in an emerging field. It took a lot of individual intestinal fortitude to overcome those problems. People shot at us because of the freedom that many of our members were using to break out of very restrictive constraints. Both the individuals and the organization rose above that to focus on what was scientific and what was not." On the other hand, within CSAM the support was striking, recalls Doctor Radcliffe. "In the beginning things were very collegial and it seemed we could always call each other and talk," he says. "We were all busy trying to do what nobody else seemed to want to do. And now, hearing President Clinton refer to substance abuse and mental health being integrated in the mainstream of his health care reform plan—not treating addiction as though it is merely some pimple on the greater body—was very rewarding. We've come a long way, and CSAM has always been there to provoke that progress."

"The organization took off slowly under the wing of the CMA, but started making an impression from the start," reflects Doctor Lundberg. "The CSAM effort was a significant beginning and model for the country in many ways and has had a substantial influence in a number of areas."

"All of this has been about the remedicalization of treatment," concludes Bromley. "And the key players were the key people in CSAM." □

References

1. Gordon J, Levy R, Perrow C. Open ward management of acute alcoholism. California Medicine 1958; 89:397-399.
2. Mandell AJ. The Nightmare Season. New York: Random House, 1976.
3. California Health and Safety Code, Section 11217.5.
4. CSAM News, Fall 1987; 14(2).
5. Discussions at two conferences on the formation of a national physicians' society on alcoholism and other drugs. CMA Resolution 14-82; Kroc Ranch, Feb 1983, Oct 1983.

CSAM Celebrates Twenty Years

Historical Review and Tribute to the Founders of CSAM
~ Garrett O'Connor, MD

Presentation of the Founder's Award
to ***Jess Bromley, MD***

Presentation of the Community Service Award
to ***Gail B. Jara***

Presentation of the Vernelle Fox Award
to ***George Lundberg, MD***

Keynote Address: "JAMA's Role in Mainstreaming Alcohol and Other Drugs"
~ George Lundberg, MD

Dinner and Awards Ceremony, Friday, November 19, 1993
Four Seasons Hotel, Newport Beach, CA,

Neuroscience and Benzodiazepine Dependence

Steven J. Eickelberg, MD

Editor's Note: This article is an edited transcript of the presentation given by Doctor Eickelberg at the 1992 California Society Review Course. Doctor Eickelberg is a physician at the Chemical Dependency Recovery Program at Kaiser Permanente Medical Center in Fontana. This article reviews the pharmacologic action, neurochemistry and clinical management of withdrawal from sedative-hypnotic drugs, with special emphasis on what neuroscientists are showing us about dependence and withdrawal from benzodiazepines.

Various substances, in particular alcohol, have been used to induce sleep (hypnosis) and calm distress (sedation) since antiquity. Bromide, our first modern agent, was introduced as a sedative in 1853, and as a hypnotic in 1864. Barbituric acid (barbital) was synthesized in 1856 and used as a hypnotic in 1903. The success of phenobarbital (introduced in 1912) led to the development of over 2,500 barbiturates, 50 of which were distributed for commercial use. Chloral hydrate and paraldehyde were the only other sedative-hypnotic agents used at the turn of the century (Kisnad, 1991; Allgulander, 1986).

In the 1950s a number of non-barbiturate sedative-hypnotic agents became available (meprobamate, glutethimide, methyprylon, etc.). Each new drug was heralded with optimism and claims of improved efficacy, decreased toxicity and lower potential for addiction. However, until the introduction of chlordiazepoxide in 1960, all sedative-hypnotic agents possessed relatively low therapeutic indices (lethal dose/therapeutic dose), untoward effects, toxicities and liabilities for abuse, dependency and addiction – despite claims to the contrary. With regard to their essential features (CNS depression, tolerance, dependence, potential for abuse and addiction) sedative-hypnotic drugs have remained the same (Miller and Gold, 1989; Kisnad, 1991). With increasing dose, sedative-hypnotics have the ability to produce, in ascending order: anxiolysis, sedation, hypnosis, anesthesia and coma.

The availability of safer, less toxic sedative-hypnotics (with higher therapeutic indices) – the benzodiazepines, beginning in 1960 with chlordiazepoxide (Sternbach, 1983) – changed the course of treatment. By 1973 the benzodiazepines

Table I: Barbiturates

	Drug Name		Dose Range (mg)		Onset (oral dose) (min)	Durations (hrs)	t 1/2 (hrs)	Metabolic Site Process	Active Metabolites	Clinical Correlates
	Generic	Trade	Sedative (daily)	Hypnotic (single dose)						
Short-Acting	Pentobarbital	Nembutal	100-400	100	10-15	3-4	15-50	Hepatic MEOS	No	Hepatic enzyme induction
	Secobarbital	Seconal	-	100	10-15	3-4	15-50	Hepatic MEOS	No	Hepatic enzyme induction
	Butalbital	Fiorinal	150-300 Tension HA	-	15-30	2-UNK	35-60	Hepatic MEOS	No	Hepatic enzyme induction
Intermediate Acting	Amobarbital	Amytal	30-480	60-200	46-60	6-8	16-40	Hepatic MEOS	No	Hepatic enzyme induction
	Amobarbital + Secobarbital	Tuinal	100-300	200	10-15	6-8	15-50	Hepatic MEOS	No	Hepatic enzyme induction
Long-Acting	Phenobarbital	-	90-320	30-120	≥60	10-12	53-118	Hepatic hydroxylation 25-50% excreted unchanged	No	Hepatic enzyme induction

had become the most widely prescribed class of medication worldwide – 87 million prescriptions were filled. By 1990 more than 300 different benzodiazepines had been synthesized, over 50 receiving world-wide acceptance for sedation or anxiolysis. Primarily due to their clinical efficacy and to the lack of awareness of abuse liability, tolerance and withdrawal, benzodiazepines all but replaced the older sedative-hypnotics (Smith, 1991). However, as published concerns gained more attention, prescriptions declined to 60 million in 1990 (Miller & Gold, 1990). Physicians became concerned with tolerance, dependency and withdrawal when choosing to prescribe or discontinue benzodiazepines and when deciding upon the dose and duration of a therapeutic regimen. Additionally, over these 30 years (1960-1990), physicians became increasingly aware of the potential for cross-tolerance and cross-dependence between all sedative-hypnotics, including alcohol (Ciraulo, Sands, et al., 1988; Ciraulo, Barnhill, et al., 1989; Dickenson, Rush, Radcliffe, 1990).

Nonbenzodiazepines

Next to the central nervous system effects, the most important clinical characteristics of nonbenzodiazepine sedative-hypnotic agents concern their rate and location of metabolism. The primary mode of metabolism for the barbiturate class (Table I) of sedative-hypnotics is through the hepatic microsomal enzyme oxidase system (MEOS), an inducible enzyme system. Concurrent use of other agents metabolized by this system, such as dilantin, anticoagulants, digoxin, tricyclic antidepressants, etc., will hasten metabolism of both drugs (American Hospital Formulary Service, 1992; Drug Facts and Comparisons, 1990). The majority of the nonbarbiturate, nonbenzodiazepine class (Table II) are also metabolized through the MEOS. Of special note in this class, two compounds, ethchlorvynol and methyprylon, display significant intrahepatic recirculation, so in overdose conditions, toxic levels stay elevated for prolonged periods (Harvey, 1985; Miller and Gold, 1989; American Hospital Formulary Service, 1992; Drug Facts and Comparisons, 1990).

Most of the nonbarbiturate, nonbenzodiazepine sedative-hypnotics have fallen out of favor since the introduction of the safer benzodiazepines. However, in the state of New York, where the prescription of benzodiazepines has required a triplicate form since 1988 (Figure I), the use of benzodiazepines has decreased by approximately 50% and prescriptions for glutethimide,

Table II: Nonbarbiturate-Nonbenzodiazepine Sedative-Hypnotics

Drug Name		Dose Range (mg)		Onset (min)	Duration (Hrs)	t 1/2 (hrs)	Metabolic Site Process	Active Metabolites	Clinical Correlates
Generic	Trade	Sedative (daily)	Hypnotic (single dose)						
Ethchlorvynol	Placidyl	200-600	500	15-60	5	10-20 20-100 with OD	Hepatic ? kidney	?	Entero-hepatic recirculation
Glutethimide	Doriden	-	250-500	30	4-8	10-12 > 100 with OD	Hepatic MEOS + hepatic conjugation	Inactive	Anticholineric erratic absorption seizures with toxic level
Methyprylon	Noludar	50-400	200-400	45	5-8	3-6	Hepatic MEOS	5-Met-Pyrithyl-Dione	20% Entero-hepatic recirculation
Methaqualone	Quaalude	300-450	150-300	15-45	5-8	10-43	Hepatic MEOS	Inactive	
Meprobamate	Miltown Equanil	1200-2400	-	30-60	3-6	6-16	Hepatic MEOS	Inactive	Seizures with toxic dose
Carisoprodol	Soma	350-1400	-	30	4-6	8-12	Hepatic MEOS	Meprobamate	Activity secondary to meprobamate
Chloral Hydrate	Notec	-	500-1000	30	4-8	7-12	Hepatic ADH erythrocytes	Trichloro-ethanol	OD induces hepatic necrosis

ethchlorvynol and methyprylon have increased proportionally (Weintraub, 1991). Meprobamate is returning to the clinical scene indirectly as the primary metabolic product of carisoprodol metabolism (Drug Facts and Comparisons, 1990). Since carisoprodol is not classified as a controlled substance (PDR, 1993) and its metabolism to meprobamate is not widely known by clinicians, its dangers as an addictive agent may be under-recognized or treated inappropriately.

Nonbenzodiazepine withdrawal

The classic sedative-hypnotic withdrawal syndrome profile (Figure II) (initially described, however, not illustrated graphically for barbiturates and nonbarbiturate-nonbenzodiazepine sedative-hypnotics) is based on three pharmacologic parameters: dose, period of use and duration of drug action (Isbell, 1950; Fraser, 1954 and 1958; Essig, 1966). Figure II depicts possible sedative-hypnotic withdrawal courses but should be used only as a rough guide because clinical experience demonstrates that the withdrawal syndrome varies greatly from person to person.

Dose, duration and the characteristics and severity of withdrawal from barbiturates were defined in studies from the 1950s (Isbell, 1950; Fraser, 1954; Fraser et al, 1958). In one study (Fraser, 1958), after receiving up to 400 mg of secobarbital or pentobarbital daily for three to 12 months, subjects ("volunteer" prisoners) experienced minor withdrawal signs and symptoms upon abrupt discontinuation. When 600 mg was given for 50 days prior to discontinuation, 50% of subjects experienced severe withdrawal and 11% seizures. When the dosages were increased to 900-2200 mg a day for 1 to 5 months, all of the subjects experienced severe withdrawal and/or seizures upon drug cessation (75% seizures and over 50% with delirium).

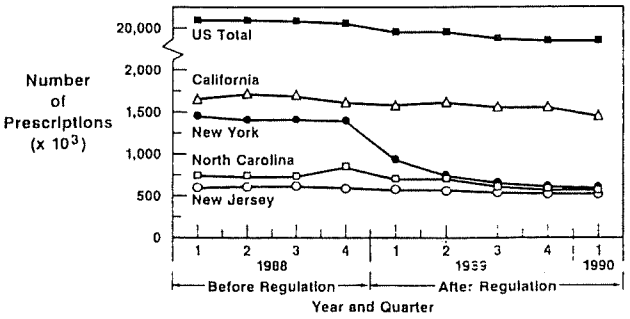

Figure I: Benzodiazepine Prescriptions (IMS American Data)

(Adapted from Weintraub et al., JAMA, 1991)

Benzodiazepines

Hepatic metabolism (as with the nonbenzodiazepine and barbiturate sedative-hypnotics) accounts for virtually

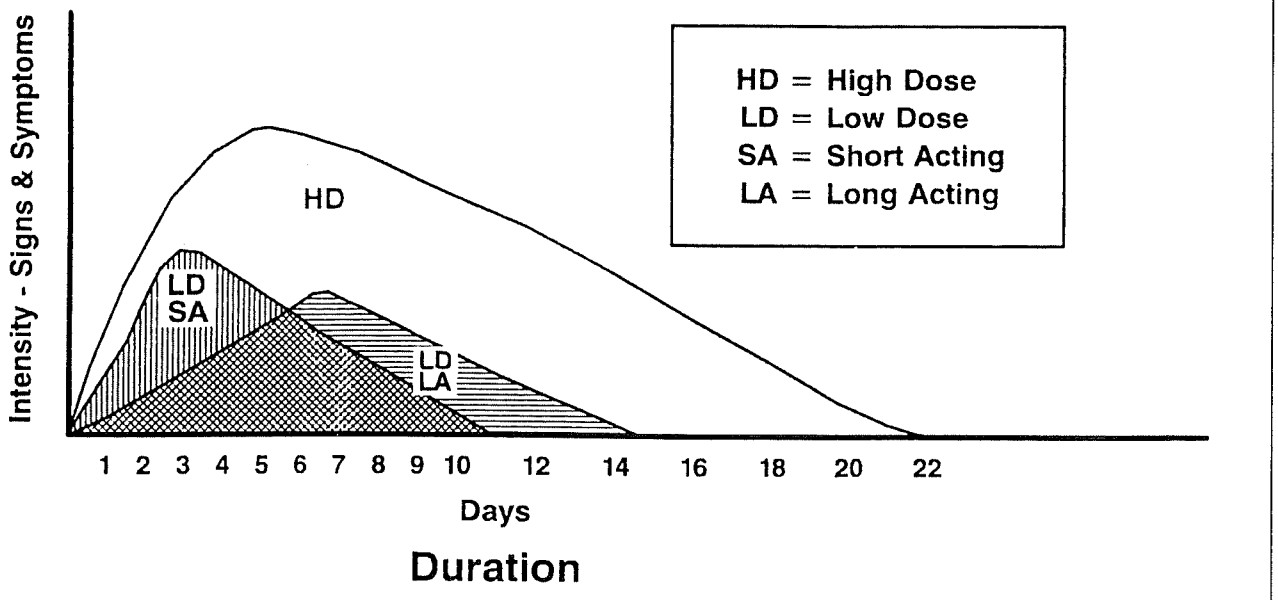

Figure II: Sedative-Hypnotic Withdrawal Courses

all benzodiazepine elimination. Two principal metabolic pathways are involved: hepatic microsomal oxidation (N-dealkylation or aliphatic hydroxylation via cytochrome P450) and glucuronide conjugation (Table III).

Both pathways, unlike the MEOS system for barbiturates and non-benzodiazepine nonbarbiturate sedative-hypnotics, are only minimally induceable; hence, benzodiazepines have little influence on their rate of metabolism (pharmacokinetic or metabolic tolerance). The oxidation system (cytochrome P450) is susceptible to impairment from age, liver disease states (e.g., cirrhosis), and drugs that diminish the oxidizing capacity through competitive inhibition (e.g., cimetitidine, estrogens, disulfiram) (Greenblatt, 1983; Klotz, 1981). Administration of a benzodiazepine metabolized through the oxidative mechanisms (e.g., diazepam, flurazepam) in a person of advanced age or with liver disease or who is concurrently receiving a drug which competes for cytochrome P450 metabolism will lead to increasing benzodiazepine levels (Greenblatt et al., 1982; Klotz, 1981). Additionally, most benzodiazepines metabolized through the oxidative route have biologically active sedative-hypnotic metabolites with longer acting half-lives than the parent compound (e.g., diazepam, chlordiazepoxide, clorazepate, flurazepam). With chronic use, accumulation of metabolites is a central clinical concern (Greenblatt, 1983).

Benzodiazepines metabolized through the conjugation route (e.g., lorazepam, oxazepam) are much less influenced by age or disease factors, and elimination is not impaired by the concurrent administration of other drugs (Greenblatt, 1981, 1983; Greenblatt et al., 1982).

In 1975 two researchers, independently of each other (Haefley et al., 1975; Costa, Guidotti et al., 1975), proposed that the primary mode of benzodiazepine action was enhanced through GABAergic neurotransmission. This hypothesis has been confirmed and the inter-relationship

Table III: Benzodiazepines

Drug Name		Dose Range (mg)		Onset (oral dose)	Duration	t 1/2 (hrs)	Primary Hepatic Metabolism	Active Metabolites	t 1/2 Metabolites (hrs)
Generic	Trade	Sedative (daily)	Hypnotic (single dose)						
Alprazolam	Xanax	0.75-4.0	-	Intermediate	Short	9-26	Oxidation	Negligible	-
Chlordiazepoxide	Librium	15-100	-	Intermediate	Long	5-30	Oxidation	DM chlordiazepoxide DM diazepam Demoxapam	18 30-100 15-100
Clonazepam	Klonopin	1.5-20	-	Rapid-Intermediate	Long	18-50	Oxidation	-	-
Clorazepate	Tranxene	15-60	-	Rapid-Intermediate Faster with ↓pH	Long	30-100	Oxidation	DM diazepam prior to absorption	30-100
Diazepam	Valium	6-40	-	Rapid	Long	20-80	Oxidation	DM diazepam	30-100
Flurazepam	Dalmane	-	15-30	Rapid-Intermediate	Long	24-100	Oxidation	Des-alkyl-flurazepam	50-100
Lorazepam	Ativan	2-6	.05-2.0	Intermediate	Short	10-20	Conjugation	-	-
Oxazepam	Serax	30-120	10-30	Intermediate-Slow	Short	5-10	Conjugation	-	-
Quazepam	Doral	-	7.5-30	Intermediate	Long	25-40	Oxidation	2-Oxo-quazepam Des-alkyl-quazepam	40 70-75
Temazepam	Restoril	-	15-30	Intermediate-Slow	Short	5-10	Conjugation	-	-
Triazolam	Halcion	-	0.125-0.5	Intermediate	Short	3-5	Oxidation	-	-

between benzodiazepine binding and GABA (gamma aminobutyric acid) action is established. To understand benzodiazepine actions as well as tolerance and withdrawal phenomena, it is important to examine GABA-ergic neurons and GABA activity first.

A simplistic conceptualization of CNS functioning views the central nervous system as wired for stimulation, with the GABA system primarily providing the brakes (inhibition) required for balanced functioning. Virtually all identified neuro-modulatory systems utilize GABA as the major inhibitory neurotransmitter. At least one third of all the neuronal synapses in the central nervous system are GABAergic (Haefley, 1983). GABAergic neurons are primarily interneurons – therefore they primarily affect neurons in close proximity (Haefley, 1983). GABAergic synapses in interneuron circuits inhibit primary neuronal transmission. In other words, GABA neurons affect the synaptic excitation of primary stimulating neurons through action on the stimulatory primary neuron, decreasing the excitation the primary neuron may exert on afferent sites.

Haefley (1986) described that benzodiazepines bind to high affinity receptors in the brain (benzodiazepine receptor) which are closely associated with GABA receptors. Further work by a number of investigators has shown that benzodiazepine receptors are part of a GABA-receptor oligomeric glycoprotein (macro or supramolecular complex) in the neural cell membrane. The GABA-receptor complex is comprised of multiple subunits including an anion conduit termed the chloride ionophore (Study, 1982; Skolnik, 1982; Haefley, 1983; Morrow, 1988). The opening and closing of the chloride ionophore channel is modulated by the GABA receptor. Activation of the GABA receptor opens the chloride channel. Chloride then flows down an electrochemical gradient from the extracellular space (high concentration) to the intracellular space (low concentration), hyperpolarizing the neuronal membrane – an inhibitory effect. The benzodiazepine receptor allosterically modulates the gating function of the GABA receptor in opposing directions. Figure III (adapted from Haefley, 1983) illustrates the interrelationships between a benzodiazepine, the benzodiazepine receptor, GABA, GABA-receptor and the chloride ionophore.

A number of ligands bind allosterically to the region termed the benzodiazepine receptor (Figure III) with the following effects:

1. GABA agonists facilitate opening the chloride channel.
2. Benzodiazepine agonists (classical benzodiazepine tranquilizers) facilitate or enhance GABA's influence on the chloride ionophore potentiating GABA's action. That is, benzodiazepines shift the GABA dose-response curve to the left (Haefley, 1986). Without an intact GABA system, benzodiazepines are ineffective in modulating sedation or anxiolysis. In other words, the GABA system sets the limits of benzodiazepine effects; benzodi- azepines have no known independent (i.e., without an intact GABA system) ability to alter mental status or consciousness.
3. Some benzodiazepine receptor ligands – most notably the beta carbolines, termed inverse agonists – decrease GABA's influence on the chloride ionophore leading to hypopolarization. This lowers the neuronal threshold to excitation, and can induce seizure activity (reducing the effect of GABA, shifting the dose response curve to the right) (Haefley, 1986).
4. Benzodiazepine agonists increase the affinity of GABA receptor for GABA, further facilitating the chloride channel opening.

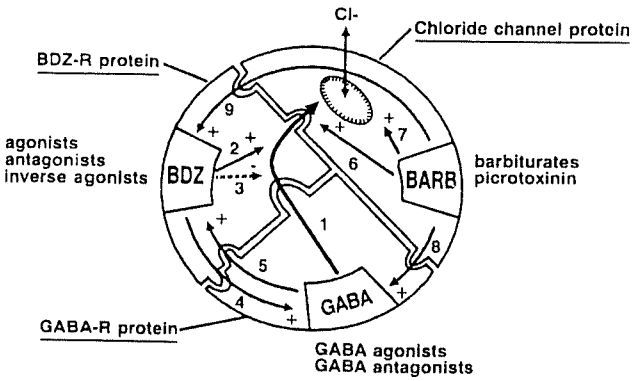

Figure III: Model of GABA-Receptor (GABA-R) Benzodiazepine-Receptor (BDZ-R)-Chloride Channel Complex

1. GABA agonists trigger opening chloride channel through BDZ-R
2. BDZ agonists enhance coupling function of BDZ-R
3. Inverse agonists reduce coupling function of DBZ-R
4. BDZ agonists increase affinity of GABA-R
5. GABA agonists enhance BDZ binding
6. Barbiturates enhance GABA activated chloride channel
7. High-dose barbiturates directly open chloride channel
8. Barbiturates increase affinity of GABA-R
9. Barbiturates increase affinity of BDZ-R.

(Adapted from Haefley, 1983. J. Psy. Drugs, Vol. 15)

5. GABA agonists facilitate benzodiazepine binding at the benzodiazepine receptor.

There is also a barbiturate receptor on the GABA supramolecular complex (Skolnik et al., 1987). At lower doses, barbiturates exert an influence on the GABA-receptor complex similar to the actions of benzodiazepines, facilitating a GABA-mediated opening of the chloride channel (Skolnik, 1981). However, at higher doses, barbiturates facilitate opening the chloride aperture *independent* of GABA functioning – an effect which may be the cause of the difference in therapeutic index (lethal dose/ therapeutic dose) between benzodiazepines (high therapeutic index) and barbiturates (low therapeutic index). This may explain why, unlike barbiturates, lethal overdose with benzodiazepines alone is almost unheard of.

A series of studies by Miller and Greenblatt (1988a; 1988b; 1989; 1990) led to a better understanding of benzodiazepine-GABA pharmacodynamics, illustrating that behavioral tolerance reflects molecular/receptor level changes. By noting cellular receptor changes and behavioral activity in mice in response to chronic benzodiazepine use and cessation, these researchers demonstrated a dose-response relationship and tolerance to the sedating and anxiolytic effect of chronic lorazepam administration. As tolerance to the sedating effects of lorazepam developed behaviorally, benzodiazepine and GABA receptors were down-regulated (fewer receptors, decreased GABA-receptor function, and diminished protein synthesis for GABA receptors). After lorazepam was administered for four weeks, it was abruptly discontinued. Subsequently GABA receptors were up-regulated and the GABA-receptor complex function was enhanced (greater affinity for GABA; greater affinity of the benzodiazepine receptor for benzodiazepines; increased number of benzodiazepine receptors; and an increased overall facilitation of the opening of the chloride ion channel).

Flumazenil (Mazicon), available in the United States from Roche since 1992, is marketed as a benzodiazepine antagonist or competitive inhibitor of benzodiazepine agonist action at the benzodiazepine receptor (PDR, 1993). Although mild agonist properties have been reported in humans and animals (Ricou, 1986) and anxiogenic properties noted when administered to patients with panic disorder (Nutt, 1990), flumazenil is used clinically as an antogonist to reverse benzodiazepine agonist effects. If, in fact, flumazenil were a *pure* antagonist, it would have no effect on the relationship of GABA to the chloride ionophore in benzodiazepine-naive subjects. However, Miller and Green-blatt (1989) demonstrated that flumazenil possesses some inverse agonist properties, at least at the receptor level (in mice) if not behaviorally. With flumazenil administration, the GABA-receptor complex is up-regulated much like what is observed in the withdrawal state from chronic benzodiazepine use, and there is an increased coupling of GABA and the chloride channel (Miller and Greenblatt, 1989).

In their fourth study, Miller and Greenblatt (1990) showed an investigational compound, Ro 16-6028, to have partial agonist effects and dose-dependant anxiolytic effects in mice without evidence of sedation. Additionally, this compound does not induce tolerance at the GABA-receptor or benzodiazepine-receptor level. In Ro 16-6028, we may have an anxiolytic compound that does not produce receptor level tolerance or sedative side effects.

The existence of a stereospecific binding site for benzodiazepines raises questions whether there may be *native* benzodiazepine (agonist or inverse agonist) ligands. No published reports demonstrate a measurable serum benzodiazepine level in normal, healthy individuals; however, in hepatic coma patients (first studied in patients with acetaminophen-induced hepatic failure), benzodiazepines (desmethyldiaze- pam and diazepam) have been measured in the serum and the brain (Basile, 1991). Hepatic coma patients treated with intravenous flumazenil can experience an increased level of consciousness. Jones (1989) reviewed 36 cases of patients with hepatic encephalopathy who received flumazenil. Twenty nine showed clinical improvement. In an NIH conference review (Jones, 1989), a case report is cited (p. 543) of a 42-year-old woman with intractable portal-systemic encephalopathy who takes 25 mg flumazenil orally twice daily to treat chronic intractable encephalopathy with episodic hepatic coma. This woman had a two-thirds hepatectomy and end-to-side portacaval shunt. Standard dietary, antibiotic and lactulose regimens did not control her encephalopathy; however, oral flumazenil therapy led to normalization of her protein tolerance, correction of abnormal EEG findings and resumption of activities of daily living. Discontinuation of flumazenil precipitates exacerbations of encephalopathy, and re-establishment of the medication leads to sustained remission.

Studies such as these provide evidence of the presence of endogenous benzodiazepine in acutely ill persons and raise questions about the "purpose" of the benzodiazepine binding site on the GABA supramolecular complex.

Benzodiazepine withdrawal

Miller and Greenblatt have described benzodiazepine tolerance as resulting from down-regulation (decrease in the number of receptors) of the benzodiazepine receptor. Hepatic metabolism (bioconversion) of benzodiazepines is only negligibly altered by dose or duration of benzodiazepine exposure. Tolerance to benzodiazepines is therefore pharmacodynamic (receptor mediated) rather than to pharmacokinetic (metabolically mediated). The concept of receptor changes induced by chronic benzodiazepine exposure has helped systematize our observations and led to clearer understanding of benzodiazepine withdrawal syndrome.

Neuroscience and Benzodiazepine Dependence *(continued)*

Hollister (1961) reported a benzodiazepine withdrawal syndrome shortly after chlordiazepoxide appeared on the market. Important factors in the development of dependence on benzodiazepines include dose, pharmacodynamics, pharmacokinetics, duration of action, period of use, and personal susceptibility factors (Ciraulo, 1988; Ciraulo, 1989; Dickenson, 1990; Schweizer, 1990). Withdrawal syndromes have been described for high-dose and low (therapeutic) dose, short-term and long-term use, and short-acting and long-acting benzodiazepines (Noyes, 1988; Roy-Byrne, 1988; Smith, Wesson, 1983; Rosenberg, 1985; Rickles, 1983; Rickles, 1986; Rickles, 1990; Busto, Sellers, Naranjo, 1986; Hermann, 1987).

Additionally, over the last nine years multiple reports document problems with triazolo-benzodiazepines (alprazolam, triazolam) during both treatment and withdrawal – problems beyond the difficulties previously documented for other benzodiazepines (Noyes, 1985; Zipursky, 1985; Juergens, 1988; Dickenson, 1990).

In evaluating a patient's dependency, it is necessary to understand the relationship between dose, duration of action, duration of use, individual patient susceptibility to dependency and the particular characteristics of the benzodiazepine used. Clinical research and experience support the following points:

1. High-dose benzodiazepine use (2-5 times recommended therapeutic dose for longer than three months or greater than five times the therapeutic dose for one to three months) is associated with an increased potential for severe withdrawal and/or protracted withdrawal symptoms.
2. When benzodiazepines are used in the therapeutic dose range over a long term (> 6 months) more severe and/or prolonged withdrawal is likely.
3. 15-100% of patients discontinuing long-term (> 6 months) therapeutic dose benzodiazepine use experience mild to moderate withdrawal (Hallstrom and Lader, 1981; Rickles, 1990; Busto, 1986).
4. Benzodiazepine use for less than six months at therapeutic doses rarely results in more than mild withdrawal symptoms.
5. There is an increased frequency and severity of withdrawal symptoms for patients using or discontinuing triazolam or alprazolam compared with other benzodiazepines (regardless of the duration of use.)
6. Patients with a personal or family history of alcohol dependence are at increased risk to develop benzodiazepine dependence and experience greater difficulty discontinuing benzodiazepine use.
7. Tolerance develops more rapidly to short-acting benzodiazepines (e.g., oxazepam, lorazepam, triazolam) than to long-acting benzodiazepines (e.g., clonazepam). Tolerance, however, is not necessarily linked to dependence or potential for addiction (Shader, 1993).
8. There is no observable difference in the type or number of signs and symptoms of withdrawal between short- or long-acting benzodiazepines; however, persons withdrawing from short-acting benzodiazepines tend to have greater difficulty early in the course of withdrawal and characterize their symptoms as more severe or intense (Tyrer, 1981; Busto, 1986; Rickles, 1986; Hermann, 1987; Rickles, 1990).

Table IV: Sedative-Hypnotic Withdrawal Signs and Symptoms

Minor-Mild	Moderate	Severe
Insomnia	Apprehension	Autonomic hyperactivity
Anxiety	Anxiety	Vital sign instability
Restlessness	Tremors	Psychomotor agitation
Agitation	Muscle spasm	Delerium
Tired	Palpitations	Psychosis
Weak	Tachycardia	Hyperpyrexia
Tachycardia	Hypertension	Seizure
Muscle twitching	Vomiting	
Nausea	Abdominal cramping	
Chills	Numbness	
Yawning	Hyperreflexia	
Sweating	Perceptual changes	
	Paresthesia	
	Hypersensitivity	
	Hyperacusis	
	Depersonalization	
	Depression	
	Visual distortions	

There are no pathognomonic signs or symptoms of acute benzodiazepine withdrawal. Withdrawal symptoms vary from person to person, and most patients experience fluctuating intensity of signs and symptoms. These variations can occur over relatively short periods of time. Table IV lists minor or mild, moderate, and severe signs and symptoms of acute withdrawal. Patients who present with symptoms of withdrawal, but who deny benzoediazepine use, may easily be misdiagnosed as suffering from anxiety disorder,

panic disorder, or thought and mood disorders. In addition, most of the symptoms and signs of withdrawal are similar to those of the condition for which the benzodiazepine may have been prescribed in the first place. Withdrawal from long-term (> 6 months) or high-dose (> 2 times therapeutic dose) use of benzodiazepines usually results in sensory hypersensitivity, photophobia, tintitis, hyperacusis, feelings of depersonalization and perceptual distortion. Simultaneous use of other drugs complicates the picture. Many benzodiazepine-dependent patients are also receiving an antidepressant, and patients with chronic dysphoria or chronic pain states may be using opioid analgesics. And, of course, many patients are also drinking. Indeed, it is rather uncommon to see a clear, "unadulterated" picture of "pure" benzodiazepine withdrawal syndrome.

Protracted benzodiazepine withdrawal

Although there is no precise definition of "protracted" benzodiazepine withdrawal, an operational definition is "signs and symptoms which continue or emerge following the expected acute withdrawal period" (Figure IV). For long-acting benzodiazepines, the acute withdrawal syndrome can begin as early as the first day or two, is usually present by day five, and resolves within 10 to 21 days. For shorter acting benzodiazepines, acute withdrawal presents within 24 hours and resolves within seven to 10 days. Signs and symptoms that persist longer than two-four weeks should be evaluated as possible protracted withdrawal syndrome (Ashton, 1991).

Assessment of protracted withdrawal is difficult (Smith and Wesson, 1983; Ashton, 1991). Etiologic possibilities, though conjectural, include receptor level alterations, reemergence of the original disorder for which benzodiazepine treatment was initially prescribed, an anxiety or panic disorder, a mood disorder, or another *new* disorder. It may even be that chronic benzodiazepine or other substance use has changed the neurochemistry of the GABA-benzodiazepine receptor complex and induced a new disorder. Patients' beliefs and expectations may also influence the severity of withdrawal and response to treatment. For example, patients may have read a *Reader's Digest* article or watched a *60 Minutes* report on the dangers of benzodiazepines, or heard of a friend's horrific withdrawal from benzodiazepines. Such patients often require more clinical support (physician, nursing and counselor time, interventions, etc.) during their withdrawal. Clinical experience leads to the conclusion that most patients experiencing protracted withdrawal are affected by a combination of etiologic and modulating factors.

The course of protracted withdrawal is characteristically erratic, wavelike (with waxing and waning symptoms varying in frequency from minutes to days to weeks) and abates with time (Smith and Wesson, 1983). Common symptoms include anxiety, depression, irritability, muscle spasms, recurrent diarrhea, insomnia, paresthesia, and feelings of depersonalization (Ashton, 1991). Symptoms that escalate progressively rather than resolve over time should be evaluated as possibly representing a more severe endogenous or organic mental illness. Psychiatric evaluation and treatment with nonsedative-hypnotic drugs should be considered.

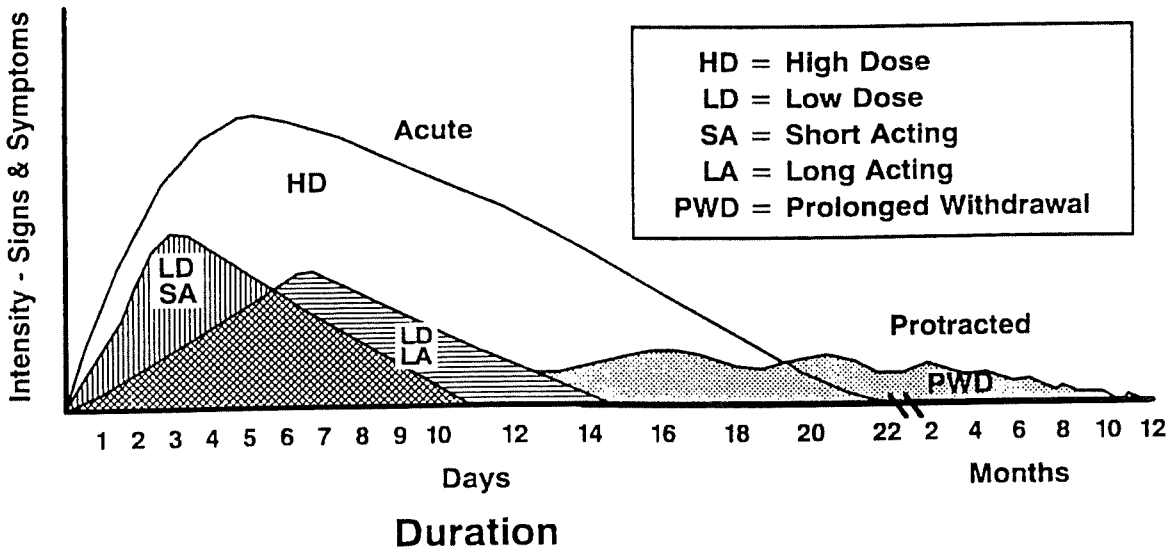

Figure IV: Benzodiazepine Withdrawal

For anxiety associated with protracted withdrawal, psychiatric consultation should be sought. The anxiety often responds to commonly prescribed antidepressants. Patients are treated with antidepressants for three to six months and then tapered off, unless a psychiatric disorder which requires longer term management emerges (or re-emerges).

Most commonly, the depression associated with protracted withdrawal is mild and resolves within a few months without the need for medication. Some patients, however, present with acute depression and/or suicidal ideation and require hospitalization for appropriate treatment and support.

Paresthesias, muscle spasms, and tremors usually resolve within a few weeks. Propranolol hydrochloride (Inderal) is effective at doses of 10 to 20 mgs, 4 to 6 times per day as needed for management of these symptoms (Tyrer, 1981). Patients tolerate it well, and decrease their utilization as symptoms resolve.

Methods of Detoxification

There are presently three primary, conventionally recognized, methods of detoxification from sedative-hypnotics: 1) slow taper, 2) substitution and taper (with three different approaches), and 3) replacement with carbamazepine (Tegretol) with or without a tapering regimen. Protocols for using carbamazepine are still experimental, (Roy-Byrne, 1988; Ries, 1989, 1991; Schweizer, 1991; Lein, 1986) and, at this time, are not used widely.

Most patients are able to discontinue therapeutic dose sedative-hypnotic medication successfully by gradually reducing the dose under medical supervision. Only those who are unable to control the dose on their own require the assistance of an addictionist, and, for them, substitution with a cross-tolerant sedative-hypnotic agent is the method used most often. The substitution method involves substituting an appropriate cross tolerant, longer-acting benzodiazepine or barbiturate, stabilizing the patient on an appropriate dose (finding and maintaining a balance between intoxication and withdrawal), and gradually tapering the substitution dose. Appropriate amounts of a cross-tolerant agent prevent autonomic hyperactivity, vital sign instability, hallucinosis and seizures. In addition, preventing withdrawal symptoms makes patients more comfortable and begins to build trust between physician and patient. This trust is an important clinical factor in keeping a patient in treatment during an acute or protracted withdrawal from benzodiazepines (which may take weeks or even months).

Dose Conversion-Substitution Method begins with predetermined doses of diazepam or phenobarbital calculated from the patient's use history, then decreases the dose gradually.

Applying the dose conversion chart (Table V) to the best available information about which sedative-hypnotic drugs the patient has been taking, and in what amounts, the physician calculates an equivalent dose of diazepam or phenobarbital to substitute for the patient's reported sedative-hypnotic dose. As a result of individual differences, and because the patient's history can be inadequate or inaccurate, the dose calculation is used as an initial guide only. Fifty to 100% (depending on the clinician's judgement) of the 24 hour calculated equivalent dose is divided by four to provide a *q.i.d.* regimen for the first twenty-four hours. Adequate stabilization maintains the patient somewhere between withdrawal and intoxication and is the key factor in determining the patient's response to the substituted agent. The patient should be on a stable dose of medication for one to four days (depending on the duration of action of the sedative-hypnotic which the patient was using) prior to commencing a graduated reduction of the dose. Longer acting sedative-hypnotics require longer stabilization periods. When the patient has been stable for 24-48 hours on a consistent substitution dose, slow taper is instituted. Tapering begins with 5-20% reduction of the substitution dose each 24-48 hours as tolerated. Larger reductions in dosage can be undertaken at the beginning of the tapering. Towards the end of the withdrawal (final 20-30% of original stablizing dose), the reduction is usually slowed to avoid emergence of withdrawal symptoms.

Pentobarbital Loading Method begins with "loading" with pentobarbital to find the dose which matches the patient's level of tolerance, then tapering.

This method rests on establishing the patient's level of tolerance to pentobarbital. Two hundred mg of pentobarbital is administered every two

Table V: Sedative-Hypnotic Drugs Dose Conversions

Drug	Dose (mg)
Barbiturates	
Pentobarbital	100
Secobarbital	100
Butalbital	100
Amobarbital	100
Phenobarbital	30
Nonbarbiturates	
Nonbenzodiazepines	
Ethchlorvynol	300
Glutethimide	250
Methyprylon	200
Methaqualone	300
Meprobamate	400
Carisoprodol	700
Chloral Hydrate	500
Benzodiazepines	
Alprazolam	1
Chlordiazepoxide	25
Clonazepam	4
Clorazepate	15
Diazepam	10
Flurazepam	15
Lorazepam	2
Oxazepam	10
Quazepam	15
Temazepam	15
Triazolam	0.25

Case #1: Carisoprodol/ chlordiazepoxide/ propoxyphene

A 31-year-old woman whose husband and children had recently moved out because of her dramatic mood changes gave an initial history of daily propoxyphene use for six years, about four tablets a day. She described using many physicians as prescribers. She had several diagnoses, including somatic pain syndrome, post-op C-section pain (her youngest child was eight), TMJ syndrome, migraine headaches, low back pain, and others. Additionally, she had a two-year history of daily carisoprodol use; in the last 12 months, she had escalated the dose to at least 10, and often more than 20 tablets a day. She had a positive family history of chemical dependency. A close relative owned a pharmacy.

She was admitted to our inpatient detoxification unit for treatment of withdrawal. She required a total of only 100 mg of pentobarbital during her first three days—much less than would have been expected, especially considering that carisoprodol is a short-acting agent. When she became intoxicated on low doses of pentobarbital (100-500 mg per day), serum quantitative levels for commonly used sedative-hypnotics were obtained. The results showed a very high desmethyldiazepam level (3000 ng/ml). When that information was presented to her, she did mention that she had visited her relative's pharmacy prior to admission. She had been taking hands-full of chlordiazepoxide for a number of days before entering the hospital, but she could not tell us how much or for how long. Enough time had passed since her last chlordiazepoxide use that little parent compound remained. Chlordiazepoxide had been metabolized to desmethyldiazepam which we found in the serum levels.

After five days, she was stabilized on 400 mg of pentobarbital per 24-hours and a slow taper was begun. When the tapering regimen was determined to be well tolerated (decreasing 50 mg per day without breakthrough withdrawal)—on the ninth day—we switched from pentobarbital 300 mg to the longer-acting phenobarbital 150 mg. She was observed 24 hours on phenobarbital to ensure an adequate dose conversion and then discharged to outpatient treatment. As an outpatient she completed the taper at 30 mg decrease per day, tolerating the tapering protocol to completion, and she was abstinent at the time of her six month follow-up. She had refused recommendations to continue chemical dependency treatment beyond the protocol tapering period or to participate in self-help support groups.

hours as the patient can tolerate, withholding doses only for signs and symptoms of barbiturate intoxication. With mild intoxication, a fine, sustained horizontal nystagmus is observed. As intoxication progresses, nystagmus becomes more coarse, followed by slurred speech, difficulty concentrating, ataxia, and somnolence. Doses are not given when signs and/or symptoms of intoxication beyond fine, sustained nystagmus are observed. After 48 hours of "loading" treatment, the total pentobarbital amount is divided by 2 to calculate the 24 hour stabilizing dose. This amount is then given in divided doses for the next 24 hours to ensure an adequate substitution dosage. Once the patient is stabilized, the dose is tapered as described previously.

There are some difficulties with this method. Patients withdrawing from long-acting sedative-hypnotics may not exhibit signs for up to five days following cessation of use. In such a situation, the physician may have already started to taper the dose prior to the development of withdrawal; thus, when the withdrawal begins, the dose of medication may be inadequate to prevent the emergence of withdrawal sequelae. Reloading to compensate for an inadequate substitution dose is confusing and taxes the patient's trust in the process, and requires careful observation for signs of intoxication.

PRN Pentobarbital Substitution begins with substituting pentobarbital as needed to suppress withdrawal symptoms until the patient is stable, then tapering.

In this method, substitution medication is used only as required by the patient's evolving signs and symptoms. It requires that a knowledgeable and astute nursing staff be available to monitor the patient's withdrawal continuously. The protocol calls for hourly medication (as needed) for as many days as are required to stabilize the patient through the initial stages of withdrawal. This is the approach I recommend because it takes into account the possibility of multiple substance use, inaccurate history, and differences in the timing and severity of the withdrawal course from patient to patient. I prefer to use 50-100 mg of pentobarbital or 30-60 mg of phenobarbital each hour as needed. Once the patient has been stable for 24-48 hours and the withdrawal course seems more predictable (i.e, 24-hour total substitution dose not varying more than one to two doses day to day), a 24-hour substitution dose is calculated. If it has taken five days to achieve stability, the doses are summed and divided by five. The calculated substitution dose is then given (individual doses) over the next 24 hours to ensure adequate dose and response. The daily dose is then reduced by 50 mg of pentobarbital or 30 mg of phenobarbital each day, as tolerated. Toward the end of the taper schedule, emerging withdrawal signs and symptoms may warrant slowing the tapering process, and if so, the dose is reduced every 48 hours rather than every 24 hours.

Summary

Regardless of our increasing ability to describe and explain dependence and withdrawal at a molecular level and despite an improved recognition of expected withdrawal courses and patient responses to treatment, clinical challenges remain.

Clinically, sedative-hypnotic dependence occurs in individuals. Our response requires awareness of and respect for the diversity of responses,

Case #2: lorazepam/ alprazolam/alcohol

A 36-year-old man was referred to the Chemical Dependence Recovery Program from the emergency room. He was quite remorseful having just received his fifth DUI within 10 years. He gave a history of near daily drinking, consuming a pint of liquor a day for the last 10 years. Additionally, for the last 10 years he carried a diagnosis of mixed anxiety and depression. Initial anxiolytic treatment had included lorazepam but he had been switched to alprazolam approximately six years ago. He'd been on a stable dose of alprazolam .5 mg *t.i.d.* for the last five years. Over the last five years nadolol (Corgard) was prescribed for progressive hypertension and upper extremity tremor. Imipramine (Tofranil) was added three years ago for his anxiety and depression and ranitidine (Zantac) for abdominal discomfort. He had a positive family history of chemical dependency and a social history replete with very short love relationships with persons who had substance use problems.

He was admitted to the inpatient detoxification unit. His admission diagnoses included alcohol dependence and long-term therapeutic dose alprazolam dependence.

He was stabilized within the first three days of admission on 450 mg of pentobarbital every 24 hours and maintained on this dose for 48 hours prior to reduction to 400 mg. Over the next two days, the dose was tapered to 300 mg and then phenobarbital was substituted at 180 mg per day. He was subsequently discharged to outpatient treatment where he completed a monitored gradual reduction of phenobarbital over the next seven days. Following completion of the phenobarbital taper he experienced some mild protracted withdrawal symptoms (including insomnia and occasional abdominal cramping) for approximately two weeks. No pharmacologic intervention was necessary for his abating protracted withdrawal. He attended two weeks of intensive outpatient treatment and continued to attend weekly group therapy and daily 12-Step meetings for eight months after admission (the time of his last follow-up).

the spectrum of susceptibility to dependence, and the variations we see in the severity of the withdrawal course.

It is my hope that this review will serve a clinical purpose, adding to our understanding of the neuroscience in a way that can be translated into patient care decisions. □

Acknowledgment

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References

Allgulander C. History and current state of sedative-hypnotic drug use and abuse. Acta Psychiatr Scand 1986; 73(5):465-478.

American Hospital Formulary Service. Drug Information 1992. American Society of Hospital Pharmlist. Bethesda, MD, 1992.

Ashton H. Protracted Withdrawal Syndrome from Benzodiazepines. In Miller, N, ed., Comprehensive Handbook of Drug & Alcohol Addiction. Marcel Dekker, Inc., 1991, 915-929.

Basile A, Huges R, et al. Elevated brain concentration of 1, 4 benzodiazepines in fulminant hepatic failure. NEJM 1991; 325:473-8.

Busto U, Sellers EM, Naranjo CA, Cappell H, Sanchez-Craig M, Sykora K. Withdrawal reaction after long-term therapeutic use of benzodiazepines. NEJM 1986; 315:854-869.

Ciraulo DA, Barnhill JG, Ciraulo MM, Greenblatt DJ, Shader RI. Parental alcoholism as a risk factor in benzodiazepine abuse: a pilot study. AM J Psych 1989; 146(10):1333-1335.

Ciraulo DA, Sands BF, Shader RI. Critical review of liability for benzodiazepine abuse among alcoholics. Am J Psych 1988; 145:1501-1506.

Costa E, Guidotti A, et al. Evidence for the involvement of GABA in the action of benzodiazepines. In Costa E, and Greengard, P, eds, Mechanisms of Action of Benzodiazepines. New York: Raven Press, 1975.

Dickenson B, Rush PA, Radcliffe AB. Alprazolam use and dependence: a retrospective analysis of 30 cases of withdrawal. West J Med 1990; 152(5):604-608.

Drug Facts and Comparison. St. Louis: JB Lippincott Company, 1990.

Essig C. Newer sedative drugs that can cause states of intoxication and dependence of barbiturate type. JAMA 1966; 196(8):126-129.

Fraser H, Wikler A, Essig C, Isbell, H. Degree of physical dependence involved by secobarbital or pentobarbital. JAMA 1958, 166(2):126-128.

Fraser H, et al. Chronic barbiturate intoxication: further studies. Arch Int Med 1954; 94:34-41.

Greenblatt D, Shader R, Abernathy P. Current status of benzodiazepines, parts I and II. NEJM 1983; Part I 309(6):354-358. Part II 309(7):410-416.

Greenblatt DJ. Clinical pharmacokinetics of oxazepam and lorazepam. Clin Pharmacokinetics 1981; 6:89-105.

Greenblatt DJ, Sellers EM, Shader RI. Drug disposition in old age. N Eng J Med 1982; 306:1081-1088.

Haefley W, et al. Possible involvement of GABA in the central actions of benzodiazepines. In Costa, E, and Greengard, P, eds., Mechanisms of Action of Benzodiazepines. New York: Raven Press, 1975.

Haefley W. Biological basis for drug-induced tolerance, rebound and dependence. Contribution of recent research on benzodiazepine actions. J Psy Drugs 1983; 15(1-2):19-39.

Haefley, W. Biological basis for drug-induced tolerance, rebound and dependence. Contribution of recent research on benzo-

Case #3 alprazolam/alcohol

A 42-year-old woman, complaining of increasing anxiety despite increasing doses of alprazolam, was referred to the Chemical Dependency Recovery Program by her psychiatrist and was admitted to the inpatient detoxification unit. After admission, the patient disclosed that she was also using increasing amounts of alcohol. She consumed alcohol initially to treat her anxiety and said that she was now unable to stop drinking. She gave a history of alcohol use for 10 years, progressing to daily use for the last year. An anxiety disorder had been diagnosed 14 years previously and she was initially treated with diazepam. Diazepam was switched to alprazolam with gradual physician-prescribed increases in dose over the last decade. In the last year she'd been using more (four 0.5 mg tablets per day) alprazolam than prescribed (three 0.5 mg tablets a day) and was experiencing progressive anxiety and depression. The patient's father and four brothers had a history of chemical dependence. Her husband was losing tolerance for her worsening mood swings.

At the time of admission, her diagnoses included alcohol dependence, long-term low-dose alprazolam dependence and anxiety-depression disorder. For the first three days, she required only 100 mg of pentobarbital daily. She subsequently stabilized on 200 mg pentobarbital and a slow taper was instituted. Pentobarbital was then switched to phenobarbital to facilitate treatment on an outpatient basis. She did well in the outpatient setting until her last day of medication, when she began to experience increasing anxiety and depression with vegetative signs, isolative behavior, and apprehensiveness. A consulting psychiatrist recommended imipramine which was gradually increased up to a dose of 150 mg a night. Unfortunately, she experienced intolerable side effects (tremors). Imipramine was discontinued and trazadone (Desyrel) therapy was begun. Despite the fact that it was somewhat more effective, she disliked it as well. She subsequently tried a number of other anti-anxiety agents, and antidepressants, both tricyclic and non-tricyclic, and was preparing to start monoamine oxidase inhibitor therapy when she commenced zealous participation in a Christian religious movement where she felt quite comfortable. Four months after detoxification she had discontinued follow-up in the chemical dependency clinic. Her psychiatrist reported that she was doing "ok," requiring no medication for management of anxiety or depression. □

diazepines. Pharmacopsychiatry 1986; 19:353-361.

Hallstrom L, Lader M. Benzodiazepine withdrawal phenomena. Int Pharm 1981; 16:235-244.

Harrison M, Busto U, Nranjo, CA. Diazepam tapering in detoxification for high-dose benzodiazepine abuse. Clin Pharm Ther 1984: 36(4):527-533.

Harvey SC. Hypnotics and sedatives. In Goodman, Gilman, Rall, and Murad, eds., The Pharmacological Basis of Therapeutics, New York: Macmillan, 1985; 339-371.

Hermann JB, Brotman AW, Rosenbaum, JF. Rebound anxiety in panic disorder patients treated with shorter-acting benzodiazepines. J Clin Psych 1987; 48(Suppl. 10):22-28.

Hollister, LE, Motzenbecker FP, Degan RO. Withdrawal reactions from chlordiazepoxide (Librium). Psychopharmacologia 1961; 2:63-68.

Isbell H. Addiction to barbiturates and the barbiturate abstinence syndrome. Ann Int Med 1950(July); 33:108-121.

Jones A, Skolnic P, et al. NIH conference: the GABA-A receptor complex in hepatic encephalopathy. An Int Med 1989; 110(7): 532-546.

Juergens SM, Morse, RM. Alprazolam dependence in seven patients. Am J Psych 1988; 145(5):625-627.

Kisnad H. Sedatives-hypnotics (not including benzodiazepines). In Miller, N, ed., Comprehensive Handbook of Drug and Alcohol Addiction, Marcel Dekker, Inc., 1991; 477-502.

Klotz U, Reimann, I. Elevation of steady-state diazepam levels by cimethidine. Clin Pharmacol Ther 1981; 30:513-517.

Lein E, Uhde T, et al. Preliminary evidence for the utility of carbamazepine in alprazolam withdrawal. Am J Psych 1986; 143(2):235-236.

Miller NS, Gold MS. Sedative-hypnotics: pharmacology and use. J Fam Pract 1989; 29(6):665-670.

Miller NS, Gold MS. Benzodiazepines: tolerance, dependence, abuse and addiction. J Psych 1990; 122(1):1-11.

Miller L, Greenblatt D, et al. Chronic benzodiazepine administration I. tolerance is associated with benzodiazepine receptor down regulation and decreased GABA-A receptor function. J. Pharm Exp Ther 1988a; 246(1):170-176.

Miller L, Greenblatt D, et al. Chronic benzodiapine administration II. discountinuation syndrome is associated with up regulation of GABA-A receptor complex binding and function. J. Pharm Exp ther 1988b; 246(1):177-181.

Miller L, Greenblatt D, et al. Chronic benzodiazepine administration III. Up regulation of GABA-A receptor binding and function associated with chronic benzodiazepine antagonist administration. J Pharm Exp Ther 1989; 248: 1096-1101.

Miller L, Greenblatt D, et al. Chronic benzodiazepine administration IV. A partial agonist produces behavioral effects without tolerance or receptor alterations. J. Pharm Exp Ther 1990; 254(1):33-38.

Morrow AL, Paul S. Benzodiazepine enhancement of GABA-mediated chloride ion flux in rat brain synaptoneurosomes. J of Neurochem 1988; 50(1):302-6.

Noyes Jr. R, Clancy J. A withdrawal syndrome after abrupt discontinuation of alprazolam. Am J Psych 1985; 142(1):114-116.

Noyes R, Garvey MJ, Cook F, Perry PJ. Benzodiazepine withdrawal: a reviw of the evidence. J Clin Psych 1988; 49(10):382-389.

Nutt D, Glue P, et al. Flumazenil provocation of panic attacks. Arch Gen Psych 1990; 47:917-925.

Physician's Desk Reference: Edition 46. Oradell, NJ: Medical Economics Company, Inc., 1993.

Rickels K, Case GW, Downing RW, Winokur, A. Long-term diazepam therapy and clinical outcome. JAMA 1983; 250(6):767-771.

Rickels K, Case GW, Schweizer EE, Swenson C, Frieman RB. Low-dose dependence in chronic benzodiazepine users: a preliminary report on 119 patients. Psychopharmacology Bulletin 1986; 22(2):407-415.

Rickles K, Schweizer E, et al. Long-term therapeutic use of benzodiazepines. I. Effects of abrupt discontinuation. Arch Gen Psychiatry 1990; 47:899-907.

Ricou B, Forster A, et al. Clinical evaluation of a specific benzodiazepine antogonist (RO1501788). Br J Anaesth 1986: 58:1005-1011.

Ries R, et al. Benzodiazepine withdrawal: clinician's ratings of carbamazepine treatment vs. traditional taper methods. J Psy Drugs 1991; 23(1):73-76.

Ries R, Roy-Byrne PP, et al. Carbamazepine treatment for benzodiazepine withdrawal. Am J Psych 1989; 146(4):536-537.

Rosenberg HC, Chiu TH. Time course for development of benzodiazepine tolerance and physical dependence. Neuroscience and Biobehavioral Reviews 1985; 9:123-131.

Roy-Byrne PP, Hammer D. Benzodiazepine withdrawal: overview and complications for the treatment of anxiety. Am J Med 1988; 84:1041-1052.

Schweizer E, Rickles K. Long-term therapeutic use of benzodiazepines. II. Effects of gradual taper. Arch Gen Psych 1990; 47:908-915.

Schweizer E, Rickles K, et al. Carbamazepine treatment in patients discontinuing long-term benzodiazepine therapy. Arch Gen Psych 1991; 48:448-452.

Shader RI, Greenblatt DJ. Use of benzodiazepines in anxiety disorders. N Eng J Med 1993; 328(19):1398-1405.

Skolnik P, Moncada V, Baker JD, et al. Pentobarbital: dual action to increase brain benzodiazepine receptor affinity. Science 1981; 211:1148-1450.

Skolnik P, Paul S. Benzodiazepine receptors in the central nervous system. Int Rev Neurobiology 1982: 23:103-140.

Skolnik P, Havoundjian H, Paul SM. Modulation of the benzodiazepine-GABA receptor chloride ionophore complex by multiple allosteric sites: evidence for a barbiturate receptor. In Dahl, Gram, Paul, Potter, eds., Clinical Pharmacology in Psychiatry, Berin-Heiddelberg: Springer-Verlag, 1987; 29-35.

Smith DE, Seymour RB. Benzodiazepines. In Miller, N, ed., Comprehensive Handbook of Drug and Alcohol Addiction, Marcel Dekker, Inc., 1991; 405-426.

Smith DE, Wesson DR. Benzodiazepine dependence syndromes. J PSy Drugs 1983; 15(1-2):85-95.

Sternbach LH. The benzodiazepine story. J Psy Drugs 1983; 15(1):15-17.

Study R, Barker J. Cellular mechanisms of benzodiazepine action. JAMA 1982; 247(15):2147-2151.

Tyrer P, Rutherford D, Hugett T. Benzodiazepine withdrawal symptoms and propranolol. Lancet 1981; 1:520-522.

Weintraub M, et al. Consequences of the 1989 New York state triplicate benzodiazepine regulation. JAMA 1991; 266(17):2392-2397.

Zipursky RS, Baker RB, Zimmer B. Alprazolam withdrawal delirium unresponsive to diazepam: case report. J Clin Psych 1985; 46:344-345.

California Diversion Program for Physicians

At the last meeting of the CMA\CSAM\MBC Liaison Committee to Diversion, Chet Pelton, Program Manager for Diversion, announced that there are openings for physician and non-physician members of the Diversion Evaluation Committees (DECs) and that the Diversion Program is seeking nominations of qualified persons.

There are six DECs, each with three physicians and two nonphysicians. DEC members are expected to have experience or knowledge in the evaluation or management of persons who are impaired due to alcohol or drug abuse, or due to mental illness (California Business and Professions Code, Section 2342).

Appointments to the DECs are made by the Division of Medical Quality of the Medical Board of California (MBC), on the recommendation of the Diversion Program Staff. Mr. Pelton said that suggestions for nominees could be sent to his office at 2135 Butano Drive, Suite 92, Sacramento, CA 95825.

CQI and Diversion

The Diversion Task Force, appointed by the Medical Board in February and chaired by John Kassabian, MD, of Los Angeles, has recommended that a program of continuous quality improvement (CQI) be considered, and has asked the Liaison Committee to Diversion to recommend how it might be designed and conducted. The Task Force report – accepted by the Division of Medical Quality in May – said, "The Liaison Committee should expand its role in quality assurance, utilization review and continuous quality improvement of the Program." In a subsequent letter, the President of the Medical Board, Jacqueline Trestrail, MD, of San Diego, said "The Medical Board is asking that the Liaison Committee assist in the creation of a program oversight function, within the constraints of personnel and financial resources."

The CSAM Committee on Physician Impairment, chaired by William Brostoff, MD, has undertaken the assignment from the Liaison Committee to recommend ways to implement such an oversight function and a program of CQI. Copies of the reports of the Committee are available to CSAM members from the Society's office.

Liaison Committee to Diversion

The Liaison Committee is comprised of representatives from the CMA, CSAM, the Medical Board's Division of Medical Quality, and each of the DECs. CSAM has agreed to support an increase in the level of activity of the Liaison Committee from two meetings per year to four. CSAM Executive Council voted to host and underwrite the costs of two meetings, while CMA continues to be responsible for two. The California Medical Association has been convening and providing staff support for the Liaison Committee since it was formed in 1982. The next meeting will be on December 8, 1993, in Los Angeles. CSAM representatives to the Liaison Committee are currently William Brostoff, MD, Donald Gragg, MD, and Gail Jara. □

President's Column

Take Time to Ask: "Is This Working?"

Research can be a very intimidating concept for many clinicians. Many physicians equate research with huge laboratories and equally large budgets. This is not the case. Earlier this year, *JAMA* published a brief report which showed that nearly one quarter of all original research articles appearing in 23 leading internal medicine and neurology journals were unfunded (Stein et al, 1993).

Stein and colleagues from Brown University School of Medicine's Division of General Internal Medicine reviewed the reports of original research published during one month in 1991 and found all types of research projects completed without designated direct support.

That article has implications for each of our practices. We all have the option of seeing our patients one by one without taking the time to ask: Is this working? More importantly, the question should continually be asked: Can this be done better? Physician means teacher. The best way to teach in the field of addiction medicine is to provide data on what works and what doesn't. As Graham stated, "The heart of research is the experiment, and each day the average physician performs many experiments."

Outline a research project to be done in your own practice setting, and bring the design to the poster session for feedback.

The California Society, at its upcoming meeting, is sponsoring its first research poster session. We hope to foster a lively discussion centering on the work of our colleagues. Come and share your thoughts, and critique the research of your colleagues. It is this exchange of ideas which is the basis for all scientific medicine. If our Society is to prosper and grow we need to incorporate a research agenda. The Society's new Committee on Research will focus attention on the value of small clinical research projects and encourage and assist members to conduct them. We encourage you to outline a research project to be done in your own practice setting, and bring the design to the poster session for feedback.

There's excitement in seeing a project materialize. The benefit to our field and our patients can be considerable!

Kevin W. Olden, MD

References

Graham, D. The role of the clinician in research. Am J Gastro 1984; 79:335.
Stein, et al. Who pays for published research? JAMA 1993; 269(5):781.

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.

Milton Bosch, MD is a board-certified internist at Kaiser Permanente Medical Center in Fairfield. He graduated from the University of Maryland Medical School in 1984 and completed a residency at UC Davis Medical Center, Sacramento.

Lawrence Bryer, MD, a board-certified psychiatrist, is Co-Director of the Alcohol and Drug Abuse Program and Assistant Chief of Psychiatry at Kaiser Permanente Medical Center in Oakland. He graduated from the University of Illinois Medical School in 1980, and completed a residency at UCSF.

Louis Prendergast, MD, a board-certified urologist, is retired and volunteers time to Sun Street Centers in Salinas. He graduated from Creighton University Medical School in 1948.

Edward Swenson, MD, is a staff phyisician at the Occupational Health Clinic at Mare Island Naval Shipyard. He graduated from the University of Nebraska's Medical School in 1950, and did a two-year residency in internal medicine at UCSF in 1959. Doctor Swenson is Associate Clinical Professor of Medicine at UCSF. □

News About Members

Gene Schoenfeld appears every Monday night on a San Francisco radio station (KITS, 105.3 FM) as the "Modern Rock Doc," answering medical and drug-related questions from listeners. □

FDA Approval of LAAM

Walter Ling, MD, and Donald R. Wesson, MD

On July 9th, the FDA approved LAAM (levo-alpha-acetylmethadol) for use as a maintenance treatment of opiate dependence. Interim guidelines for its use have been incorporated into the federal methadone regulations (21 CFR 291) and became effective July 20, 1993 (FDA, 1993).

LAAM is the first alternative to methadone that the FDA has approved for opiate maintenance. Between 1969 and the early 1980s, LAAM was clinically tested in 27 studies that involved about 6,000 patients (FDA, 1993). For various reasons, the New Drug Application (NDA) process was never completed and further clinical development of LAAM was stalled until NIDA's Medication Development Division became the sponsor of LAAM and let a contract to Biometric Research Institute in April, 1990 to prepare the New Drug Application. The New Drug Application was submitted to the FDA on June 18, 1993.

LAAM is the first alternative to methadone that the FDA has approved for opiate maintenance.

When the FDA's Drug Abuse Advisory Committee recommended approval of LAAM (CSAM News, Summer 1993), it also recommended postmarketing studies of LAAM's pharmacokinetics in patients with clinically significant liver and kidney disease, additional studies of its cardiac effects, and additional studies of its effects on reproduction.

The rights to market LAAM have been granted to BioDevelopment Corporation, a new pharmaceutical company established to develop treatments for addictive disorders. LAAM will be manufactured by Orpharm, a subsidiary of BioDevelopment Corporation, and distributed under its trade name, ORLAAM.

FDA's speedy approval heralds a new era in cooperation between FDA and NIDA's Medical Development Division to bring effective new medications to clinicians for treatment of drug abuse.

For the immediate future, LAAM can be used only by Federal drug treatment facilities, such as VA hospitals. Before LAAM can be dispensed by state-licensed methadone maintenance clinics, State legislation must be passed to place LAAM into Schedule II of California's Uniform Controlled Substances Act and new regulations must be drafted.

Representatives of the manufacturer, BioDevelopment Corporation, have said that sales of ORLAAM will initially be restricted to clinics that have received training in its use. A series of conferences, seminars, and educational materials are being developed by Bio-Development Corporation. Training of clinicians will be an integral part of the information distribution process.

Clinical Use of LAAM

Although LAAM is often referred to as "long-acting methadone," its comparison to methadone is misleading and may interfere with realization of LAAM's full clinical potential. LAAM is a pro-drug, which itself has little opiate effect. It is well absorbed orally and is metabolized by the liver to two active, long-acting metabolites – nor-LAAM and dinor-LAAM – which account for LAAM's opiate activity. Effects develop slowly and, as the long-acting metabolites accumulate, are prolonged. Because the metabolites are long-acting, most patients can be successfully maintained with doses of LAAM administered three times a week, instead of daily.

Parenteral injection of LAAM produces no immediate opiate effects. The slow onset of the opiate effects after oral or parenteral administration reduces the chances that addicts will want to inject it or even ingest it. LAAM should have minimal street value as a drug of abuse, and consequently, patients should have little incentive to divert it.

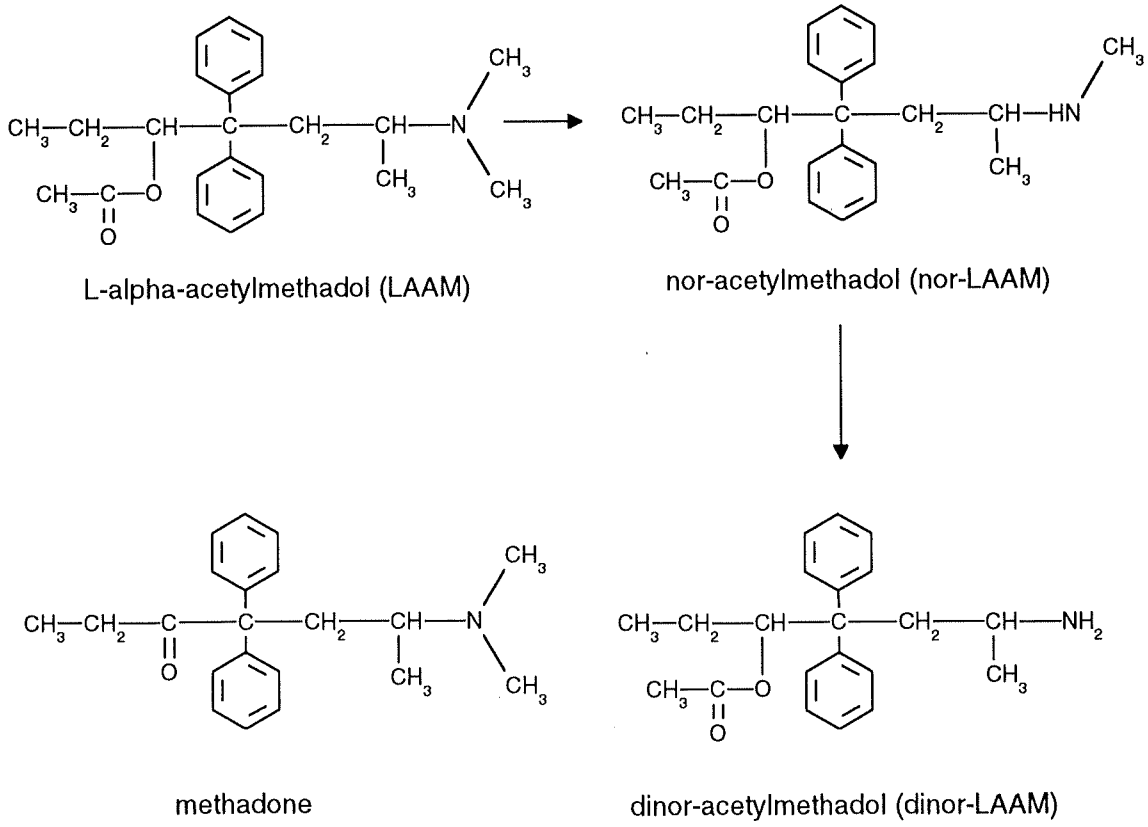
References

FDA, Levo-alpha-acetyl-methadol (LAAM) in maintenance: revision of conditions for use in the treatment of narcotic addiction. Federal Register, July 20, 1993; 58 (137):38704-38711.

Department of Justice, Drug Enforcement Administration, LAAM moved to schedule II. Federal Register, August 18, 1993; 58(158):43795.

MERF Scholarship

To increase the learning opportunities for residents, the Medical Education and Research Foundation for the Treatment of Alcoholism and Other Drug Dependencies offers scholarships for physicians in training to attend the conference "Addiction Medicine: State of the Art 1993" in Newport Beach on November 18-20. As part of the application, the resident is asked for suggestions for how to incorporate training and clinical experiences into his/her residency training program. The suggestions will be forwarded to the Committee on Education. □



Comparison of the chemical structure of LAAM and its metabolites to methadone

New Clinical Trial of Naltrexone in Treatment of Alcoholism

Dupont Merck is setting up a large, multi-center "usage study" of naltrexone (Trexan) in the treatment of alcoholism to start this year. The study will become part of a New Drug Application (NDA) seeking to add treatment of alcoholism as an indication for prescribing naltrexone. Currently, the only FDA-approved indication for naltrexone is prevention of relapse to opiate use. Although clinicians can prescribe medications outside FDA-approved indications, pharmaceutical companies cannot detail or advertize for an indication that is not FDA-approved.

A "usage study" is a relatively new type of open-label, clinical trial devised by FDA to learn how physicians will use a medication in actual clinical practice. The primary purpose is to aid in writing the package insert, not to establish safety or clinical efficacy. Physician investigators are given some flexibility in issues of medication induction and monitoring side-effects and toxicity.

Two completed clinical trials (CSAM News, Spring 1993) suggest that naltrexone is efficacious in preventing relapse to alcohol use. While the article in NEWS proposed that naltrexone's mechanism of action in reducing alcohol relapse was related to blocking the effect of endogenously produced opiates (TIQs), the mechanism is still being debated. □

Donald R. Wesson, MD

CMESA

Medical School Curriculum

The Consortium of Medical Educators in Substance Abuse (CMESA) has published *Essential Requirements for Medical Education in Substance Abuse,* a seven-page outline of essential knowledge, attitudes, skills and behaviors, and activities for undergraduate medical education. In the introduction, the authors explain "the emphasis in these 'essentials' is on experience and course work most likely to produce changes in practice behavior, rather than on those that may only increase general knowledge of substance abuse." Copies are available from the CSAM office.

CMESA is comprised of faculty representatives from the California and Nevada schools of medicine. CSAM is an associate member represented by Spencer W. Shaw, MD, and Gail Jara. □

An Overview of the Membership of the California Society of Addiction Medicine

California Society surveys its members periodically to gather descriptive information about the members and to learn how members evaluate the services and benefits provided. The responses to the survey completed in 1993 are displayed here and compared to the 1991 information. The specialty distribution has changed only slightly in the last two years; in the same period the number of members has dropped, but individuals appear to be more responsive (more returned survey forms this year). In 1993 there is an equal number of psychiatrists and internists; in 1991, psychiatrists outnumbered internists by about 10%. In 1993, most members report their specialty as internal medicine (26%), psychiatry (26%), family practice (17%), or addiction medicine (16%). All other specialties account for the remaining 15%. That proportional distribution has not changed from 1991. □

Survey Responses		
	1993	*1991*
Responded to survey	135 (47%)	112 (35%)
ASAM certified	197 (71%)	231 (71.5%)
Total number of members	278	323

What percent of your time is devoted to working in the public sector?		
% time in public sector	*Number in 1993*	*Number in 1991*
100%	9% (12)	6% (7)
80-99%	3% (4)	4$ (5)
50-79%	4% (5)	4% (5)
20-49%	4% (5)	6% (7)
less than 20%	13% (17)	21% (24)
No response	67% (94)	57% (64)

Do you treat patients for diseases other than chemical dependency?*		
	Number in 1993	*Number in 1991*
Gambling	16% (22)	21% (22)
Eating Disorders	36% (48)	39% (44)
Sexual Compulsion	19% (26)	21% (24)
Co-dependency	52% (70)	53% (59)

**Respondents marked as many answers as were applicable; therefore, the total percent of responses for this question does not equal 100%.*

What percent of your practice is devoted to addiction medicine?		
Percent of practice	*Number in 1993*	*Number in 1991*
100%	18% (24)	23% (26)
80-99%	10% (14)	95 (10)
50-79%	15% (20)	19% (21)
20-49%	25% (34)	27% (34)
less than 20%	21% (29)	15% (17)
No response	11% (16)	7% (8)

What percent of your income is derived from your practice in addiction medicine?		
Percent of income	*Number in 1993*	*Number in 1991*
100%	16% (21)	22% (25)
80-99%	9% (12)	8% (9)
50-79%	17% (23)	17% (19)
20-49%	17% (22)	21% (24)
Less than 20%	27% (37)	17% (19)
No response	14% (19)	14% (6)

Over the last four years, has the percentage of your income which is derived from your work in addiction medicine gone up, down, or has it remained the same?		
Income from ADM work	*Number in 1993*	*Number in 1991*
Gone up	17% (24)	26% (29)
Remained the same	42% (57)	52% (57)
Gone down	23% (31)	18% (2)

SURVEY RESPONSES

What is the *one* most important thing the California Society can accomplish for its members in the next 12 months?

Give a voice to addiction medicine in California and national heath care reform.

Make sure that Hilary pays us for addiction Rx!!

Treatment outcome research results communicated to public policy makers.

Taking a public stance in ending the drug war, developing options to criminalization and absolute prohibition. This drug war is the most devastating social problem and drugs are not the cause of the problems – it's prohibition and the violent black market.

Establish addiction medicine as a primary specialty.

Work on recognition of Certificates of Added Qualifications with the medical boards; continue working toward Board status; recognition of specialty in eyes of medical boards and third-party payers.

More focus on specific treatment and public policy. Do not waste time on creating a board. ASAM certification is reputable, recognized, and credible. Enough of processing paper! Get more visibility for clinical work and participate in getting included in medical payment reform before we are forgotten.

Political action regarding treatment programs – positioning the Society/providers for the era of managed competition. Forming a statewide IPA and going after what's necessary to have a viable system. Local IPAs succeed.

Research (clinical).

Work to coordinate treatment with database and payers.

Successful and well-run State of the Art Course; bring us the best and latest info on treatment.

Accessible, modestly priced, one-day or weekend "State of the Art" educational meeting(s).

Improve and expand teaching of addiction in medical schools; support for teachers and residents.

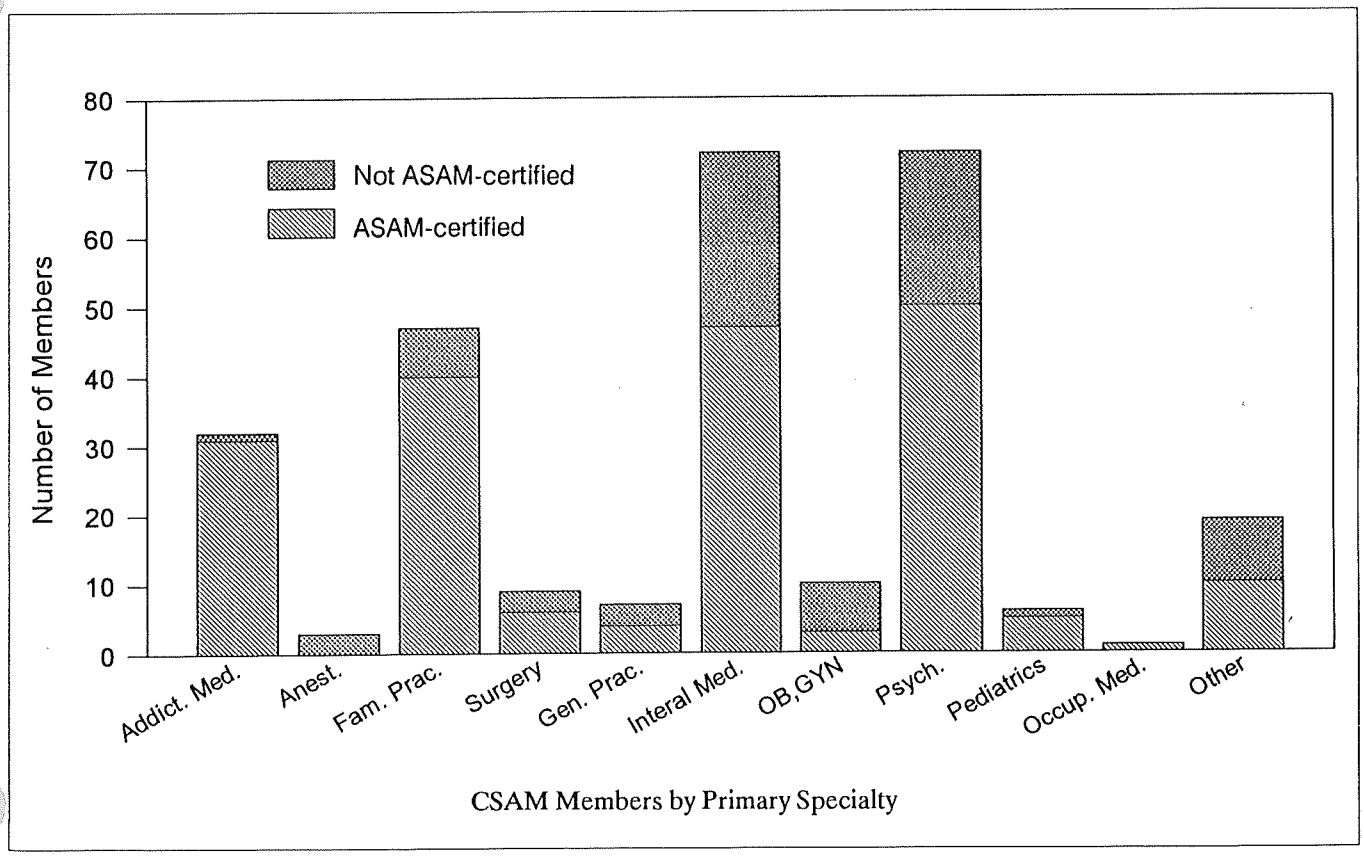
Inform members about current issues/topics in addiction medicine field (medical-political) and present a balanced representation of controversial topics.

Help the members confront problematic issues in MRO work.

Ensure a viable Diversion Program for physicians.

Newsletter updates.

A unity of spirit and a vision of a shared and common purpose! □



CSAM Members by Primary Specialty

CONTINUING MEDICAL EDUCATION

ASAM's 6th National Conference on Nicotine Dependence

November 11-14, 1993, Marriott Marquis Hotel, Atlanta
Fees: $250 for members; $300 for non-members; $200 for non-physicians
Credit: 13 hours
Speakers include Paul Earley, MD; Terry Rustin, MD; David P. Sachs, MD; Max Schneider, MD; John Slade, MD
For information, contact ASAM, 5225 Wisconsin Avenue, NW, Washington, DC 20015; 202/244-8948.

CSAM Leadership Conference

Hospital Medical Staff Committees on the Well-being of Physicians

Saturday, February 5, 1994, Sacramento
Fees: $75 for individuals; $130 for hospitals plus $15 per person from the hospital
Speakers include Chet Pelton; William Brostoff, MD; Donald Gragg, MD: Garrett O'Connor, MD; Kimberly Davenport, Esq.
For information, contact CSAM, 3803 Broadway, Oakland, CA 94611; 510/428-9091.

At the California Medical Association Western Scientific Assembly, March 17-20, 1994

Recognition and Management of Drug and Alcohol Emergencies in Primary Care

March 19, 1994, Disneyland Hotel, Anaheim
Sponsored by the CMA Section on Psychiatry and the California Society of Addiction Medicine
Speakers include Steven Batki, MD; William Brostoff, MD; John J. McCarthy, MD; Richard K. Ries, MD; Max Schneider, MD
For information, contact Robert Sparacino, CMA, 415/882-5180.

ASAM's 25th Annual Medical-Scientific Conference

April 15-17, 1994; Marriott Marquis Hotel, New York
Speakers include Enoch Gordis, MD; Dorynne Czechowicz, MD; Richard Fuller, MD; John Slade, MD; Sidney Schnoll, MD, PhD; John Morgan, MD; David Gorelick, MD
For information, contact ASAM, 5225 Wisconsin Avenue, NW, Washington, DC 20015; 202/244-8948.

CSAM Activities

At the meeting of the Executive Council in August, an **ad hoc Committee on Social Model Treatment Programs** was named and charged to explore methods of providing the services of physicians to treatment programs in the public sector and to serve as a broker to bring physicians into contact with the programs. Donald Gragg is the Acting Chair of this new group; Nicola Longmuir, Spencer W. Shaw, and Merritt Smith are members. At their first meeting, it was agreed to meet with the Director and key staff members of a program which administers a number of social model residential and nonresidential recovery programs in Alameda, Contra Costa and Solano Counties.

The **Committee on Physician Impairment** and the **Committee on Education** are the planners for a Leadership Conference on Hospital Medical Staff Committees on the Well-being of Physicians to be held in Sacramento in February. Registration by hospital is encouraged; one fee, $130 (plus $15 per person), pays for as many persons as the medical staff wants to send. Individuals can register for $75. This is the second in this series of workshops; the first was given in San Francisco in March, 1993. Twenty-seven hospitals were represented. The 102-page syllabus from this workshop is available from the CSAM office; the cost is $5.

The **Collaborative Study of Addiction Treatment Outcome** completed its second workshop for representatives of managed care companies, treatment providers and payers. On September 10-11, 1993, 16 registrants gathered for a day and a half to discuss how to reach consensus on common variables to be used in a database to describe patients and treatment. This project responds to the need for a common language to aid communication among these three groups and with outcome researchers. Participants ranked proposed patient variables according to their usefulness in assessing the patient's short-term response to treatment, the patient's long-term response, the cost-benefit implication of providing the treatment. The variables were also ranked for how easy/difficult it would be to gather the appropriate information. □