Defeating DTs

33 years ago a groundbreaking study established the new benzodiazepine drugs as the treatment of choice for preventing life-threatening complications from alcohol withdrawal, making detoxification safer and easier for thousands of alcoholics. Below, expert commentary on the study; opposite, the reflections of the lead researcher.

by **Edward M. Sellers**

At the time of writing Dr Sellers was Professor of Pharmacology, Medicine, and Psychiatry, at the University of Toronto and a senior scientist at the Addiction Research Foundation in Toronto

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Background text

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The seriousness of alcohol withdrawal and its widespread occurrence in the 166 US Veterans Administration hospitals for ex-service men and women in the 1960s was the principal stimulus for this pivotal study.[1] The important work by Kaim and colleagues has endured over the years, because alcohol withdrawal still is common, potentially life-threatening, and often not recognised and treated promptly and effectively.

Kaim and colleagues studied the efficacy of four drugs commonly used at that time to treat alcohol withdrawal, specifically the more serious symptoms of delirium tremens and convulsions. The four were chlordiazepoxide (a benzodiazepine), chlorpromazine (a neuroleptic or antipsychotic), hydroxyzine (a sedating antihistamine), and thiamine (a vitamin). The results helped establish benzodiazepines as drugs of choice in treating alcohol withdrawal. To fully understand the context for the study, it is useful to consider the state of pharmacological treatment of withdrawal at that time.

A commentary on: Kaim S.C., Klett C.J., Rothfeld B. "Treatment of the acute alcohol withdrawal state: a comparison of four drugs." American Journal of Psychiatry: 1969, 125 (12), p. 1640–1646.

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Randomised trial cuts through the confusion

During the 1950s and early to mid-1960s, several initial studies had suggested that the antipsychotics promazine and chlorpromazine were effective in treating alcohol withdrawal. Later studies did not confirm these findings; several suggested that the incidence of serious symptoms such as seizures and delirium might actually be *higher* after administration of these agents.[2] Based on today's knowledge, such complications would indeed be expected because these drugs decrease the seizure threshold by making the brain more susceptible to spontaneous cellular electrical activity. They also disrupt cellular communication, resulting in changes in body function such as gastrointestinal disorders.

Chlordiazepoxide was first marketed in 1961. That same year, Kaim and Rosenstein observed that in alcohol withdrawal:[3] "Librium [chlordiazepoxide], in higher dosage of 200 to 300mg, daily, brings prompt and gratifying control of both the psychotic and convulsive phenomena without the toxicity experienced with the use of phenothiazines, reserpine, or even the barbiturates."

Research evidence to support this clinical observation was first presented orally by the authors in 1967 and then published in their 1969 report. Presumably, these early impressions provided the stimulus for their more formal study of the four agents.

Another of the four agents was thiamine. It may seem curious now that a vitamin was included. However, because many alcoholics do not eat a well-balanced diet, in the 1960s it was believed that nutritional deficiencies might be related to the severity of withdrawal and its complications. Only in the mid-1950s was it first demonstrated that abrupt discontinuation of alcohol in well-nourished individuals was still followed by alcohol withdrawal and seizures.[4]

In the 1960s there was also controversy over whether early treatment of alcohol withdrawal symptoms could prevent progression to delirium tremens.[5] In their article, Kaim and colleagues suggested that early treatment could indeed halt progression of the withdrawal state. Similarly, what caused seizures during withdrawal and how they could be prevented was uncertain. Kaim and co-workers found that compared to placebo, chlordiazepoxide decreased the risk of seizures and that chlorpromazine increased it. Based on these findings, the researchers deduced that the seizures resulted from a general neuroadaptive change in the brain caused by the withdrawal of alcohol. Such changes could be modified by pharmacological factors and varied among individual patients.

'60s study still relevant

Several important aspects have continued to set the work of Kaim and colleagues' apart from that of other researchers. For example:

- The study was quite large (537 patients); no study, before or after, has been larger.
- It was conducted in 'real life' clinical care settings across the United States.
- A significant number of patients who received only a placebo (inactive medication) had positive treatment outcomes, demonstrating what a powerful treatment simple supportive care could be in some patients. Later work has confirmed a high placebo response in terms of subjective symptoms such as anxiety and non-serious physical signs such as tremor.[6] However, placebo does not decrease the risk of serious complications including seizures and delirium.
- It demonstrated that progression of alcohol withdrawal to delirium tremens could be prevented by chlordiazepoxide. Incidentally, it probably understated the drug's potential in this regard because patients received only 50mg every six hours administered intramuscularly and orally. A more flexible dosing schedule with higher doses might well have shown better efficacy, and intramuscular injections probably resulted in rather low and initially inconsistent levels of the drug in the blood.
- It also showed that chlorpromazine *increased* the risk of seizures during withdrawal. Treatment of alcohol withdrawal syndrome with a benzodiazepine is rarely associated with seizures.[6]
- The study used appropriate clinical criteria to identify and diagnose alcohol withdrawal: gastrointestinal distress, sweating and flushing, insomnia, tremor, irritability, apprehension, depression,

and clouded sensory perception or confusion. Since the 1960s, these criteria have been quantified and defined more precisely, but still they have largely been validated.[7] The study did not use a graded measure of withdrawal severity so was unable to detect differences in patients' times of response to each drug. As a result it probably presented a conservative estimate of the differences between them.

A similar study today would probably: include a more detailed characterisation of the patients; use a validated and standardised measure of alcohol withdrawal;[8] show the patient's time of response to each drug; statistically analyse the likelihood that a patient would experience complications or have a successful treatment outcome; and allow researchers to administer more medication earlier in the treatment.[6] Finally, considering what is now known about thiamine, it is unlikely that it would be included. Even the use of a placebo control group would be controversial because of the substantial risk of serious complications among non-treated patients.

Apart from its general lessons, this seminal article probably had still another major impact on treatment. It created within the Veterans Administration system an increased awareness of, and interest in, treating alcohol withdrawal effectively. From a broader perspective, since shortly after its publication benzodiazepines have continued to be the drugs of choice for alcohol withdrawal.[5] Although refinements have been made in measurement, dose schedules, research designs, and data analysis, the results of this seminal trial have been repeatedly confirmed in clinical practice. Furthermore, many of the observations have been incorporated into 'clinical pearls' (eg, always treat a patient experiencing alcohol withdrawal with a benzodiazepine first before you give a neuroleptic if the patient is hallucinating). We now know that some patients may need a drug such as haloperidol in addition to a benzodiazepine to fully treat their withdrawal.

1 Kaim S.C. *et al*. "Treatment of the acute alcohol withdrawal state: a comparison of four drugs." *American Journal of Psychiatry*: 1969, 125 (12), p. 1640–1646.

2 Sereny G. *et al*. "Comparative clinical evaluation of chlordiazepoxide and promazine in treatment of alcohol withdrawal syndrome." *British Medical Journal*: 1965, 1, p. 92–97.

3 Kaim S.C. *et al*. "Experience with chlordiazepoxide in the management of epilepsy." *Journal of Neuropsychiatry*: 1961, 3, p. 12–17.

4 Isbell H. *et al*. "An experimental study of the etiology of 'Rum Fits' and delirium tremens." *Quarterly Journal of Studies on Alcohol*: 1955, 16, p. 1–33.

5 Sellers E.M. *et al*. "Drug therapy: alcohol intoxication and withdrawal." *New England Journal of Medicine*: 1976, 294, p. 757–762.

6 Sellers E.M. *et al*. "Diazepam loading: simplified treatment of alcohol withdrawal." *Clinical Pharmacology and Therapeutics*: 1983, 34(6), p. 822–826.

7 Sellers E.M. *et al*. "Characterization of DSM–III–R criteria for uncomplicated alcohol withdrawal provides an empirical basis for DSM–IV." *Archives of General Psychiatry*: 1991, 48(5), p. 442–447.

8 Sullivan J.T. *et al*. "Assessment of alcohol withdrawal: the revised Clinical Institute Withdrawal Assessment of Alcohol scale (CIWA–Ar)." *British Journal of Addiction*: 1989, 84, p. 1353–1357.

HINDSIGHT

Keen eye and collaboration helped clarify 'muddied' field

by **Samuel C. Kaim**

At the time of the study Dr Kaim was director of alcoholism and related disorders at the US Veterans Administration

In 1958–1959 I was one of the original clinical investigators of the first benzodiazepine, chlordiazepoxide. My study[1] was conducted in a Veterans Administration hospital, where I headed the neuropsychiatry section. Among the subjects were eight alcoholic patients who had suffered convulsive seizures. At doses of 200 to 300mg daily, chlordiazepoxide appeared to prevent further seizures and the onset of delirium tremens.

Ten years later, when I headed the Veterans Administration's Drug and Alcohol Dependence Service, I decided to test chlordiazepoxide against three other agents and a placebo in the treatment of alcohol withdrawal states. At the time it was said that there was no adequate data to prove that any of the newer psychoactive drugs was effective in preventing the development of delirium tremens.[2] Indeed, the field was muddied: paraldehyde, thiamine, phenothiazines, barbiturates, alcohol tapering, all had their advocates.

The Veterans Administration system played a pioneering role in establishing collaborative, multi-site drug studies. Jim Klett headed the lab entrusted with the collection and analysis of data from psychotropic drug studies. With Jim's capable help and the contributions of the investigators in 23 Veterans Administration hospitals, we embarked on this large-scale study.

The first indication that the study was influencing the alcohol field came from Dr Favazza, psychiatry professor at the University of Missouri. In 1973 he sent a questionnaire to hospitals with psychiatry residencies.[3] Of the 101 useable responses, 64 listed chlordiazepoxide as their primary drug of choice for treating alcohol withdrawal and 22 another benzodiazepine, diazepam. Our study was cited most often as influencing their adoption of chlordiazepoxide.

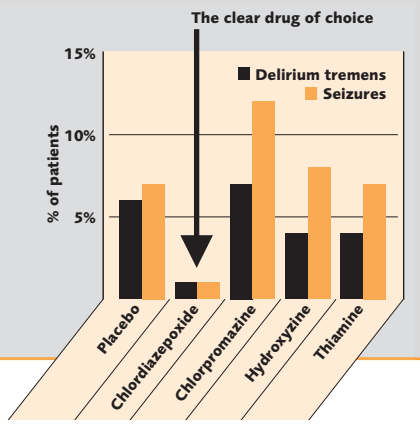
A further indication of the acceptance of our study's results was its inclusion by the US National Institute on Alcohol Abuse and Alcoholism in their selection of 16 "seminal" articles over the past 25 years in the field of alcohol research. Commentaries on the studies were featured in the edition of *Alcohol Health & Research World* which marked the NIAAA's 25th anniversary in 1995.[4] It is gratifying to know that one's work has led to a 'standard' therapy in medicine, at least in the US. Perhaps your re-publication of Dr Sellers' commentary will do the same in Europe.

1 Kaim S.C. *et al*. "Anticonvulsant properties of a new psychotherapeutic drug." *Diseases of the Nervous System*: 1960, 21 (suppl.), p. 46–48.

2 Victor M. "Treatment of intoxication and the withdrawal syndrome." *Psychosomatic Medicine*: 1966, 28, p. 636–650.

3 Favazza A.R. *et al*. Chemotherapy of delirium tremens. Personal communication, 1973

4 *Alcohol Health & Research World*: 1995, vol. 19, no. 1, p. 34–35.



The results which clinched the issue of how to treat alcohol withdrawal: chlordiazepoxide reduced the incidence of seizures and delirium, chlorpromazine was worse than doing nothing (ie, placebo), the other two substances were simply useless. Suddenly the choice was clear, but up to then ineffective or downright dangerous drugs had often been the order off the day.