Therapeutic Reviews

The Treatment of Alcohol Withdrawal

Sally K. Guthrie, Pharm.D.

Abrupt cessation of regular use of alcohol in a dependent person causes a withdrawal syndrome that may range from mild to extremely severe. Most patients require pharmacologic intervention, especially those with severe symptoms. Historically, the pharmacotherapy of alcohol withdrawal has involved a wide variety of agents. Benzodiazepines are currently preferred due to their consistently high degree of efficacy and laudable record of safety. In addition, ß blockers and clonidine are useful, as both effectively combat the hypertension and tachycardia commonly associated with withdrawal. They are ineffective as anticonvulsants; however. Opinions differ concerning the best treatment for withdrawal seizures. Prophylaxis with benzodiazepines may be all that is required, although some authors advocate the use of phenytoin for 5 days, especially in persons with a history of prior seizures during alcohol withdrawal. Once established, delirium tremens are difficult to treat. Benzodiazepines are most commonly used to provide sedation, and extremely large doses may be required. Careful clinical assessment is essential to the proper treatment of patients undergoing alcohol withdrawal since the coexistence of medical problems may complicate the condition.
(Pharmacotherapy 1989;9(3):131–143)

OUTLINE

Alcohol abuse is a widespread problem in Western society, implicated in at least 50% of single-vehicle traffic accidents in the United States.[1] It is also a predisposing factor to death from medical causes such as pancreatitis,[2,3] damage to the liver resulting in cirrhosis and esophageal varices,[4,5] and cardiac failure.[6] Abrupt cessation of intake frequently results in a withdrawal syndrome that ranges in severity from very mild to fatal.

From the College of Pharmacy, University of Michigan, Ann Arbor, Michigan.

Address reprint requests to Sally K. Guthrie, Pharm.D., College of Pharmacy, University of Michigan, Ann Arbor, MI 48109-1065.

The natural progression of the alcohol (in this review, ethanol exclusively) withdrawal syndrome was studied by two groups of researchers in the 1950s and 1960s. Alcohol was administered to 10 adequately nourished morphine addicts for varying periods of time, to determine if an alcohol withdrawal syndrome would occur in the absence of nutritional deficiency.[7] Of the 10 patients originally entering the study, 4 dropped out after 34 or fewer days of continuous alcohol ingestion. All experienced mild withdrawal symptoms consisting of tremulousness, nausea, perspiration, and insomnia. The remaining six patients drank for periods ranging between 48 to 87 days. On withdrawal all developed tremors, marked weakness, nausea, vomiting, diarrhea, fever, and hypertension. Two experienced seizures, two had transient visual or auditory hallucinations or both, and three developed delirium tremens. The authors concluded that withdrawal symptoms are related to the duration of alcohol ingestion rather than a specific nutritional deficiency.

In another study 10 prison inmates with prior histories of alcoholism received 86 proof (43%) alcohol for 24 days.[8] The amount was increased daily in a stepwise manner, ending with 40 ounces per day

Table 1. Alcohol Withdrawal Symptoms

Symptom	Usual Time of Onset After Last Drink	Usual Duration
Vivid dreams, insomnia	As alcohol leaves the body	48 hrs
Tremor, nausea and/or vomiting, tachycardia (>110 bpm), hypertension (<150/90)	Within 6–24 hrs	48 hrs
Hallucinations	Variable	Variable
Convulsions	6–48 hrs	Usually 1–2 grand mal-type convulsions (although can be more numerous and possibly fatal)
Delirium tremens	Day 3–5	2–3 days

[a]Data derived from references 7, 8, and 9.

during the last 6 days. After alcohol ingestion was abruptly discontinued on day 24, eight subjects developed withdrawal symptoms within 24 hours. Tremor and hyperreflexia occurred first. Four subjects experienced visual hallucinations within 24 hours of discontinuing alcohol. Most had episodes of mild tachycardia, occurring frequently within 3–8 days after stopping drinking. Most were also anorexic for the first 2 days of withdrawal, although no nausea and or vomiting was reported. This study provided a useful clinical description of mild to moderate alcohol withdrawal syndrome, but factors other than the duration of continuous intake appeared to account for the severity of the symptoms.

Clinical Features

The clinical manifestations of alcohol withdrawal range from mild to severe (Table 1). Symptoms developing as the alcohol concentration in the body decreases include insomnia and vivid dreams. Within several hours after stopping drinking symptoms typically include anxiety, mild agitation, anorexia, tremor, sleeplessness, mild tachycardia (>110 beats/min), hypertension (blood pressure >150/90 mm Hg), diaphoresis, and nausea and vomiting. These symptoms usually peak between 24 and 36 hours and may disappear after 48 hours. It is often stated that the relationship between the blood alcohol level and the severity of the alcohol withdrawal syndrome is more closely related to the rapidity of the level's fall than its height at the onset of withdrawal.

Hallucinations

Hallucinations unrelated to the presence of delirium tremens may occur in 3–10% of patients during withdrawal.[10,11] They are most likely to be visual, although they may be auditory, tactile, or even olfactory. Both duration and onset of the hallucinations are highly variable. They can occur within hours of the last drink and have been reported while the patient is still drinking, but typically begin after several days of abstinence. The hallucinations may last only hours, persist for weeks, or even on occasion become permanent. Patients are rarely disoriented and may retain the ability to recall the hallucinations at a later date.[12] Since the content and intensity of these hallucinations may be similar to those seen in schizophrenics,[13] an accurate history of previous alcohol use is essential for proper diagnosis.

Withdrawal Seizures

Withdrawal seizures or "rumfits" occur within 6–48 hours of alcohol cessation or decrease in intake. They generally consist of one or two grand mal seizures, and rarely develop into status epilepticus.[14] A careful differential diagnosis should be entertained, as withdrawal seizures may be hastened by underlying pathologic states such as previous head injury and epilepsy. They are not usually associated with an epileptic focus on postictal electroencephalogram (EEG).[15,16] If the patient has not previously been evaluated, an EEG performed during and after recovery from the seizure will help rule out idiopathic epilepsy. Focal seizures during withdrawal are unusual and deserve further evaluation to rule out space-occupying lesions or a seizure focus secondary to head trauma. The possibility of simultaneous withdrawal from numerous drugs should always be considered. Therefore, a serum or urine toxicology screen is appropriate in all of these patients. Status epilepticus may be associated with meningitis, head trauma, cowithdrawal from sedative hypnotic agents, or epilepsy.[17]

Seizures occur in between 5 and 15% of patients undergoing withdrawal and their likelihood increases with the duration of alcohol abuse.[9,14] Their etiology is unknown, although a so-called kindling model was hypothesized[18] in which withdrawal results in hyperirritability providing low-intensity electrical stimulus of the central nervous system. Seizures may occur after numerous withdrawal episodes. There is some evidence to support this theory, as the drop in seizure threshold during withdrawal has been shown to be directly related to the duration of alcohol ingestion.[19]

Delirium Tremens

Delirium tremens (DTs) is the most severe mani-

festation of this syndrome. It occurs in less than 5% of patients hospitalized for alcohol withdrawal.[9] Seizures frequently precede DTs and rarely follow its onset; however, the occurrence of seizures does not automatically indicate that DTs will follow. Onset is usually on the third to fifth day of withdrawal, although the range is large.[9] In one study DTs lasted a mean of 56 hours, with a range of 10–150 hours.[20]

The key symptoms are disorientation, confusion, visual hallucinations, and profound autonomic hyperarousal. Patients may also be hyperpyrexic, tremulous, incontinent, and diaphoretic. As a result, they often are unable to feed themselves or take oral medication. Because of the extreme agitation that is frequently observed, patients often require physical restraints not only for their safety but for the safety of the hospital staff as well.[21]

Early withdrawal manifestations are reversible and much more readily treated than DTs.[20] Patients with DTs are frequently febrile, agitated, and disoriented, and thus concurrent illnesses such as pneumonia and encephalopathy may be difficult to diagnose.

Early in this century, mortality for patients experiencing untreated DTs was estimated to be as high as 15%; the current estimate is approximately 2%.[9, 22] This is almost certainly due to earlier and more appropriate supportive and pharmacologic management. Patients at greatest risk of dying are those older than 45 years who have concomitant medical or surgical illness such as fever (>104°F, 40°C), pneumonia, pancreatitis, malnutrition, dehydration, electrolyte imbalance, trauma, or hemorrhage.[21, 23, 24] Death most often results from medical complications such as myocardial infarction, respiratory arrest, or sepsis.

Treatment

Therapeutic objectives guiding the treatment of alcohol withdrawal include providing symptomatic relief and preventing medical complications. Although nonpharmacologic means may achieve the former, drug therapy is almost always required to meet both objectives. In addition, these patients are almost always more uncomfortable without some form of medication. Patients undergoing severe withdrawal and those with concomitant medical or surgical complications almost always require pharmacotherapy and always must be admitted to the hospital. Persons experiencing mild withdrawal may respond to nonpharmacologic therapy but prudence usually dictates hospital admission for careful observation.

Nonpharmacologic Intervention

Several groups have investigated the efficacy of nonpharmacologic intervention in alcohol withdrawal.[11, 25, 26] Such measures as reassurance, reality orientation, monitoring signs and symptoms of withdrawal, and general nursing care are frequently sufficient. It is important, however, to assess these patients carefully and manage them vigorously when necessary, and not run the risk of undertreating them.

A randomized, placebo-controlled trial was conducted in 41 withdrawing alcoholics.[26] Half received supportive care plus 2 mg sublingual lorazepam every 2 hours for a total of 3 doses; the rest received supportive care with sublingual placebo. The treatment was judged successful if the score on the clinical institute withdrawal assessment scale for alcohol (CIWA-A) was above 10. Treatment failures were more common in the placebo than in the lorazepam group (15% vs 4.8%), but 85% of those receiving placebo underwent withdrawal without pharmacologic intervention. Of three patients in the nondrug group who were considered treatment failures, one experienced a seizure and the other two had a CIWA-A score above 10. One patient of the 21 receiving lorazepam had a CIWA-A score above 10. No patient in either group developed DTs. The rate of decrease in symptoms was more rapid during the first 2 hours in the group receiving lorazepam.

Vitamin, and Fluid and Electrolyte Management

Hydration during alcohol withdrawal is not usually necessary[21] unless intractable vomiting or diarrhea is present. Withdrawal is associated with an increase in vasopressin plasma levels, which have been associated with an increase in brain water.[27] Aldosterone plasma levels are also elevated.[28] Consequently, overaggressive hydration is not only unnecessary, but could be harmful. Most patients are able to take sufficient fluids orally, and intravenous administration is rarely required. The presence of DTs may, however, cause severe dehydration[21] due to increased body temperature, diaphoresis, and agitation, combined with inability to take fluids orally. In these patients, inadequate rehydration may result in increased mortality.

Several vitamin deficiencies occur in alcoholics; for example, overt or subclinical thiamine deficiency has been reported in 30–80%.[29, 30] Thiamine deficiency is particularly important because it has been associated with the Wernicke-Korsakoff syndrome. In its severe, classic form, it is manifested by drowsiness, confusion, ataxia, abnormal ocular movements (which include paralysis of eye muscles and nystagmus), and an amnestic confabulatory state. Milder forms clearly exist, however. While thiamine deficiency may occur in 30% or more of chronic alcoholics, the Wernicke-Korsakoff syndrome only occurs in 3–10%.[31] Thiamine is nonetheless frequently given to withdrawing alcoholics in dosages of 50–100 mg daily. It is unknown if daily thiamine replenishment is necessary, however, most experts recommend that a dose of 100 mg be given initially.[21, 32] The abnormal ocular findings that occur with this deficiency reverse within 6–8 hours after emergency thiamine administration.[32] The vitamin should

Table 2. Alcohol Withdrawal Studies

Reference	Drug Therapy	Design	Population	Dose	Outcome
Acute withdrawal					
Benzodiazepines					
43	Cdx vs m+p	Double-blind, placebo-controlled	70	50 mg qid & 25 mg qid cdx 400 mg + 50 mg m+p	Promazine felt to be superior by authors; both superior to placebo.
44	Cdx, chlorpromazine, hydroxyzine, thiamine	Double-blind, placebo-controlled	538	Flexible dosing after 1st day	All patients improved, but cdx patients had fewer seizures and fewer developed DTs; all superior to placebo.
45	Cdx vs promazine	Double-blind, placebo-controlled	58	200 or 400 mg/day cdx 400 or 800 mg/day prom	Both drugs effective, but promazine caused worse hypotension and more patients developed DTs; both superior to placebo.
Beta blockers					
46	Prop vs cdx vs cdx + prop	Double-blind, placebo-controlled	47	40 mg prop 25 mg cdx 40 + 25 mg prop + cdx	Prop effective for HR and BP but caused unacceptable level of hallucinations; combination more effective than placebo.
47	Atenolol	Double-blind, placebo-controlled	101	Dose individualized based on HR (none had greater than 100 mg/day)	Atenolol patients had shorter hospital stay and fewer benzodiazepines; vital signs normalized more quickly with atenolol.
Carbamazepine					
48	Carb vs chlormethiazole	Double-blind	68	800 mg carb, then tapered over 6 days	No significant differences in rate of decrease of symptoms or final outcome.
52	Carb vs barbital	Double-blind	72	Individualized	No significant differences, slightly more side effects in carb group.
53	Tiapride vs carb	Double-blind	60	600 mg/day carb	No significant differences in outcome, but more rapid decrease in fear and hallucinations in carb group.
54	Carb	Double-blind, placebo-controlled	105	800 mg/day tapered over 7 days	Both effective but withdrawal symptoms decreased more rapidly in carb group.
Clonidine					
55	Clon	Double-blind, placebo-controlled	60	0.15 mg tid tapered over 4 days	Clon had noticeable effects on tremor, sweating, systolic BP, tension, anxiety, and depression; patients also received other medication.
56	Clon	Double-blind, placebo-controlled, crossover	11	5 μg/kg	Clon significantly reduced HR, arterial BP, and overall withdrawal symptoms compared with placebo.
57	Clon vs chlormethiazole	Double-blind	17	300–600 μg q6h clon	All patients also received carbamazepine; greater reductions in HR and BP for clon but overall clinical withdrawal course did not differ.
58	Clon vs cdx	Double-blind	47	0.2-mg doses tapered over 60 hours	Both drugs effective for physiologic and psychologic withdrawal symptoms; clon significantly better for reducing systolic BP and HR.
Withdrawal seizures					
Phenytoin					
49	Phenytoin + cdx vs cdx + placebo	Double-blind, placebo-controlled	157	Phenytoin 300 mg/day × 5 days	All patients had seizure histories; 11 in placebo & 0 patients in phenytoin groups seized within 48 hours.

Table 2. Alcohol Withdrawal Studies (continued)

Reference	Drug Therapy	Design	Population	Dose	Outcome
50	Phenytoin + cdx vs placebo + cdx	Placebo-controlled	200	Phenytoin 200 mg bid × 5 days	No patients in either experienced seizures
Delirium tremens					
Benzodiazepines					
20	Diazepam vs paraldehyde	Randomized	34	Diazepam 10 mg i.v. then 5 mg i.v. q 5 min until calm, or paraldehyde 10 ml by rectum q30 min until calm	Both drugs calmed patients but paraldehyde was associated with apnea in 4, 2 of whom died.
51	Diazepam vs barbital	Double-blind	91	Diazepam up to 200 mg/day, barbital up to 5 g/day	No difference in milder withdrawal, but barbital superior in fully developed DTs.

Cdx = chlordiazepoxide; m + p = meprobamate plus promazine; prop = propranolol; clon = clonidine; HR = heart rate; BP = blood pressure.

be administered prior to intravenous glucose, as it is a cofactor necessary for glucose metabolism. In an already thiamine-deficient patient, intravenous glucose alone can precipitate a dramatic fall in plasma thiamine levels. Indeed, severe and irreversible cerebellar and brain stem damage has been reported when glucose was administered to withdrawing alcoholics without concomitant thiamine.

Deficiencies of folic acid, pyridoxine, and nicotinic acid are also common in alcoholics, although B_{12} deficiency is rare.[29, 31, 33] In addition to malnutrition, thiamine and folic acid deficiency may result from an alcohol-induced decrease in intestinal absorption of these nutrients or a genetic abnormality in transketolase, the enzyme that uses thiamine as a cofactor.[34–36] If these or other vitamin deficiencies are present they should be corrected specifically. Although their value is unproved at present, multivitamin preparations are often given to these patients. They are certainly not likely to be harmful, and may be helpful.

Total-body levels of magnesium, calcium, phosphate, and zinc may be reduced. This may be due to decreased intake as well as increased urinary losses associated with alcohol ingestion.[32, 37, 38] Many withdrawing alcoholics have hypomagnesemia associated with respiratory alkalosis, and it was hypothesized that this might cause the development of DTs[39]; however, such does not appear to be the case.[40, 41] Hypomagnesemia can be corrected with magnesium sulfate 2 g every 6 hours intravenously for the first day of withdrawal,[21] assuming renal function is intact. Magnesium may be difficult to replenish with any rapidity using oral magnesium preparations because they cause diarrhea.

Hypokalemia may also be present, especially in patients suffering DTs.[24] It should be corrected as soon as possible to avoid cardiac arrhythmias. Some patients may also exhibit decreased plasma bicarbonate, but severe acidosis should prompt a search for complicating factors, such as ethylene glycol ingestion.

Drug Therapy

In general, many of the studies evaluating the efficacy of pharmacotherapy for alcohol withdrawal are poorly designed. A review of the currently available literature revealed that of the 89 papers published in English since 1954, only 29 randomized their subjects.[42] Most of these 29 studies contained other design deficiencies, such as highly subjective end points, no listing of exclusion criteria or dropouts, and no blinding of patients and physicians. Although more recent trials are better designed, many of their conclusions are based on the older, more poorly designed studies (Table 2).

Alcohol itself can be used to treat its own withdrawal syndrome. Most commonly this is the method chosen by alcoholics when symptoms occur. However, the ingestion of relatively large amounts[59] at frequent intervals is required to maintain a blood alcohol level of approximately 80 mg %. The amount then must be gradually decreased to zero. Alcohol follows Michaelis-Menten pharmacokinetics, and predicting dosage requirements is difficult. To complicate management further, the maximum concentration of alcohol that can be given intravenously is about 8%, and oral alcohol may aggravate gastrointestinal complaints.[60, 61] Other agents are clearly easier and safer to use.

Alcohol ingestion alters the clearance of many drugs that are metabolized hepatically, including those used to treat manifestations of alcohol withdrawal, such as phenytoin and chlormethiazole.[62] Short-term ingestion results in decreased clearance of many drugs while alcohol is in the body, and increased clearance once it has been eliminated from the body of a chronic user. In the case of a drug with a wide therapeutic range, such as diazepam, this is not of paramount importance. In the case of one with a narrow therapeutic range, however, such as phenytoin, this may assume great importance, since a small alteration in plasma concentration may result in a large difference in efficacy or toxicity.

Effective control can be achieved with agents that exhibit cross-tolerance to alcohol, such as the benzodiazepines, barbiturates, or nonbarbiturate hypnosedatives like paraldehyde and chlormethiazole. In addition, drugs such as clonidine, ß-adrenergic antagonists, and carbamazepine, which do not exhibit cross-tolerance with alcohol, also appear to be effective.

Benzodiazepines

High-affinity stereospecific receptors for benzodiazepines have been identified in the mammalian central nervous system.[63, 64] Binding of a benzodiazepine to its receptor appears to potentiate the pharmacologic actions of γ-aminobutyric acid (GABA) through actions at the benzodiazepine-GABA-chloride channel complex. Alcohol is thought to alter the binding of the benzodiazepine to its receptor.[65] Interactions at this receptor complex may be the basis for benzodiazepine-alcohol cross-tolerance.

Benzodiazepines are now the standard treatment for symptoms of alcohol withdrawal, although the belief that they are more effective than placebo is based on old and rather badly designed studies.[43-45] This class of drugs has superior anticonvulsant activity combined with a higher therapeutic index and ease of use when compared with other agents such as paraldehyde and barbiturates. Although they all do not have specific indications for alcohol withdrawal, many different benzodiazepines have been successfully used, including chlordiazepoxide, diazepam, lorazepam, oxazepam, clobazam, clorazepate, alprazolam, bromazepam, and flurazepam.[66, 67] They all possess anticonvulsant, antianxiety, and sedative effects that are effective in this condition.[68] Unfortunately, they are not effective in withdrawal hallucinations. Their potencies, onset of effect, and metabolic pathways clearly differ (Table 3).

The most widely studied agents are chlordiazepoxide and diazepam. Chlordiazepoxide has been shown to be more effective than placebo or no drug therapy in decreasing seizure frequency, restlessness, anxiety, tremor, and the development of DTs.[71] Both diazepam and chlordiazepoxide are biotransformed to desmethyldiazepam, a long-lived, active metabolite, and continuous dosing results in its accumulation. If this is not taken into consideration, excessive drowsiness, confusion, diplopia, ataxia, and sedation may occur. To avoid toxicity, large initial doses are often administered on the first day of withdrawal (e.g., chlordiazepoxide 100 mg or diazepam 20 mg titrated acutely to the patient's clinical state) until the patient is appropriately sedated. Both should be administered orally when possible, or intravenously if necessary, but intramuscular ad-

Table 3. Characteristics of Benzodiazepines Used in the United States[50]

Benzodiazepine	Onset After Oral Dose	Elimination Half-Life (hrs)	Clinically Important Metabolites
Oxidatively metabolized			
Chlordiazepoxide[a]	Intermediate	10–30	*N*-desmethylchlordiazepoxide *N*-desmethyldiazepam Demoxepam
Diazepam[a]	Rapid	20–80	*N*-desmethyldiazepam Oxazepam
Flurazepam	Rapid to intermediate	2.3	*N*-desalkylflurazepam
Prazepam	Slow	1.1	*N*-desmethyldiazepam
Alprazolam	Intermediate	10–12	None
Halazepam	Intermediate to slow	14	*N*-desmethyldiazepam
Triazolam	Intermediate	2–4	None
Clorazepate[a]	Rapid	Prodrug	*N*-desmethyldiazepam
Conjugated			
Oxazepam[a]	Intermediate to slow	6–12	None
Lorazepam	Intermediate	7–35	None
Temazepam	Intermediate to slow	6–13	None

Half-life of metabolites: *N*-desmethylchlordiazepoxide 16 hrs; *N*-desmethyldiazepam 50–200 hrs; *N*-desalkylflurazepam >100 hrs; demoxepam 40 hrs.

[a]Approved FDA indication for alcohol withdrawal.

Data derived from references 69 and 70.

ministration should be avoided. Doses are reduced to 25–50% of initial doses in a stepwise fashion on subsequent days.[66,71] Several treatment regimens for different benzodiazepines have been used, some of which are listed in Table 4.

A variation of the stepwise reduction strategy uses the long half-life of desmethyldiazepam and gives loading doses of diazepam 20 mg every 1–2 hours on the first day of withdrawal.[76] (In this study a median of 60 mg was given over 7.6 hours.) Dosing is titrated by clinical assessment of the patient at hourly intervals. This strategy affords the presence of a tapering plasma concentration of active drug over the entire withdrawal period of approximately 1 week.

Drugs with a long half-life are also useful for the large number of patients who refuse to stay in the hospital for the full course of therapy. Although any of the benzodiazepines may be used for symptomatic relief of withdrawal, those without active metabolites, such as oxazepam or lorazepam, must be dosed more frequently.

The use of benzodiazepines with a short half-life has been advocated in patients with possible hepatic dysfunction because these agents are not dependent on hepatic enzymatic metabolism, as they are generally glucuronidated rather than oxidatively metabolized. There is no convincing evidence that these agents are better tolerated than those with a long half-life when they are administered using a regimen that avoids long-term dosing and accumulation of active metabolites, such as the loading dose protocol described above. In the event that patients cannot take oral medication, lorazepam may be preferred, since it is available in a parenteral form that is completely absorbed intramuscularly.[77,78] Chlordiazepoxide is erratically absorbed when given intramuscularly, and the absorption of intramuscular diazepam varies depending on the site of injection.[69,79]

Table 4. Benzodiazepine Dosing Options in Acute Alcohol Withdrawal

Drug	Regiman (oral unless otherwise stated)		Reference
Chlordiazepoxide	Day 1	100 mg q6h	46
	Day 2	100 mg q8h	
	Day 3	100 mg q12h	
	Day 4	100 mg hs	
	Day 1	50 mg q8h + 50 mg × 1	72
	Day 2	50 mg q8h	
	Day 3	25 mg q8h	
	Day 4	25 mg bid	
Clorazepate	Day 1	30 mg initially, followed by 15 mg bid	73
	Day 2	15 mg tid	
	Day 3	15 mg bid	
	Day 4	7.5 mg tid	
	Day 5	7.5 mg bid	
Diazepam	Day 1	10 mg tid	74
	Day 2	10 mg, 5 mg, 10 mg	
	Day 3	5 mg tid	
	Day 4	5 mg bid	
	Day 1	20 mg initially, followed by 20 mg q2h until reaction controlled	17
Lorazepam	Day 1	2 mg q8h + 2 mg × 1	72
	Day 2	2 mg q8h	
	Day 3	1 mg q8h	
	Day 4	1 mg bid	
	Day 1	5 mg i.m.	75
	Day 2	Average daily oral dose 2 or 3 mg continued as long as needed	

ß Blockers

Elevated plasma and urinary concentrations of norepinephrine have been documented during alcohol withdrawal and symptoms such as tachycardia, hypertension, and tremors are probably due to increased noradrenergic activity.[80,81] Benzodiazepines, although effective against many withdrawal symptoms, do not possess any direct antiadrenergic effects.[46] In an investigation of hand tremor in alcoholic withdrawal, propranolol caused a 95% decrease in tremor magnitude.[82] A double-blind, placebo-controlled clinical trial randomized 60 patients to four different groups: placebo, chlordiazepoxide 25 mg every 6 hours for 24 hours, propranolol 40 mg every 6 hours for 48 hours, or propranolol combined with chloridiazepoxide.[46] Cardiac response was measured by ambulatory electrocardiogram. During the first 12–24 hours both propranolol and the combination decreased total arrhythmias and blood pressure more effectively ($p < 0.05$) than chlordiazepoxide alone. However, the dose of chlordiazepoxide was quite low. Four (27%) of 15 patients who received propranolol alone experienced hallucinations compared to none who received placebo or chlordiazepoxide. The occurrence of hallucinations secondary to propranolol administration is typically rare,[83] but appears to be increased during alcohol withdrawal.

Atenolol has been recently advocated in the treatment of alcohol withdrawal. When heart rate was 50–79 beats/minute patients received atenolol 50 mg daily; when it was 80 beats/minute they received 10 mg or a look-alike placebo. The length of hospital stay was significantly reduced for those receiving atenolol ($p < 0.02$), and vital signs (heart rate, blood pressure, temperature) returned to normal more rapidly.[47] The baseline clinical severity scores were never reported for this study, although the authors state that the patients were undergoing mild to mod-

erate alcohol withdrawal. There was no evidence of adverse effects in the atenolol group, including hallucinations. The decreased lipophilicity of atenolol should result in decreased accumulation in the central nervous system compared with propranolol.[84] Although atenolol's effects on vital signs were significantly greater, no significant differences were noted between atenolol and placebo with respect to clinical features (tremor, seizures, level of consciousness) or behavioral signs (anxiety, agitation, hallucinations). Because ß blockers cannot be expected to have significant effects on anxiety or seizures, a benzodiazepine will probably still be required in conjunction with a ß blocker for the optimum treatment of alcohol withdrawal.

Carbamazepine

Carbamazepine has been used extensively in Scandinavia for the treatment of alcohol withdrawal, but only four double-blind trials have been conducted. The drug was compared with chlormethiazole in 68 patients, with 34 randomly assigned to each treatment group.[48] The initial daily doses of carbamazepine and chlormethiazole were 800 and 2400 mg, respectively, and doses of both drugs were tapered over a 7-day period. No significant differences were reported between the groups in either the rate of decrease of withdrawal symptoms or final outcome. A Danish group[52] compared carbamazepine (n = 37) with barbital (n = 35) in 72 inpatients undergoing mild to moderate alcohol withdrawal. The duration of treatment and the dosages were individualized based on clinical judgment. No statistically significant differences were recorded in the rate of decrease of withdrawal symptoms, ultimate outcome, or patients' subjective evaluations. The group receiving carbamazepine reported slightly more side effects (dizziness and nausea).

Carbamazepine or tiapride was administered to 60 "predelirium" inpatients for 7 days.[53] Withdrawal symptoms, especially fear and hallucinations, were relieved more rapidly in the group receiving carbamazepine 600 mg/day, fixed dose, but the outcome was the same in both groups. In the only placebo-controlled, multicenter study, 105 outpatients undergoing mild to moderate alcohol withdrawal were randomly assigned to receive carbamazepine 800 mg initially and tapered over 7 days, or placebo.[54] Although both treatments were effective, symptoms, including tremor, diaphoresis, tachycardia, anorexia, restlessness, and anxiety, improved more rapidly in the group receiving carbamazepine on days 2 (p 0.01) and 4 (p 0.1). Side effects associated with carbamazepine included nausea, vomiting, and dizziness.

Carbamazepine appears to be as effective as barbital, tiapride, and chlormethiazole. Since these agents are not available in the United States, however, a study comparing carbamazepine with a benzodiazepine would be helpful. Carbamazepine does not lead to dependence but it may occasionally cause some severe side effects, such as hematologic or dermatologic reactions.

Clonidine

Five studies have been conducted using clonidine in the treatment of alcohol withdrawal. The increased noradrenergic activity present during withdrawal is associated with not only cardiovascular symptoms, but also tremulousness, anxiety, diaphoresis, and insomnia.[85] Clonidine acts centrally as an α_2-receptor agonist, causing a reduction in norepinephrine release in the locus ceruleus.

Using a double-blind design, a tapering dose of oral clonidine 0.15 mg 3 times daily on the first day and reduced by 1 dose daily, was compared with placebo in 60 withdrawing alcoholics.[55] On day 2 of treatment those receiving clonidine reported significantly reduced tension, tremor, anxiety, palpitations, and restlessness. The results of this study are confounded, however, because the patients in both groups had also received other medications including phenytoin, chlorpromazine, and a hypnotic containing diphenhydramine and methaqualone. In another study, the effects of clonidine were compared with placebo in 11 patients with well-developed withdrawal symptoms.[85] Clonidine significantly decreased not only heart rate and blood pressure, but also subjective anxiety.

Withdrawal symptoms were significantly suppressed by clonidine compared to chlormethiazole.[86] Another comparison of these agents (n = 9 and 8, respectively) recorded significantly greater reductions of blood pressure and heart rate in the clonidine group.[57] However, the overall measurement of clinical withdrawal course (which included such variables as sweating, restlessness, anxiety, and hallucinations) did not differ between the two drugs.

A recent study provides the best evidence supporting the efficacy of clonidine for the treatment of alcohol withdrawal.[58] Forty-seven medically stable alcoholic patients undergoing mild to moderate withdrawal were randomly assigned to receive clonidine (n = 26) or chlordiazepoxide (n = 21). Patients received 0.2 mg clonidine or 50 mg chlordiazepoxide tapered over 4 days. All subjects received a dose at 9 PM on day 1; at 9 AM, 1 PM, and 6 PM on day 2; 9 AM and 6 PM on day 3; and 9 AM on day 4. Both drugs caused significant decreases in systolic and diastolic blood pressures and heart rate, but the reduction in systolic blood pressure and heart rate was significantly greater with clonidine than with chlordiazepoxide. There were no statistically significant differences between the two drugs with respect to decreases in respiratory rate, diaphoresis, tremor, restlessness, or anxiety. No major differences in adverse effects were reported between the two groups, except that more nausea and vomiting occurred with chlordiazepoxide. Subjects were observed for 24 hours after the final dose, and those receiving clonidine experienced no clinically signifi-

cant hypotension or rebound hypertension.

The hypothesized mechanism of clonidine's efficacy in alcohol withdrawal involves stimulation of central α_2 adrenergic receptors. The locus ceruleus (LC) is the largest collection of noradrenergic neurons in the central nervous system. Axons from neurons in the LC project into the forebrain area. The LC noradrenergic neurons contain α_2 receptors, as well as opiate receptors. When these central α_2 receptors are stimulated, inhibition of noradrenergic output results, secondary to increased potassium conductance intracellularly and a hyperpolarization of the cellular membrane. Alcohol withdrawal is clearly associated with hyperactivity of the LC, although the precise mechanism is not clearly defined. The inhibition of noradrenergic firing in the LC produced by clonidine and other α_2 agonists putatively results in a decrease in withdrawal effects associated with LC hyperactivity, such as increases in blood pressure and heart rate, restlessness, diaphoresis, and insomnia.[87] Clonidine has no anticonvulsant activity, however, and it is unknown if its use is associated with any difference in the frequency of withdrawal seizures compared with benzodiazepines, since the only study comparing these two agents excluded subjects with a previous history of seizures or severe withdrawal.

Paraldehyde

Paraldehyde used to be employed commonly for treatment of the alcohol withdrawal syndrome. As the benzodiazepines have gained in popularity, its use has diminished sharply. Paraldehyde exhibits complete cross-tolerance with alcohol and, as such, is as effective in the treatment of withdrawal as the barbiturates and benzodiazepines.[88] Although paraldehyde is an effective sedative and prevents progression to withdrawal seizures or DTs when used early in the course of withdrawal, it is much more toxic than the benzodiazepines.[20] Tolerance also develops quickly, and weaning patients from the drug is often difficult. Administration is problematic because intramuscular injection frequently results in local irritation and may progress to the formation of sterile abscesses. Intravenous injection has less commonly been associated with pulmonary edema.[71, 88] Paraldehyde may be given orally or rectally, but rectal administration may result in proctitis or slow and erratic absorption.[89] Because of its irritating nature, paraldehyde should always be mixed with 60–100 ml olive or mineral oil prior to rectal instillation. In addition, its pharmacologic action is short so it must be dosed frequently.[71]

Other Agents

Phenothiazines and butyrophenones have both been reported to be as effective as chlordiazepoxide in the treatment of alcohol withdrawal.[43, 44, 90, 91] All of these studies are quite old, and numerous faults can be found with their designs; consequently, considerable doubt remains concerning the comparable efficacy of these agents. This may be a minor point since there is no doubt that the neuroleptics are more toxic than benzodiazepines. They lower the seizure threshold, and their use in alcohol withdrawal has resulted in an increased frequency of seizures.[44] The drugs also possess other undesirable pharmacologic side effects. Their α_1-adrenergic receptor-blocking effects can cause considerable orthostatic hypotension, their anticholinergic effects can result in anticholinergic delirium at high doses, and they can interfere with thermoregulation. They are also capable of causing extrapyramidal movement disorders and the neuroleptic malignant syndrome.

Neuroleptics are not generally recommended because of their side effects and their questionable efficacy. Nonetheless, haloperidol is occasionally used, always in conjunction with a benzodiazepine, for the treatment of hallucinations that are not responsive to benzodiazepines alone.[17, 66, 92] Small doses (0.5–2 mg intramuscularly) are typically used.[19] The use of haloperidol without a benzodiazepine in alcohol withdrawal is not recommended since it lowers seizure threshold.

Barbiturates were frequently employed in the treatment of this syndrome prior to the advent of the benzodiazepines. They can no longer be recommended even though they have proven anticonvulsant activity and can effectively control the withdrawal reaction. Their therapeutic index is much too narrow, they cause hepatic enzyme induction, and their abuse potential is high.[66, 88]

Chlormethiazole is administered for this syndrome in many countries outside the United States. Its chemical structure is similar to that of thiamine, although this has no bearing on its pharmacologic effect. It possesses sedative-hypnotic as well as anticonvulsant effects. It is considerably more toxic than benzodiazepines and, in high doses, it produces marked respiratory depression combined with increased bronchial secretion.[93] Elimination from the body is fairly rapid, with a plasma half-life of 4–6 hours; thus it requires frequent dosing.[94] Ironically, chlormethiazole's bioavailability is increased when it is administered with alcohol,[95] and it has been associated with successful suicide attempts when taken with alcohol.[96, 97]

Hydroxyzine, a sedative antihistaminic agent, has also been employed for symptomatic relief of alcohol withdrawal. Its efficacy as an anxiolytic is questionable and it does not possess anticonvulsant activity.[44, 98] In addition, large doses may result in anticholinergic toxicity, which is often manifested as confusion, disorientation, urinary retention, hallucinations, and tachycardia.[99] These side effects may be difficult to distinguish from those caused by the withdrawal syndrome itself, and in any case they are undesirable reactions in this population.

Although many pharmacologic agents have been used to allay the symptoms of alcohol withdrawal,

Table 5. Drugs Used in Alcohol Withdrawal

Drug	Anti-convulsant	Anxiolysis/ Sedation	Toxicity: Safety Ratio
Antihistamines	–	+	+ +
Barbiturates	+ + +	+ + +	+
Benzodiazepines	+ +	+ + +	+ + +
ß blockers	0	+	+ +
Carbamazepine	+ + +	+ +	+ +
Chlormethiazole	+ +	+ +	+
Clonidine	0	+	+ +
Haloperidol	–/0	+	+ +
Paraldehyde	+ +	+ + +	+
Phenothiazines	–	+ +	+

0 = none; – = negative; + = mild; + + = moderate; + + + = marked.
Data derived from references 9, 20, and 22.

the current drugs of choice are clearly the benzodiazepines. Of the agents reviewed above, they exhibit the most attractive antiwithdrawal profile (Table 5).

Treatment of Seizures

Most patients experiencing alcohol withdrawal suffer only one or two seizures,[100] and it is generally agreed that in most cases, they do not require prophylactic anticonvulsant therapy. Some authors claim that prophylaxis with benzodiazepines is sufficient to prevent seizures.[44, 50] Phenytoin is commonly used although its prophylactic efficacy in the seizures of withdrawal is not well-established.

Using a placebo-controlled design, phenytoin 300 mg/day orally was administered in combination with sedative doses of oral chlordiazepoxide[49] to 157 withdrawing alcoholics. The chlordiazepoxide dosage was determined on an individual basis by the nursing staff, but on average it was 400 mg in the first 24 hours, 200 mg in the second 24 hours, and none after the fourth day. All patients had a history of seizures during adult life (no distinction was made between seizures of alcohol withdrawal and other disorders). Within the first 48 hours 11 patients in the placebo group, but none in the phenytoin group, experienced seizures. The authors recommended that phenytoin 300 mg/day be given to patients experiencing alcohol withdrawal who have histories of seizures.

In a similar study in 200 patients, those randomly designated to the phenytoin group received 200 mg twice daily for 5 days.[50] Although 40 of these patients had histories of previous withdrawal seizures, none in either the placebo or phenytoin groups had such episodes. The author concluded that chlordiazepoxide was effective in preventing seizures and that the addition of another anticonvulsant is unwarranted.

Only one group measured phenytoin plasma concentrations.[49] Values were all in the subtherapeutic range (4 μg/ml). It is possible that the concentrations required for prophylaxis in alcohol withdrawal seizures may be lower than those required for epileptic seizures (i.e., 10–20 μg/ml). It should also be noted that phenytoin is highly protein bound, and total, not unbound, plasma concentrations were reported in this study. Since the drug is bound primarily to albumin, protein binding might have been decreased in this population. Phenytoin's pharmacokinetics in the alcoholic population are altered by the effects of alcohol on hepatic metabolism. The agent's clearance was increased in patients undergoing withdrawal once drinking ceased, and the author concluded that the standard dosage (300 mg/day) will often result in subtherapeutic plasma concentrations in these patients.[101]

Most literature sources currently advise the use of phenytoin in withdrawing patients who are at high risk for seizures (i.e., those with a history of epilepsy or recurrent withdrawal seizures).[9, 102] Prophylactic anticonvulsant therapy is recommended for only 5 days unless an underlying epileptic focus is present.[9] Long-term prescribing of anticonvulsants to chronic alcoholics may actually increase their predisposition to seizures due to erratic compliance with the regimen.[103, 104] Phenytoin is poorly absorbed after intramuscular injection, and therefore oral or intravenous administration is recommended. A loading dose of 10 mg/kg may be given intravenously at a rate of 50 mg/minute to achieve adequate anticonvulsant plasma concentrations.[88] Plasma concentrations should be monitored during maintenance dosing, since drug clearance may be altered in patients undergoing alcohol withdrawal.

In addition to phenytoin, other anticonvulsants that have been used to treat withdrawal seizures include carbamazepine,[52, 54, 105–107] valproic acid,[108, 109] and primidone.[110] A retrospective study found the combination of primidone and chlordiazepoxide (1000 patients) to be more efficacious than phenytoin and chlordiazepoxide (500 patients).[110] Little can be inferred from these data, however, as the trial was not randomized. The dosage of chlordiazepoxide was not reported, nor was the history of preexisting epilepsy clearly stated. Carbamazepine has been evaluated in humans[52, 107] as well as in rats[106] undergoing alcohol withdrawal. Again, design flaws in these studies preclude objective clinical interpretation. Indeed, placebo-controlled studies measuring carbamazepine's efficacy in alcohol withdrawal seizures in humans are not available. Valproic acid has been shown to have some efficacy in these seizures in animals,[111–113] but both human studies were retrospective chart reviews.[108, 109]

Treatment of Delirium Tremens

Delirium tremens is the most dramatic and dangerous manifestation of acute alcohol withdrawal. Oral medications are frequently not a viable option. These patients are almost always quite agitated and combative, and they frequently describe vivid, fright-

ening, threatening hallucinations, adding to their agitation. Once DTs are established they are not reversible, and the main objective of treatment is to provide sedation.[21] Many sedative agents have been used to treat DTs,[20, 51, 114–117] and the same advantages and disadvantages of each drug in the treatment of less severe withdrawal apply to this use.

Paraldehyde 10 ml rectally every 30 minutes was compared to diazepam 10 mg then 5 mg intravenously every 5 minutes in 34 patients with DTs.[20] Although both drugs effectively calmed the patients, paraldehyde proved much more toxic, causing adverse reactions in 9 of 17 patients who received it. Two of these patients died from unknown causes, one bit his nurse, another bit the physician, two developed sudden apnea during paraldehyde induction, one was caught while attempting to jump from the window, and two experienced brachial plexus injury secondary to violent agitation. No adverse reactions occurred in the diazepam group.

A double-blind comparison between intramuscular diazepam and oral barbital was performed in 30 patients experiencing DTs.[51] Barbital resulted in a more satisfactory effect, defined as time to sedation, patient cooperation, and course of clinical condition. Evaluation of this study is difficult, however, because the route of diazepam administration was not optimal, and the nursing staff was very familiar with barbital effects, so that the double-blind was difficult to maintain.

Patients experiencing DTs may require very large doses of sedatives, therefore a drug with a large therapeutic index will always be attractive. No studies have compared the benzodiazepines with agents other than paraldehyde or barbital in the treatment of DTs; however, the available data overwhelmingly support the benzodiazepines as being the drugs of choice.

Summary

While many pharmacologic agents have been used in alcohol withdrawal, it is important to remember that not all patients, especially those undergoing mild withdrawal, require pharmacologic intervention. A full assessment of any patient undergoing alcohol withdrawal is necessary to detect any medical complications and to assure that optimal pharmacotherapy is given, since early treatment will prevent progression to the more severe forms of withdrawal. It is crucial that a placebo control group, or, more realistically, a control group that is treated with a standard regimen, such as a benzodiazepine, be part of any study designed to evaluate the safety and efficacy of a new agent proffered for the treatment of mild to moderate alcohol withdrawal. Currently, benzodiazepines represent the agents with the most tasteful blend of efficacy and safety. Although they are not perfect agents, in that they can cause somnolence and are themselves subject to abuse, they are clearly the best agents presently available. Phenytoin is currently recommended if a preexisting seizure disorder is present or if recurrent withdrawal seizures occur.

References

1. **Anonymous.** Accident facts, 1984 edition. Chicago: National Safety Council, 1984.
2. **Durbec JP, Sarles H.** Multicenter survey of the etiology of pancreatic diseases. Digestion 1978;18:337–50.
3. **Sarles H, Cros RC, Bidart JM.** A multicenter inquiry into the etiology of pancreatic diseases. Digestion 1979;19:110–25.
4. **Patek AJ Jr.** Alcohol, nutrition, and alcoholic cirrhosis. Am J Clin Nutr 1979;32:1304–12.
5. **Lieber CS, Jones DP, DeCarli LM.** Effects of prolonged ethanol intake: production of fatty liver despite adequate diets. J Clin Invest 1965;44:1009–21.
6. **Robin E, Goldschlager N.** Persistence of low cardiac output after relief of high output by thiamine in a case of alcoholic beriberi and cardiac myopathy. Am Heart J 1970;80:103–8.
7. **Isbell H, Fraser HF, Wikler A, Belleville RE, Eisenman AJ.** An experimental study of the etiology of "rum fits" and delirium tremens. Q J Stud Alc 1955;16:1–33.
8. **Mendelson JH, LaDou J.** Experimentally induced chronic intoxication and withdrawal in alcoholics. Q J Stud Alc (Suppl) 1964;2:1–39.
9. **Naranjo CA, Sellers EM.** Clinical assessment and pharmacotherapy of the alcohol withdrawal syndrome. In: Galanter M, ed. Recent developments in alcoholism. New York: Plenum Press, 1986:265–81.
10. **Gorlick DA, Wilkins JN.** Special aspects of human alcohol withdrawal. In: Galanter M, ed. Recent developments in alcoholism. New York: Plenum Press, 1986:283–305.
11. **Whitfield CL, Thompson G, Lamb A, Spencer V, Pfiefer M, Browning-Ferrando M.** Detoxification of 1024 alcoholic patients without psychoactive drugs. JAMA 1978;239:1409–10.
12. **Victor M, Hope JM.** The phenomenon of auditory hallucinations in chronic alcoholism. J Nerv Ment Dis 1958;126:451–8.
13. **Alpert M, Silvers KN.** Perceptual characteristics distinguishing auditory hallucinations in schizophrenia and acute alcoholic psychoses. Am J Psychiatry 1970;127:298–302.
14. **Victor M, Brausch C.** The role of abstinence in the genesis of alcoholic epilepsy. Epilepsia 1967;8:1–20.
15. **Deisenhammer E, Klinger D, Tragner H.** Epileptic seizures in alcoholism and diagnostic value of EEG after sleep deprivation. Epilepsia 1984;25:526–30.
16. **Gerson IM, Karabell S.** The use of the electroencephalogram in patients admitted for alcohol abuse with seizures. Clin Electroencephalogr 1979;10:40–9.
17. **Foy A.** The management of alcohol withdrawal. Med J Aust 1986; 145:24–7.
18. **Ballenger JC, Post RM.** Kindling as a model for alcohol withdrawal syndromes. Br J Psychiatry 1978;133:1–14.
19. **McQuarrie DG, Fingl E.** Effects on single doses and chronic administration of ethanol on experimental seizures in mice. J Pharmacol Exp Ther 1958;124:264–71.
20. **Thompson WL, Johnson AD, Maddrey WL.** Diazepam and paraldehyde for treatment of severe delirium tremens. Ann Intern Med 1975;82:175–80.
21. **Thompson WL.** Management of alcohol withdrawal syndromes. Arch Intern Med 1978;138:278–83.
22. **Linnoila M, Martin PR.** Benzodiazepines and alcoholism. In: Trimble MR, ed. Benzodiazepines divided. New York: John Wiley & Sons, 1983:291–308.
23. **Tavel ME, Davidson W, Batterton TD.** A critical analysis of mortality associated with delirium tremens. Review of 39 fatalities in a 9-year period. Am J Med Sci 1961;242:18–29.
24. **Tonnesen E.** Delirium tremens and hypokalaemia. Lancet 1982; 2:97.
25. **Shaw JM, Kolesar GS, Sellers EM, Kaplan HL, Sandor P.** Development of optimal treatment tactics for alcohol withdrawal. I. Assessment and effectiveness of supportive care. J Clin Psychopharmacol 1981;1:382–7.
26. **Naranjo CA, Sellers EM, Chater K, Iverson P, Roach C, Sykora K.** Nonpharmacologic intervention in acute alcohol withdrawal. Clin Pharmacol Ther 1983;34:214–19.
27. **Eisenhofer G, Whiteside E, Lambie D, Johnson R.** Brain water during alcohol withdrawal. Lancet 1982;1:50.
28. **Farmer RW, Fabre LF Jr.** Some endocrine aspects of alcoholism. In: Majchrowicz E, ed. Biochemical pharmacology of ethanol. New York: Plenum Press, 1975:277–89.
29. **Leevy CM, Baker H, TenHove W, Frank O, Cherrick GR.** B-complex vitamins in liver disease of the alcoholic. Am J Clin Nutr 1965;16:339–46.

30. **Camilo ME, Morgan MY, Sherlock S.** Erythrocyte transketolase activity in alcoholic liver disease. Scand J Gastroenterol 1981; 16:273–9.
31. **Morgan MY.** Alcohol and nutrition. Br Med Bull 1982;38:21–9.
32. **Feldman EB.** Malnutrition in the alcoholic and related nutritional deficiencies. In: Pattison EM, Kaufman E, eds. Encylopedic handbook of alcoholism. New York: Gardner Press, 1982:255–62.
33. **Lumeng L, Li T-K.** Vitamin B_6 metabolism in chronic alcohol abuse. J Clin Invest 1974;53:693–704.
34. **Balaghi M, Neal RA.** Effect of chronic ethanol administration on thiamine metabolism in the rat. J Nutr 1977;107:2144–52.
35. **Halsted CH, Robles EA, Mezey E.** Intestinal malabsorption in folate-deficient alcoholics. Gastroenterology 1973;64:526–32.
36. **Blass JP, Gibson GE.** Abnormality of a thiamine-requiring enzyme in patients with Wernicke-Korsakoff syndrome. N Engl J Med 1977; 297:1367–70.
37. **Kalbfleisch JM, Lindeman RD, Ginn HE, Smith WO.** Effects of ethanol administration on urinary excretion of magnesium and other electrolytes in alcoholic and normal subjects. J Clin Invest 1963; 42:1471–5.
38. **McDonald JT, Margen S.** Wine versus ethanol in human nutrition. III. Calcium, phosphorus, and magnesium balance. Am J Clin Nutr 1979;32:823–33.
39. **Victor M.** The role of hypomagnesemia and respiratory alkalosis in the genesis of alcohol-withdrawal symptoms. Ann NY Acad Sci 1973;215:235–48.
40. **Heaton FW, Pyrah LN, Beresford CC, Bryson RW, Martin DF.** Hypomagnesemia in chronic alcoholism. Lancet 1962;2:802–5.
41. **Wilson A, Vulcano B.** A double-blind, placebo-controlled trial of magnesium sulfate in the ethanol withdrawal syndrome. Alcoholism Clin Exp Res 1984;8:542–5.
42. **Moskowitz G, Chalmers TC, Sacks HS, Fagerstrom RM, Smith H.** Deficiencies of clinical trials of alcohol withdrawal. Alcoholism Clin Exp Res 1983;7:42–6.
43. **Wegner ME, Fink DW.** Chlordiazepoxide (Librium) compared with meprobamate and promazine (Prozine) for the withdrawal symptoms of acute alcoholism. Wisc Med J 1965;64:436–40.
44. **Kaim SC, Klett CJ, Rothfeld B.** Treatment of the acute alcohol withdrawal state: a comparison of four drugs. Am J Psychiatry 1969;125:1640–46.
45. **Sereny G, Kalant H.** Comparative clinical evaluation of chlordiazepoxide and promazine in treatment of alcohol-withdrawal syndrome. Br Med J 1965;1:92–7.
46. **Zilm DH, Jacob MS, MacLeod SM, Sellers EM, Ti TY.** Propranolol and chlordiazepoxide effects on cardiac arrhythmias during alcohol withdrawal. Alcoholism Clin Exp Res 1980;4:400–5.
47. **Kraus ML, Gottlieb LD, Horwitz RI, Anscher M.** Randomized clinical trial of atenolol in patients with alcohol withdrawal. N Engl J Med 1985;313:905–9.
48. **Ritola E, Malinen L.** A double-blind comparison of carbamazepine and clomethiazole in the treatment of alcohol withdrawal syndrome. Acta Psychiatr Scand 1981;64:254–9.
49. **Sampliner R, Iber FL.** Diphenylhydantoin control of alcohol withdrawal seizures. JAMA 1974;230:1430–2.
50. **Rothstein E.** Prevention of alcohol withdrawal seizures: the roles of diphenylhydantoin and chlordiazepoxide. Am J Psychiatry 1973;130: 1381–2.
51. **Kramp P, Rafaelsen OJ.** Delirium tremens: a double-blind comparison of diazepam and barbital treatment. Acta Psychiatr Scand 1978;58:174–90.
52. **Flygenring J, Hansen J, Holst B, Petersen E, Sorensen A.** Treatment of alcohol withdrawal symptoms in hospitalized patients. Acta Psychiatr Scand 1984;69:398–408.
53. **Agricola R, Mazzarind M, Urani R.** Treatment of acute alcohol withdrawal syndrome with carbamazepine: a double-blind comparison with tiapride. J Int Med Res 1982;10:160–5.
54. **Bjorkqvist S-E, Isohanni M, Makela R, Malinen L.** Ambulant treatment of alcohol withdrawal symptoms with carbamazepine: a formal multicentre double-blind comparison with placebo. Acta Psychiatr Scand 1976;53:333–42.
55. **Bjorkqvist SE.** Clonidine in alcohol withdrawal. Acta Psychiatr Scand 1975;52:256–63.
56. **Wilkins AJ, Jenkins WJ, Steiner JA.** Efficacy of clonidine in treatment of alcohol withdrawal state. Psychopharmacology 1983; 81:78–80.
57. **Manhem P, Nilsson LH, Moberg A-L, Wadstein J, Hokfelt B.** Alcohol withdrawal: effects of clonidine treatment on sympathetic activity, the renin-aldosterone system, and clinical symptoms. Alcoholism Clin Exp Res 1985;9:238–43.
58. **Baumgartner GR, Rowen RC.** Clonidine vs chlordiazepoxide in the management of acute alcohol withdrawal syndrome. Arch Intern Med 1987;147:1223–6.
59. **Sellers EM, Naranjo CA, Giles HG, Frecker RC, Beeching M.** Intravenous diazepam and oral ethanol interaction. Clin Pharmacol Ther 1980;28:638–45.
60. **Wilkinson PK, Sedman AJ, Sakmar E, Kay DR, Wagner JG.** Pharmacokinetics of ethanol after oral administration in the fasting state. J Pharmacokinet Biopharm 1977;5:207–24.
61. **Dundee JW.** Intravenous ethanol anesthesia. A study of dosage and blood levels. Anesth Analg 1970;49:467–75.
62. **Lane EA, Guthrie S, Linnoila M.** Effects of ethanol on drug and metabolite pharmacokinetics. Clin Pharmacokinet 1985;10:228–47.
63. **Squires RF, Braestrup C.** Benzodiazepine receptors in rat brain. Nature 1977;266:732–4.
64. **Mohler H, Okada T.** Benzodiazepine receptor: demonstration in the central nervous system. Science 1977;198:849–51.
65. **Ticku MK.** The effects of acute and chronic ethanol administration and its withdrawal on aminobutyric acid receptor binding in rat brain. Br J Pharmacol 1980;70:403–10.
66. **Sellers EM, Kalant H.** Alcohol withdrawal and delirium tremens. In: Pattison EM, Kaufman E, eds. Encyclopedic handbook of alcoholism. New York: Gardner Press, 1982:147–66.
67. **Greenblatt DJ, Shader RI.** The treatment of alcoholism and other drug-dependent states. In: Greenblatt DJ, Shader RI, eds. Benzodiazepines in clinical practice. New York: Raven Press, 1974:217–29.
68. **Greenblatt DJ, Shader RI, Abernethy DR.** Current status of benzodiazepines (parts 1 & 2). N Engl J Med 1983;309:354–8, 410–16.
69. **Greenblatt DJ, Shader RI, Koch-Weser J.** Slow absorption of intramuscular chlordiazepoxide. N Engl J Med 1974;291:1116–18.
70. **Dommisse CS, Hayes PE.** Current concepts in clinical therapeutics: anxiety disorders. 2. Clin Pharm 1987;6:196–215.
71. **Sellers EM, Kalant H.** Pharmacotherapy of acute and chronic alcoholism and alcohol withdrawal syndrome. In: Clark WG, DelGiudice J, eds. Principles of psychopharmacology. New York: Academic Press, 1978:721–40.
72. **Solomon J, Rouck LA, Koepke HH.** Double-blind comparison of lorazepam and chlordiazepoxide in the treatment of the acute abstinence syndrome. Clin Ther 1983;6:52–8.
73. **Daghestani AN.** Alcohol withdrawal: a comprehensive approach to treatment. Postgrad Med 1987;81(6):111–18.
74. **O'Brien JE, Meyer RE, Thoms DC.** Double-blind comparison of lorazepam and diazepam in the treatment of the acute alcohol abstinence syndrome. Curr Ther Res 1983;34:825–31.
75. **Hosein IN, DeFreitas R, Beaubrun MH.** Intramuscular/oral lorazepam in acute alcohol withdrawal and incipient delirium tremens. Curr Med Res Opin 1978;5:632–6.
76. **Sellers EM, Naranjo CA, Harrison M, Devenyi P, Roach C, Sykora K.** Diazepam loading: simplified treatment of alcohol withdrawal. Clin Pharmacol Ther 1983;34:822–6.
77. **Greenblatt DJ, Joyce TH, Comer WH, et al.** Clinical pharmacokinetics of lorazepam. II. Intramuscular injection. Clin Pharmacol Ther 1977;21:222–30.
78. **Greenblatt DJ, Shader RI, Franke K, et al.** Pharmacokinetics and bioavailability of intravenous, intramuscular, and oral lorazepam in humans. J Pharm Sci 1979;68:57–63.
79. **Korttila K, Linnoila M.** Absorption and sedative effects of diazepam after oral administration and intramuscular administration into the vastus lateralis muscle and the deltoid muscle. Br J Anaesth 1975; 47:857–61.
80. **Carlsson C, Haggendal J.** Arterial noradrenaline levels after ethanol withdrawal. Lancet 1967;2:889.
81. **Giacobini E, Izikowitz S, Wegmann A.** Urinary norepinephrine excretion in delirium tremens. Arch Gen Psychiatry 1960;3:289–96.
82. **Zilm DH, Sellers EM, MacLeod SM, Degani N.** Propranolol effect on tremor in alcoholic withdrawal. Ann Intern Med 1975;83:234–6.
83. **Frishman W, Silverman R, Strom J, Elkayam U, Sonnenblick E.** Clinical pharmacology of the new beta-adrenergic blocking drugs. 4. Adverse effects, choosing a ß-adrenoceptor blocker. Am Heart J 1979;98:256–62.
84. **Cruickshank JM, Neil-Dwyer G, Bartlett J, McAinsh J.** Beta blockers and the blood-brain barrier. Primary Cardiol 1980;(suppl 1):34–7.
85. **Linnoila M, Mefford I, Nutt D, Adinoff B.** Alcohol withdrawal and noradrenergic function. Ann Intern Med 1987;107:875–89.
86. **Walinder J, Balldin J, Bokstrom K, Karlsson I, Lundstrom B.** Clonidine suppression of the alcohol withdrawal syndrome. Drug Alcohol Depend 1981;8:345–8.
87. **Koob GF, Bloom FE.** Cellular and molecular mechanisms of drug dependence. Science 1988;242:715–23.
88. **Sellers EM, Kalant H.** Alcohol intoxication and withdrawal. N Engl J Med 1976;294:757–62.
89. **Anthony RM, Andorn AC, Sunshine I, Thompson WL.** Paraldehyde pharmacokinetics in ethanol abusers. Fed Proc 1977;36:285.
90. **Palestine ML, Alatorre E.** Control of acute alcoholic withdrawal symptoms: a comparative study of haloperidol and chlordiazepoxide. Curr Ther Res 1976;20:289–99.
91. **Muller DJ.** A comparison of three approaches to alcohol-withdrawal states. South Med J 1969;62:495–6.

92. **Leroy JF.** Recognition and treatment of the alcohol withdrawal syndrome. Primary Care 1979;6:529–39.
93. **Illingworth RN, Stewart MJ, Jarvie DR.** Severe poisoning with chlormethiazole. Br Med J 1979;2:902–3.
94. **Moore RG, Triggs EJ, Shanks CA, Thomas J.** Pharmacokinetics of chlormethiazole in humans. Eur J Clin Pharmacol 1975;8:353–7.
95. **Neuvonen PJ, Pentikainen PJ, Jostell KG, Syvalahti E.** Effect of ethanol on the pharmacokinetics of chlormethiazole in humans. Int J Clin Pharmacol Ther Toxicol 1981;19:552–60.
96. **Jakobsson S, Moller M.** Deaths due to chlormethiazole. Forensic Sci Int 1972;1:114.
97. **Robinson AE, McDowall RD.** Toxicological investigations of six chlormethiazole-related deaths. Forensic Sci Int 1979;14:49–55.
98. **Dilts SL, Keleher DL, Hoge G, Haglund B.** Hydroxyzine in the treatment of alcohol withdrawal. Am J Psychiatry 1977;134:92–3.
99. **Greenblatt DJ, Shader RI.** Rational use of psychotropic drugs. II. Antianxiety agents. Am J Hosp Pharm 1974;31:1077–80.
100. **Victor M.** Treatment of alcoholic intoxication and the withdrawal syndrome. Psychosom Med 1966;28:636–50.
101. **Sandor P, Sellers EM, Dumbrell M, Khouw V.** Effect of short- and long-term alcohol use on phenytoin kinetics in chronic alcoholics. Clin Pharmacol Ther 1981;30:390–7.
102. **Brown CG.** The alcohol withdrawal syndrome. Ann Emerg Med 1982;11:276–80.
103. **Hillbom ME, Hjelm-Jager M.** Should alcohol withdrawal seizures be treated with anti-epileptic drugs? Acta Neurol Scand 1984;69:39–42.
104. **Josephson GW, Sabatier HS Jr.** Rational management of alcohol withdrawal seizures. South Med J 1978;71:1095–7.
105. **Poutanen P.** Experience with carbamazepine in the treatment of withdrawal symptoms in alcohol abusers. Br J Addict 1979;74:201–4.
106. **Chu N-S.** Carbamazepine: prevention of alcohol withdrawal seizures. Neurology 1979;29:1397–1401.
107. **Brune F, Busch H.** Anticonvulsant-sedative treatment of delirium alcoholism. Q J Stud Alcohol 1971;32:334–42.
108. **Bonfiglio G, Falli S, Pacini A.** Proposta di introduzione nella pratica ospedaliera di una nuova sostanza: il dipropilacetato di sodio nella prevenzione e terapia del delirium tremens alcoolico. Minerva Med 1977;68:4233–45.
109. **Bastie Y.** Suppression des crises d'epilepsie du sevrage par le depakine dans les cures de desintoxication ethylique. Ann Med Psychol (Paris) 1970;128II:400–4.
110. **Smith RF.** Relative effectiveness of primidone (Mysoline) and diphenylhydantoin (Dilantin) in the management of sedative withdrawal seizures. Ann NY Acad Sci 1976;273:378–80.
111. **Noble EP, Gillies R, Vigran R.** The modification of the ethanol withdrawal syndrome in rats by di-*N*-propylacetate. Psychopharmacology 1976;46:127–31.
112. **Goldstein DB.** Sodium bromide and sodium valproate: effective suppressants of ethanol withdrawal reactions in mice. J Pharmacol Exp Ther 1979;208:223–7.
113. **Hillbom ME.** The prevention of ethanol withdrawal seizures in rats by dipropylacetate. Neuropharmacology 1975;14:755–61.
114. **Brown JH, Moggey DE, Shane FH.** Delirium tremens: a comparison of intravenous treatment with diazepam and chlordiazepoxide. Scott Med J 1972;17:9–12.
115. **Kaim SC, Klett CJ.** Treatment of delirium tremens. Q J Stud Alcohol 1972;33:1065–72.
116. **Salum I.** Treatment of delirium tremens. Br J Addict 1975;(suppl I):75–80.
117. **Smith JA.** Methods of treatment of delirium. JAMA 1953;152:384–7.