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**Pharmacological Management of
Alcohol Withdrawal:**

A Meta-Analysis and Evidence-Based Practice Guideline

Developed by:

The American Society of Addiction Medicine, Committee on
Practice Guidelines, Working Group on Pharmacological
Management of Alcohol Withdrawal

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Management Committee
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PHARMACOLOGICAL MANAGEMENT OF ALCOHOL WITHDRAWAL:

A Meta-Analysis and Evidence-Based Practice Guideline

Developed by the **American Society of Addiction Medicine**, Committee on Practice Guidelines, Working Group on Pharmacological Management of Alcohol Withdrawal

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ABSTRACT:

Objective: To provide an evidence-based practice guideline on the pharmacological management of alcohol withdrawal.

Data Sources: English-language articles published before July 1995 identified through MEDLINE search on "substance withdrawal - ethyl alcohol" and review of references from identified articles.

Study Selection: Articles with original data on human subjects.

Data Abstraction: Structured review to determine study design, sample size, interventions used and outcomes of withdrawal severity, delirium, seizures, completion of withdrawal, entry into rehabilitation, adverse effects and costs. Data from prospective controlled trials with methodologically sound endpoints corresponding to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition were abstracted by two independent reviewers and underwent meta-analysis.

Data Synthesis: Benzodiazepines reduce withdrawal severity, reduce incidence of delirium (-4.9 cases/100 patients, 95%CI-9.0, -0.7, p=0.04) and reduce seizures (-7.7 seizures/100 patients, 95%CI-12.0, -3.5, p=0.003). Individualizing therapy with withdrawal scales results in administration of significantly less medication and shorter treatment (p <0.001). Beta-blockers, clonidine and carbamazepine ameliorate withdrawal severity but inadequate evidence is inadequate to determine their effect on delirium and seizures. Phenothiazines ameliorate withdrawal but are less effective than benzodiazepines in reducing delirium (p=0.002) or seizures (p=0.000003).

Conclusions: Benzodiazepines are suitable agents for alcohol withdrawal, with choice among different agents guided by duration of action, rapidity of onset and cost. Dosage should be individualized, based on withdrawal severity measured by withdrawal scales, comorbid illness

and history of withdrawal seizures. Beta-blockers, clonidine, carbamazepine and neuroleptics may be used as adjunctive therapy but are not recommended as monotherapy.

Alcohol dependence continues to be a major public health problem, and among its many associated medical problems is a well characterized withdrawal syndrome. Withdrawal signs and symptoms are frequently minor but can develop into a severe, even fatal, condition. Because of its medical complications alcohol dependence is seen frequently by physicians, occurring in 15-20% of primary care and hospitalized patients.¹⁻³ Physicians in all areas of medicine therefore frequently encounter the problem of managing withdrawal, particularly as medical encounters such as hospital admission or pregnancy, are often a precipitating event for cessation of alcohol. In recent decades there has been extensive research on pharmacologic interventions aimed at ameliorating withdrawal. However these studies are widely dispersed in the medical literature, generally involve few subjects and are often of uncertain methodologic quality.⁴ Uncertainty continues to exist about the role of pharmacotherapy⁵ and its effectiveness in reducing the rate of major complications such as seizures or delirium. Significant variation in physician management of withdrawal has been documented, even among specialists in the field, with a wide range in choice of medication, approaches to medication delivery and method of patient monitoring.⁶ Recommendations from authoritative sources such as medical and surgical textbooks vary even more widely, with recommendations for agents which have never been tested in clinical trials⁷ or for approaches that have been shown to result in administration of unnecessary medication.⁸ Given the frequency with which this condition is encountered by physicians, the wide variety of settings in which it occurs and the variation in the way it is managed, we felt an evidence-based guideline would have widespread utility.

The purpose of this review and guideline, therefore, is to aid physicians in providing the appropriate pharmacological management of alcohol withdrawal. This guideline does not address treatment of the patient who is examined after having an alcohol withdrawal seizure or who has already developed alcohol withdrawal delirium (delirium tremens), or the optimal setting for withdrawal management (inpatient or outpatient). These are important issues and will be addressed in separate guidelines. The role of phenytoin in alcohol withdrawal is the topic of a guideline already published.⁹

METHODS:

Selection of the Topic

Pharmacologic management of alcohol withdrawal was a topic identified for guideline development by the Practice Guideline Committee of the American Society of Addiction Medicine. A work group was appointed that included individuals with training in internal medicine, family practice, psychiatry and pharmacology and individuals involved in primary care medicine, addiction medicine and research on alcohol withdrawal.

Outcomes

Outcomes studied were 1) severity of alcohol withdrawal syndrome, corresponding to the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition^{10 (PP197-199)} 2) alcohol withdrawal delirium, corresponding to the DSM IV definition,^{10 (PP123-132)} 3) withdrawal seizures, 4) completion of withdrawal 5) entry into rehabilitation, 6) adverse effects and 7) cost. Acquisition costs were determined by averaging wholesale prices listed in the Red Book.¹¹

Options

Pharmacologic management was defined as the use of any pharmacological agent to affect one or more of the outcomes listed above. Different strategies for administering medication were reviewed when data were available.

Review of the Evidence

The English-language medical literature was reviewed by searching MEDLINE using the key words "Substance Withdrawal Syndrome, Ethyl Alcohol" from MEDLINE's initial entries in 1996 through June 1995. References from selected articles and reviews were also examined. Articles were considered only if they involved human subjects and included clinical data. Articles that met these criteria underwent structured review. Prospective, controlled trials with methodologically sound end points and documented reporting of the endpoint in question underwent further review with two authors independently extracting data from each article. Differences reported in individual studies were analyzed by means of the Fisher exact test and 95% confidence intervals for the relative risk calculated by means of Taylor series.¹² When appropriate meta-analysis was performed by means of a random effects model¹³⁻¹⁵ with risk differences used as the measure of effect. All tests were 2 tailed and differences were considered statistically significant when $p \leq 0.05$.

Recommendations

Recommendations based on the evidence were drafted and graded according to a published system (Table 1).¹⁶ In several areas it was recognized that a single recommendation could not be formulated to guide the management of all patients, but that the decisions should be guided by a series of clinical considerations. In such areas the level of evidence supporting these considerations was identified. In formulating recommendations, greatest value was placed on patient safety followed by facilitation of treatment of alcohol dependence, patient comfort and then cost.

Guideline Review

The draft guideline was sent for review to first authors of articles from the past ten years that met inclusion criteria and to representatives of 68 medical organizations. The American Society of Addiction Medicine Board of Directors approved the final version in June 1996 with review and revision scheduled for June 2001, unless new information requires revision before then.

RESULTS:

Original data were found in 134 articles,¹⁷⁻¹⁵⁰ which included 65 prospective controlled trials and involved 42 different medications. In the following sections data on different agents are reviewed.

Benzodiazepines and Other Sedative Hypnotic Agents

Six prospective trials involving 5 different agents all demonstrated that benzodiazepines are more effective than placebo in reducing the signs and symptoms of alcohol withdrawal.^{27,41,67,69,61,150} Summary and meta-analysis of prospective, placebo-controlled trials (Table 2) also demonstrated a highly significant reduction of seizures (risk reduction of 7.7 seizures/100 patients treated, $p=0.003$) as well as delirium (risk reduction of 4.9 cases delirium/100 patients treated, $p=0.04$).

Trials comparing different benzodiazepines demonstrated that all appear similarly efficacious in reducing signs and symptoms of withdrawal (References 26,63,68,70,77,88,90, 98, 150).

However, there is some evidence that longer-acting agents may be more effective in preventing seizures.^{139,149} A summary of prospective controlled trials (Table 3) also demonstrates a trend in this direction. There are little data on the comparative efficacy in reducing delirium. Pharmacological data and clinical experience¹³⁹ suggest that longer acting agents can pose a risk of excess sedation in selected groups, including the elderly and those with marked liver disease. Longer-acting agents however contribute to an overall smoother withdrawal course with less breakthrough or rebound symptoms.⁹⁸

Another consideration in the choice of benzodiazepine is their potential for abuse. Prospective, double-blind, randomized controlled trials have shown that certain agents are preferred by individuals with addictive disorders,^{65,151-153} evidence substantiated by patterns of illicit drug use. Agents with rapid onset of action, including diazepam, alprazolam and lorazepam, demonstrate higher abuse potential than those with slower onset of action, such as chlordiazepoxide, oxazepam or halazepam. This consideration may be of relevance in an outpatient setting or for patients with a history of benzodiazepine or other substance abuse. However, when rapid control of symptoms is needed, the quicker onset of these medications may offer an advantage.

A final consideration is cost. The average wholesale cost in oral form at approximately equivalent dosages, are as follows: chlordiazepoxide 25mg, \$0.033; diazepam 5mg, \$0.071; lorazepam 1 mg, 11.5 cents; oxazepam 15 mg, 25 cents; prazepam 10mg, 37 cents; alprazolam 0.5mg, 56 cents; and chlorazepate 7.5mg, \$1.05.¹² Some practitioners have also described the use of continuous infusion of short-acting benzodiazepines such as lorazepam or midazolam.^{144,154-5} Such infusions can require very large amounts of medication over several hours or days, and reports of direct drug costs (excluding costs of preparation, administration and monitoring) of \$50,335 for a 25-hour infusion of midazolam in one patient¹⁵⁴ and \$26,045 for a hospital stay for another individual patient¹⁴⁴ have been published. There is no evidence that continuous infusion therapy with short-acting agents provides better outcomes than oral or intravenous bolus therapy with longer-acting agents. In one institution implementation of a guideline emphasizing the use of longer-acting agents instead of continuous infusion of short-acting agents was prospectively studied. This change led to substantial decreases in costs, from a mean of \$1008.72/patient to \$59.79 per patient, with equivalent outcomes and no increase in adverse effects.¹⁴⁵

Prospective controlled trials involving other sedative hypnotic agents indicate that chlormethiazole, an agent used in Europe, is better than placebo for reducing signs and symptoms of withdrawal.^{24,81} and that barbital (a long-acting barbiturate), and tetrabamate are equal to benzodiazepines in this regard.^{44,119} The size of these studies was not adequate to draw conclusions on preventing seizures and delirium. Case series describe the use of paraldehyde^{27,31} and one controlled trial showed this drug is superior to promazine,²² but no controlled trials have compared it with placebo or benzodiazepines. Although barbiturates are used by approximately 10% of detoxification programs in the United States,⁶ no controlled trials using phenobarbital could be identified, although uncontrolled studies^{96,105,110,137} support its effectiveness. In contrast to many other barbiturates, it has low abuse potential.¹⁵¹ It is long-acting, can be reliably administered by oral, intramuscular, and intravenous routes, has well-documented anticonvulsant activity, and is inexpensive, with an average cost of 1.4 cents/30mg tablet.¹¹ However, barbiturates, including phenobarbital, pose a greater risk of respiratory depression, particularly when combined with alcohol, and an overall lower safety profile than benzodiazepines when used in high doses.¹⁵⁶

Structured Assessment Scales and Determination of Dosage

Because alcohol withdrawal involves a constellation of nonspecific findings, efforts have been made to develop structured withdrawal severity assessment scales to objectively quantify the severity of withdrawal. The most extensively studied are the Clinical Institute Withdrawal Assessment - Alcohol, or CIWA-A, and a shortened version, CIWA-A revised or (CIWA-Ar).¹⁵⁷ These scales have well-documented reliability, reproducibility and validity based on comparison with ratings by experienced clinicians^{56,157,158} and shown to be usable in a variety of settings including detoxification units,^{69,146} and psychiatry units.^{127, 159} Studies have also shown that they can be used by nursing staff on general hospital medical/surgical wards, to monitor and treat not only patients admitted specifically for alcohol withdrawal but also patients admitted because of coexisting medical or surgical problems.^{107,131} Furthermore, high scores are predictive of the development of seizures and delirium.⁶⁹⁻¹⁰⁷

In most studies medications were given in fixed amounts at scheduled times: e.g., chlordiazepoxide 50mg every 6 hours for 5 days. However, it has been shown that many patients can go through withdrawal with only minor symptoms despite receiving little or no medication.^{44,56,122} An alternative to giving medication on a fixed schedule has been developed known as symptom-triggered therapy. In this approach the patient is monitored by means of a structured assessment scale and given medication only when symptoms cross a threshold of severity.^{56,127,132} Two prospective, randomized controlled trials have demonstrated this approach to be as effective as fixed dose therapy, but if results in the administration of significantly less medication and a significantly shorter duration of treatment.^{140,146} In the larger of these studies the median amount of chlordiazepoxide given to the symptom-triggered group was 100mg compared to 425mg in the fixed dose group, and the median duration of treatment was only 9 hours compared with 68 hours.¹⁴⁶

Withdrawal seizures usually occur early in the course of withdrawal. Because a history of withdrawal seizures is a strong risk factor for seizures during a withdrawal episode,^{149,160} some practitioners administer medication on a fixed dose schedule to patients with a history of withdrawal seizures. Seizures were not observed in series of patients treated with symptom-triggered therapy however,^{127,146} so it is possible that provision of symptom-triggered therapy alone may be adequate to prevent seizures.

Beta Adrenergic Antagonists

There is some evidence that beta adrenergic antagonists reduce manifestations of withdrawal.^{41,86,88,115,148} Review of these studies reveals that these effects are primarily caused by reductions in the autonomic manifestations of withdrawal. Beta blockers have no known anticonvulsant activity and large enough studies have not been performed to determine whether they reduce, or increase, seizures during withdrawal. Furthermore, delirium is a known side effect of beta blockers, particularly those with good central nervous system penetration such as propranolol.¹⁶¹ In at least one study, the incidence of delirium was increased with propranolol,⁵³ but studies of adequate size have not been done to accurately assess the effect of beta blockers on this outcome. The selective reduction in certain manifestations of withdrawal may mask the development of other significant withdrawal symptoms, and make it difficult to use withdrawal scales to guide therapy. In one case report, the diagnosis of withdrawal delirium was significantly delayed in a patient who presented with marked confusion because the patient had earlier been placed on a regimen of propranolol and thus demonstrated none of the autonomic hyperactivity classically associated with alcohol withdrawal delirium.⁶²

Clonidine

Well-designed studies have consistently demonstrated the effectiveness of centrally acting alpha adrenergic agonists such as clonidine in ameliorating symptoms in patients with mild to moderate withdrawal (References 133, 52, 72, 87, 101, 102, 111, 120, 128). As with beta blockers, studies of adequate size have not been reported to indicate what effect these agents have on the rate of delirium or seizures.

Carbamazepine

Carbamazepine has been widely used in Europe for alcohol withdrawal. Methodologically sound studies have shown it to be superior to placebo and equal in efficacy to barbitol and oxazepam for patients with mild to moderate withdrawal.^{36,74,118,136} Data comparing its efficacy in preventing seizures or delirium are limited. Carbamazepine was documented to be without significant hematologic or hepatic toxic effects when used in seven-day protocols for alcohol withdrawal^{118,136} and was associated with less psychiatric distress and a faster return to work.^{58,82,136}

Carbamazepine has well-documented anticonvulsant activity and has been shown to prevent alcohol withdrawal seizures in animals studies.¹⁶² It does not potentiate the Central Nervous System and respiratory depression caused by alcohol, does not inhibit learning (an important side effect of larger doses of benzodiazepines) and has no abuse potential. It has also been proposed that it may retard a kindling-like phenomenon in which repeated episodes of alcohol withdrawal may be associated with increasing severity of withdrawal.¹⁶³

Neuroleptic Agents

Neuroleptic agents, including the phenothiazines and the butyryphenone haloperidol, demonstrate some effectiveness in reducing signs and symptoms of withdrawal,^{25,26,37} but phenothiazines are less effective than benzodiazepines in preventing delirium (risk difference, 6.6 cases/100 patients treated, p=0.002) (Table 4). These agents increase the incidence of seizures compared with placebo and are much less effective than benzodiazepines in preventing seizures (risk difference, 12.4 seizures per 100 patients treated, p=0.000002)(Table 4). There are differences in the epileptogenic potential among the neuroleptic agents and the agents used in these studies, chlorpromazine and promazine, are among the agents with the greatest effect on seizure threshold. Neuroleptic agents are widely used to calm agitated patients and uncontrolled clinical experience indicates that they are useful for this purpose in the setting of alcohol withdrawal as well.¹⁶⁴

Magnesium

It has long been recognized that magnesium levels are frequently low during alcohol withdrawal.¹⁶⁵⁻⁷ Closer study showed that magnesium level is usually normal on admission, but then drops during the course of withdrawal before spontaneously returning to normal as symptoms subside.¹⁶⁵⁻⁷ A double-blind, placebo-controlled randomized trial studying intramuscular administration of magnesium as a supplement to benzodiazepines showed no significant difference in severity of withdrawal symptoms,⁸⁰ even after adjustment for magnesium levels. There were also no differences in the incidence of seizures and delirium, although the power to detect these outcomes was limited. Thus, while supplementation with magnesium is without significant risk, no evidence indicates such supplementation reduces withdrawal severity nor the frequency of delirium or seizures.

Ethyl Alcohol

By definition, intake of alcohol alleviates the initial symptoms of alcohol withdrawal. Alcohol has long been used for this purpose, both by those with alcohol dependence and by some practitioners. Case series describing alcohol given orally or by intravenous drip for the prevention or treatment of withdrawal symptoms have been published.^{27,42,49,75,80,126,141} These reports have been small, and uncontrolled and did not use objective or quantitative assessment of withdrawal severity. There are no controlled trials evaluating its safety or relative efficacy, compared with either placebo or to benzodiazepines. Intravenous alcohol infusions require close monitoring because of the toxicity of higher doses, involve expense in preparation and administration, and pose risks of tissue damage at the infusion site. As a pharmacological agent, ethyl alcohol has numerous adverse effects, including its well known hepatic, gastrointestinal, hematological and neurological toxicities, as well as its effects on mental status and judgment.

Thiamine

In one large trial thiamine did not reduce delirium or seizures.²⁹ However, individuals with alcohol dependence are frequently thiamine deficient, with a high risk for Wernicke's disease and Wernicke-Korsakoff's syndrome,¹⁶⁹ sequelae that can be prevented by administration of thiamine.

Other Agents

Results of trials involving other agents show that some ameliorate withdrawal, but no evidence has been published to indicate that any are effective in reducing delirium or seizures (References 29, 66, 81, 103, 114, 117, 129, 133).

Special Populations

No studies were identified on managing withdrawal in adolescents. While the signs and symptoms of withdrawal may differ in older individuals compared with younger individuals,^{169,170} no studies of different treatment approaches in the elderly were identified. Similarly, no studies on managing withdrawal in pregnant women were identified. Ethyl alcohol is a well-known teratogen, to be avoided in pregnant women.¹⁵⁶ Retrospective studies have indicated a risk of congenital malformation with both benzodiazepines and barbiturates^{171,172} and a recent study also indicated an association of intelligence deficits with in utero exposure to phenobarbital.¹⁷³ Overall, these risks for both classes of agents appear small and must be weighed against the risk of harm to the fetus should severe withdrawal or seizures develop.

No studies were identified which reported on clinical experience in managing alcohol withdrawal in patients with specific coexisting medical or substance abuse disorders. However, concurrent sedative hypnotic abuse has been identified as a risk factor for major complications during withdrawal.^{174,175} In one cohort study of hospitalized psychiatric patients, symptom-triggered therapy with a long-acting benzodiazepine was found to be safe and effective.¹⁶⁰

RECOMMENDATIONS:

1. CHOICE OF PHARMACOLOGICAL AGENT

Because of their documented efficacy benzodiazepines are recommended as suitable agents for alcohol withdrawal (Grade A recommendation). All benzodiazepines appear equally efficacious in reducing signs and symptoms of withdrawal, and the choice among them can be guided by the following clinical considerations:

- A. Long acting agents may be more effective in preventing withdrawal seizures (Level II evidence).
- B. Long acting agents can contribute to a smoother withdrawal with fewer rebound symptoms (Level I evidence).
- C. Short acting agents may have a lower risk of oversedation (Level III evidence).
- D. Certain benzodiazepines have a higher liability for abuse (Level I evidence).
- E. Cost of these agents varies significantly.

Benzodiazepines are recommended over most non-benzodiazepine sedative-hypnotics because they have better documented efficacy, a greater margin of safety, and lower abuse potential. However, phenobarbital appears to be a clinically acceptable alternative, although the margin of safety for this agent may be lower than for benzodiazepines when very high doses are needed (Grade C recommendation).

2. DETERMINATION OF DOSE

Withdrawal severity varies greatly and the amount of medication needed to control symptoms can also vary significantly. Alcohol withdrawal cannot be adequately treated by providing only a fixed standardized dose for all patients. Treatment should allow for a degree of individualization so patients can receive large amounts of medication rapidly if needed (Grade A recommendation).

In substance abuse treatment programs the use of structured assessment scales, such as the CIWA-Ar, for initial assessment and subsequent monitoring is recommended, as this allows objective titration of doses to individual need and reduces administration of unnecessary medication (Grade A recommendation). In patients with acute concomitant medical or psychiatric illness, or concurrent withdrawal from other drugs, these scales should be used with caution because they rate signs and symptoms which may be caused by the other condition and not by the alcohol withdrawal.

Determination of the dosage of medication administered should be based on the following clinical considerations:

- A. For those with mild symptoms (for example, CIWA-Ar scores under 8-10), a reasonable clinical option is supportive nonpharmacological therapy and continued monitoring (Level I evidence). Those with moderate symptoms, (for example, CIWA-Ar scores between 8-15), benefit symptomatically from medication that will also reduce the risk of major complications. Those with severe symptoms (for example, CIWA-Ar scores 15 or above) have a significant risk of major complications if untreated (Level I evidence). It is recommended that such patients receive benzodiazepines in the amounts necessary to control symptoms, as well as continued close monitoring until symptoms are controlled.
- B. For patients with a history of prior withdrawal seizures, it is a reasonable option to provide one of the recommended medications at the time of presentation, regardless of the severity of withdrawal symptoms (Level III evidence). Monitoring the patient and providing symptom-triggered therapy without fixed schedule therapy is also a reasonable option.

C. For patients who have notable co-morbid medical illness, medications should be considered even if withdrawal is mild to moderate. In addition, caution should be exercised in treating patients who are using sedative-hypnotic medications, as they may be at higher risk for major complications and may exhibit tolerance to benzodiazepines requiring adjustment of dosage (Level III evidence).

The use of structured assessment scales and symptom-triggered therapy is possible in other settings such as psychiatric inpatient units and general medical/surgical wards, but requires training of staff. Where such training has not taken place, the use of fixed-schedule therapy, with the provision of additional medicine when symptoms are not controlled with scheduled doses, is an acceptable alternative. While this may result in the provision of unnecessary medicine, it provides a margin of safety.

Examples of specific treatment regimens which meet these recommendations are provided in Table 5.

3. OTHER AGENTS

Beta blockers, clonidine and carbamazepine are not recommended as monotherapy (Grade B recommendation). While they reduce selected signs and symptoms of withdrawal, they have not been shown to reduce delirium or seizures. They may be considered for use in conjunction with benzodiazepines in patients with certain coexisting conditions such as coronary artery disease for beta-blockers, opiate withdrawal for clonidine and benzodiazepine withdrawal for carbamazepine.

It is recommended that neuroleptic agents not be used as monotherapy as they do not reduce delirium and increase seizures (Grade A recommendation). Neuroleptics may be considered for use in conjunction with benzodiazepines for marked agitation or hallucinations.

Routine parenteral administration of magnesium is not recommended because existing controlled data do not demonstrate improvement in alcohol withdrawal severity, delirium or seizures (Grade B recommendation).

Ethyl alcohol is not recommended due to the lack of controlled studies as well as its known adverse effects as a pharmacologic agent (Grade C recommendation).

It is recommended that thiamine be administered to all patients with alcohol dependence at presentation (Grade C recommendation).

4. SPECIAL POPULATIONS

There is no evidence that the recommendations should change for adolescent or geriatric populations. As noted shorter acting benzodiazepines may have a lower risk of oversedation, which may be of particular relevance in the elderly (Grade C recommendation). Ethyl alcohol should not be used in pregnant women due to its teratogenic effects (Grade C recommendation). In addition, because both benzodiazepines and barbiturates have been associated with adverse effects on the fetus, the amount of these medications administered should be limited to that necessary to prevent the major complications of withdrawal (Grade C recommendation).

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Table 1. Method of grading levels of evidence and recommendations.¹⁷

Levels of Evidence:

Level I studies are randomized trials with low false-positive and low false-negative errors.

Level II studies are randomized trials with high false-positive and/or high false-negative errors.

Level III studies are nonrandomized, concurrent cohort comparisons.

Level IV studies are nonrandomized historical cohort comparisons.

Level V studies are case series without controls.

Recommendations:

Grade A recommendations are supported by one or more level I studies or by a meta-analysis in which the lower limit of the confidence interval for the effect of treatment exceeds the minimally clinically significant benefit.

Grade B recommendations are supported by either one or more level II studies or by a meta-analysis in which the estimate of treatment effect exceeds the minimally clinical significant benefit but the lower limit of the confidence does not.

Grade C recommendations are supported by data other than prospective controlled trials, including secondary analyses of level I or II studies.

Table 2. Prospective, placebo-controlled trials examining the effectiveness of benzodiazepines in reducing the incidence of delirium or seizures.

Source, y	Intervention	No. of Patients with Delirium/ No. of Patients in Group	No. of Patients with Seizures/ No. of Patients in Group
Rosenfeld and Bizzoco 1961 ²⁰	chlordiazepoxide	2/30	--
	placebo	2/30	--
Sereny and Kalant 1965 ²⁵	chlordiazepoxide	0/24	0/24
	placebo	1/11	0/11
Kiam et al, 1969 ²⁹	chlordiazepoxide	1/103	1/103
	placebo	8/130 RR=0.16, 95% CI, 0.02 to 1.24 p=0.08	9/130 RR=0.14, 95% CI, 0.02-1.09 p=0.046
Zilm et al, 1980 ⁵³	chlordiazepoxide	0/15	0/15
	placebo	0/15	2/15
Sellers et al, 1983 ⁶⁷	diazepam	--	0/25
	placebo	--	4/25
Naranjo 1983 ⁶⁸	lorazepam	--	0/15
	placebo	--	2/15
Summary and meta-analysis	benzodiazepine vs placebo	risk difference with benzodiazepine -4.9 cases delirium/100	risk difference with benzodiazepine: -7.7 cases seizures/100

		patients 95% CI, -9.0 to -0.7 p=0.04	patients 95% CI, -12.0 cases to -3.5 cases p=0.0003
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Table 3. Prospective, controlled trials examining the effectiveness of different benzodiazepine agents in reducing the incidence of seizures.

Source, y	Intervention	No. of Patients With Seizures/ No. of Patients in Group
Solomon et al, ⁷⁰ 1983	chlordiazepoxide	0/25
	lorazepam	2/25
Wilson and Vulcano, ⁸⁰ 1984	chlordiazepoxide	5/50
	alprazolam	9/50
Ritson and Chick, ⁹⁸ 1986	diazepam	0/20
	lorazepam	1/20
Summary and meta-analysis	long-acting agents vs short-acting agents	risk difference with long acting agents: -6.7 cases seizures/100 patients 95% CI:-13.0 cases to -0.0 cases p=0.07

Table 4. Prospective, controlled trials examining the effectiveness of neuroleptic agents in reducing the incidence of delirium or seizures.

Source, y	Intervention	No. of Patients with Delirium/ No. of Patients in Group	No. of Patients with Seizures/ No. of Patients in Group
Thomas and Freedman, ²² 1964	promazine	4/34	--
	paraldehyde	0/33	--
Sereny and Kalant, ²⁵ 1965	promazine	1/23	2/23
	placebo	1/11	0/11
	chlordiazepoxide	0/24	0/24
Chambers and	promazine	--	5/34

Schultz, ²⁹ 1965	diazepam	--	0/35
	chlordiazepoxide	--	0/34
Kaim et al., ²⁹ 1969	chlorpromazine	7/98	12/98
	placebo	8/130	9/130
	chlordiazepoxide	1/103	1/103
		chlorpromazine vs chlordiazepoxide	chlorpromazine vs chlordiazepoxide
		RR=7.4, 95% CI, 0.9 to 54	RR=12.6, 95% CI 1.6 to 95
		p=0.03	p=0.001
Summary and meta-analysis	phenothiazine vs placebo	risk difference phenothiazine vs placebo: 0.0 cases delirium/100 patients 95% CI: -5.8 cases to +6.6 cases p=.92	risk difference +4.6 cases seizures/100 patients with phenothiazine 95% CI: -2.6 cases to +11.9 cases p=.19
	phenothiazine vs cross tolerant medication (benzodiazepine or paraldehyde)	risk difference +6.6 cases delirium/100 patients with phenothiazine 95% CI: +2.4 cases to +10.8 cases p=0.002	risk difference +11.4 cases seizures/100 patients with phenothiazine 95% CI: +6.2 cases to +16.6 cases p=0.000003

Table 5. Examples of specific treatment regimens.*

Monitoring:

Monitor the patient every 4-8 hours by means of CIWA-Ar until the score has been below 8-10 for 24 hours. Use additional assessments as needed.

Symptom-triggered regimens:

Administer one of the following medications every hour when the CIWA-Ar is $\geq 8-10$:

Chlordiazepoxide 50-100mg

Diazepam 10-20mg

Lorazepam 2-4mg

Repeat CIWA-Ar one hour after every dose to assess need for further medication.

Fixed-schedule regimens:

Chlordiazepoxide 50 mg every 6 hours for 4 doses, then 25mg every 6 hours for 8 doses

Diazepam 10mg every 6 hours for 4 doses, then 5 mg every 6 hours for 8 doses

Lorazepam 2mg every 6 hours for 4 doses, then 1mg every 6 hours for 8 doses

Provide additional medication as needed when symptoms not controlled (i.e. CIWA-Ar $\geq 8-10$) with above.

Other benzodiazepines may be used at equivalent doses.

*CIWA-AR indicates Clinical Institute Withdrawal Assessment - Alcohol, revised.



ADDICTION MEDICINE ESSENTIALS

CLINICAL INSTITUTE WITHDRAWAL ASSESSMENT OF ALCOHOL SCALE, REVISED (CIWA-AR)

Many quantification instruments have been developed for monitoring alcohol withdrawal (Guthrie, 1989; Sullivan et al, 1989; Sellers and Naranjo, 1983). No single instrument is significantly superior to the others. What is clear is that there are significant clinical advantages to quantifying the alcohol withdrawal syndrome. Quantification is key to preventing excess morbidity and mortality in a group of patients who are at risk for alcohol withdrawal. Such instruments help clinical personnel recognize the process of withdrawal before it progresses to more advanced stages, such as *delirium tremens*. By intervening with appropriate pharmacotherapy in those patients who require it, while sparing the majority of patients whose syndromes do not progress to that point, the clinician can prevent over- and undertreatment of the alcohol withdrawal syndrome. Finally, by quantifying and monitoring the withdrawal process, the treatment regimen can be modified as needed.

The best known and most extensively studied scale is the Clinical Institute Withdrawal Assessment - Alcohol (CIWA-A) and a shortened version, the CIWA-A revised (CIWA-Ar). This scale has well-documented reliability, reproducibility and validity, based on comparison to ratings by expert clinicians (Knott, et al, 1981; Wiehl, et al 1994; Sullivan, et al, 1989). From 30 signs and symptoms, the scale has been carefully refined to a list of 10 signs and symptoms in the CIWA-Ar (Wiehl, et al, 1994). It is thus easy to use and has been shown to be feasible to use in a variety of clinical settings, including detoxification units (Naranjo, et al, 1983; Hoey, et al, 1994), psychiatry units (Heinala, et al, 1990), and general medical/surgical wards (Young, et al, 1987; Katta, 1991). The CIWA-Ar has added usefulness because high scores, in addition to indicating severe withdrawal, are also predictive of the development of seizures and delirium (Naranjo, et al, 1983; Young, et al, 1987).

The CIWA-Ar scale can measure 10 symptoms. Scores of less than 8 to 10 indicate minimal to mild withdrawal. Scores of 8 to 15 indicate moderate withdrawal (marked autonomic arousal); and scores of 15 or more indicate severe withdrawal (impending *delirium tremens*). The assessment requires 2 minutes to perform (Sullivan, et al, 1989).

CIWA-Ar categories, with the range of scores in each category, are as follows:

Agitation	(0-7)
Anxiety	(0-7)
Auditory disturbances	(0-7)
Clouding of Sensorium	(0-4)
Headache	(0-7)
Nausea/Vomiting	(0-7)
Paroxysmal Sweats	(0-7)
Tactile disturbances	(0-7)
Tremor	(0-7)
Visual disturbances	(0-7)

The instrument also has been adapted for benzodiazepine withdrawal assessment (Clinical Institute Withdrawal Assessment-Benzodiazepine).

A study of the revised version of the CIWA predicted that those with a score of >15 were at increased risk for severe alcohol withdrawal (RR 3.72;95% confidence interval 2.85-4.85); the higher the score, the greater the risk. Some patients (6.4%) still suffered complications, despite low scores, if left untreated (Foy, et al, 1988).

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CLINICAL INSTITUTE WITHDRAWAL ASSESSMENT OF ALCOHOL SCALE, REVISED (CIWA-AR)

Patient: _____ Date: _____ Time: _____ (24 hour clock, midnight = 00:00)

Pulse or heart rate, taken for one minute: _____ Blood pressure: _____

NAUSEA AND VOMITING — Ask “Do you feel sick to your stomach? Have you vomited?” Observation.

- 0 no nausea and no vomiting
- 1 mild nausea with no vomiting
- 2
- 3
- 4 intermittent nausea with dry heaves
- 5
- 6
- 7 constant nausea, frequent dry heaves and vomiting

TREMOR — Arms extended and fingers spread apart. Observation.

- 0 no tremor
- 1 not visible, but can be felt fingertip to fingertip
- 2
- 3
- 4 moderate, with patient's arms extended
- 5
- 6
- 7 severe, even with arms not extended

PAROXYSMAL SWEATS — Observation.

- 0 no sweat visible
- 1 barely perceptible sweating, palms moist
- 2
- 3
- 4 beads of sweat obvious on forehead
- 5
- 6
- 7 drenching sweats

ANXIETY — Ask “Do you feel nervous?” Observation.

- 0 no anxiety, at ease
- 1 mild anxious
- 2
- 3
- 4 moderately anxious, or guarded, so anxiety is inferred
- 5
- 6
- 7 equivalent to acute panic states as seen in severe delirium or acute schizophrenic reactions

AGITATION — Observation.

- 0 normal activity
- 1 somewhat more than normal activity
- 2
- 3
- 4 moderately fidgety and restless
- 5
- 6
- 7 paces back and forth during most of the interview, or constantly thrashes about

TACTILE DISTURBANCES — Ask “Have you any itching, pins and needles sensations, any burning, any numbness, or do you feel bugs crawling on or under your skin?” Observation.

- 0 none
- 1 very mild itching, pins and needles, burning or numbness
- 2 mild itching, pins and needles, burning or numbness
- 3 moderate itching, pins and needles, burning or numbness
- 4 moderately severe hallucinations
- 5 severe hallucinations
- 6 extremely severe hallucinations
- 7 continuous hallucinations

AUDITORY DISTURBANCES — Ask “Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?” Observation.

- 0 not present
- 1 very mild harshness or ability to frighten
- 2 mild harshness or ability to frighten
- 3 moderate harshness or ability to frighten
- 4 moderately severe hallucinations
- 5 severe hallucinations
- 6 extremely severe hallucinations
- 7 continuous hallucinations

VISUAL DISTURBANCES — Ask “Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?” Observation.

- 0 not present
- 1 very mild sensitivity
- 2 mild sensitivity
- 3 moderate sensitivity
- 4 moderately severe hallucinations
- 5 severe hallucinations
- 6 extremely severe hallucinations
- 7 continuous hallucinations

HEADACHE, FULLNESS IN HEAD — Ask “Does your head feel different? Does it feel like there is a band around your head?” Do not rate for dizziness or lightheadedness. Otherwise, rate severity.

- 0 no present
- 1 very mild
- 2 mild
- 3 moderate
- 4 moderately severe
- 5 severe
- 6 very severe
- 7 extremely severe

ORIENTATION AND CLOUDING OF SENSORIUM —

- Ask “What day is this? Where are you? Who am I?”
- 0 oriented and can do serial additions
 - 1 cannot do serial additions or is uncertain about date
 - 2 disoriented for date by no more than 2 calendar days
 - 3 disoriented for date by more than 2 calendar days
 - 4 disoriented for place/or person

The CIWA-Ar is *not* copyrighted and may be reproduced freely.
Sullivan, J.T.; Sykora, K.; Schneiderman, J.; Naranjo, C.A.; and Sellers, E.M.
Assessment of alcohol withdrawal: The revised Clinical Institute Withdrawal
Assessment for Alcohol scale (CIWA-Ar). *British Journal of Addiction* 84:1353-1357, 1989.

Patients scoring less than 10 do not usually need additional medication for withdrawal.

Total CIWA-Ar Score _____

Rater's Initials _____

Maximum Possible Score 67

Screening and Brief Interventions for Alcoholism

SCREEN:

At each visit, ask about alcohol use:

- How many drinks per week?
- Maximum drinks per occasion in past month?

Use CAGE questions to probe for alcohol problems:

- Have you ever tried to Cut down on your drinking?
- Do you get Annoyed when people talk about your drinking?
- Do you feel Guilty about your drinking?
- Have you ever had an Eye-opener? (A drink first thing in the morning)

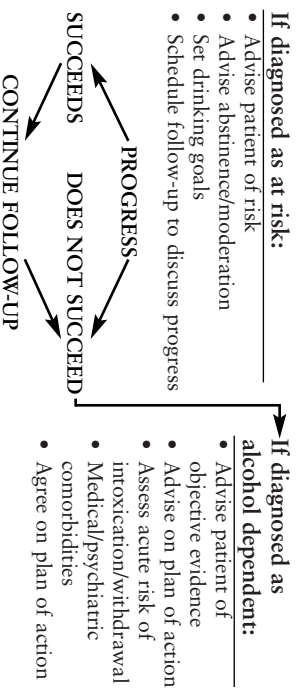
SCREEN IS POSITIVE IF:

- Consumption is > 14 drinks/week or > 4 drinks/occasion (men)
- Consumption is > 7 drinks/week or > 3 drinks/occasion (women)
- CAGE score > 1

THEN ASSESS FOR:

- *Medical problems:* e.g., blackouts; depression; hypertension; trauma; abdominal pain; liver dysfunction; sexual problems; sleep disorders
- *Laboratory:* elevated GGTP or other LFTs; elevated MCV; +BAC
- *Behavioral problems:* work; family; school; accidents
- *Alcohol dependence:* 3+ on CAGE or one or more of: compulsion to drink; impaired control; withdrawal symptoms; increased tolerance; relief drinking

GIVE SPECIFIC FEEDBACK TO PATIENT, THEN ADVISE — FIRM BUT EMPATHIC:



PLAN OF ACTION:

- Refer the patient to an addiction medicine specialist for formal assessment and development of a treatment plan.
- Educate the patient, significant other/s, and family about the nature of addiction, the effectiveness of treatment, and the prospects for recovery.
- Remain engaged in care of the patient by addressing medical issues as needed and supporting the patient's commitment to the treatment process.

*For more information, see Principles of Addiction Medicine,
Third Edition. (AW Graham, TK Schultz, M Mayo-Smith & RK
Ries), published by ASAM, 2002.*

American Society of Addiction Medicine



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