Management of Alcohol Withdrawal Delirium

An Evidence-Based Practice Guideline

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Background: Alcohol withdrawal delirium is the most serious manifestation of alcohol withdrawal. Evidence suggests that appropriate care improves mortality, but systematic reviews are unavailable.

Methods: Articles with original data on management of alcohol withdrawal delirium underwent structured review and meta-analysis.

Results: Meta-analysis of 9 prospective controlled trials demonstrated that sedative-hypnotic agents are more effective than neuroleptic agents in reducing duration of delirium and mortality, with a relative risk of death when using neuroleptic agents of 6.6. Statistically significant differences among various benzodiazepines and barbiturates were not found. No deaths were reported in 217 patients from trials using benzodiazepines or barbiturates.

Conclusions: Control of agitation should be achieved using parenteral rapid-acting sedative-hypnotic agents that are cross-tolerant with alcohol. Adequate doses should be used to maintain light somnolence for the duration of delirium. Coupled with comprehensive supportive medical care, this approach is highly effective in preventing morbidity and mortality.

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ALCOHOL DEPENDENCE IS commonly encountered by physicians, and it occurs in 15% to 20% of hospitalized patients in some settings.[1-3] Alcohol withdrawal is among the many medical problems associated with alcohol dependence. Withdrawal signs and symptoms are usually minor, but they can be considerable and even fatal. Alcohol withdrawal delirium (AWD), commonly known as delirium tremens or "DTs," is the most serious manifestation of alcohol withdrawal syndrome.

Current diagnostic criteria for AWD include disturbance of consciousness, change in cognition or perceptual disturbance developing in a short period, and the emergence of symptoms during or shortly after withdrawal from heavy alcohol intake (**Table 1**).[4] The classic clinical presentation of AWD also includes hyperpyrexia, tachycardia, hypertension, and diaphoresis. The incidence of AWD averages 5% in placebo-treated alcohol-dependent patients entered into clinical trials of inpatient drug treatment for alcohol withdrawal.[5] Clinical features of alcohol withdrawal syndrome can appear within hours of the last drink, but delirium typically does not develop until 2 to 3 days after cessation of drinking. Alcohol withdrawal delirium usually lasts 48 to 72 hours, but there have been case reports[6-8] of much longer duration. Initial studies found mortality to be as high as 15%,[8] but with advances in treatment, mortality rates have fallen, with more recent studies[9] indicating mortality of 0% to 1%.

Given the seriousness of AWD and the apparent value of appropriate treatment in preventing morbidity and mortality, the development of an evidence-based guideline would have widespread utility. The purpose of this guideline, therefore, is to assist physicians and other health care professionals in providing appropriate treatment for all patients with AWD. This guideline does not address the management of uncomplicated alcohol withdrawal syndrome or the prevention of AWD as these topics are covered in a previously published guideline.[5]

METHODS

Management of AWD was a topic identified for guideline development by the American Society of Addiction Medicine Committee on Practice Guidelines. A working group was appointed that included individuals with training

Table 1. *DSM-IV* Diagnostic Criteria for Alcohol Withdrawal and Alcohol Withdrawal Delirium*

Alcohol Withdrawal
A. Cessation of (or reduction in) alcohol use that has been heavy and prolonged.
B. Two (or more) of the following, developing within several hours to a few days after criterion A:
(1) Autonomic hyperactivity (eg, sweating or pulse rate >100/min)
(2) Increased hand tremor
(3) Insomnia
(4) Nausea or vomiting
(5) Transient visual, tactile, or auditory hallucinations or illusions
(6) Psychomotor agitation
(7) Anxiety
(8) Grand mal seizures
C. The symptoms in criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.
Specify whether with perceptual disturbances.
Alcohol Withdrawal Delirium†
A. Disturbance of consciousness (ie, reduced clarity of awareness of the environment), with reduced ability to focus, sustain, or shift attention.
B. A change in cognition (such as memory deficit, disorientation, or language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia.
C. The disturbance develops in a short period (usually hours to days) and tends to fluctuate during the day.
D. There is evidence from the history, physical examination, or laboratory findings that the symptoms in criteria A and B developed during, or shortly after, a withdrawal syndrome.

*Data from the American Psychiatric Association.[4]

†This diagnosis should be made instead of a diagnosis of substance withdrawal only when the cognitive symptoms are in excess of those usually associated with the withdrawal syndrome and when the symptoms are sufficiently severe to warrant independent clinical attention.

Table 2. Methods of Grading Levels of Evidence and Recommendations[12]

Definition	
Levels of Evidence	
Level I studies	Randomized trials with low false-positive and low false-negative errors
Level II studies	Randomized trials with high false-positive or high false-negative errors
Level III studies	Nonrandomized, concurrent cohort comparisons
Level IV studies	Nonrandomized, historical cohort comparisons
Level V studies	Case series without controls
Recommendations	
Grade A	Supported by 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	Supported by level II studies or by a meta-analysis in which the estimate of treatment effect exceeds the minimal clinically significant benefit but the lower limit of the confidence interval does not
Grade C	Supported by data other than prospective controlled trials, including secondary analyses of level I or II studies

in internal medicine, family practice, psychiatry, and pharmacology and individuals involved in primary care medicine, addiction medicine, and research on alcohol withdrawal.

The primary outcomes considered by the working group included (1) mortality rate, (2) duration of delirium, (3) time required for control of agitation, (4) adequate control of delirium, (5) treatment complications, and (6) costs. Acquisition costs were determined by averaging wholesale prices listed in the *2001 Red Book*.[10]

The options considered for managing AWD included pharmacologic and nonpharmacologic strategies. Any pharmacologic agent that has been studied in the management of AWD was considered. Nonpharmacologic strategies included the choice of the setting for treatment, evaluation, monitoring, and supportive and psychosocial care.

REVIEW OF THE EVIDENCE

Searches of the English-language medical literature were conducted through MEDLINE using the key words "substance withdrawal syndrome and alcohol," "alcohol withdrawal delirium," and "delirium tremens" from the initial entries in MEDLINE (January 1, 1966, through September 30, 2001). Articles were selected if they involved human subjects and included new clinical data on the management of AWD (ranging from a single case report to a prospective randomized trial). References from the selected articles, including those from before 1966, from review articles, and from textbooks were also examined and included when appropriate. Members of the working group, using a structured data collection form, abstracted all articles meeting the initial inclusion criteria. Articles identified as prospective controlled trials with patients meeting explicit inclusion criteria, including the basic elements of the *DSM-IV* criteria for AWD, underwent further independent review by a second member, with abstraction of data for meta-analysis. Any differences of interpretation were resolved by consensus. Meta-analysis was performed when possible using the logit method.[11]

RECOMMENDATIONS

Recommendations based on the evidence were drafted and graded according to a published system (**Table 2**).[12] In several areas, it was recognized that a single recommendation could not be formulated to guide the treatment 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, greater weight was given to studies with higher grades of evidence, as defined in Table 2. When no evidence from controlled studies was available, expert opinion was considered. Among outcomes, greatest value was given to patient safety, followed by patient comfort, and then cost. Given the seriousness of the outcomes involved, it was believed that there would be little or no variation in patient preference for treatment and that patients would prefer improved medical outcomes (decreased mortality, shorter duration of delirium, etc).

GUIDELINE REVIEW

The draft guideline was sent for review to first authors of articles from the past 10 years that met the inclusion criteria and to representatives of organizations of medical interest (drawn from the list published by the American Medical Association) for whom this guideline may have been of interest. The American Society of Addiction Medicine Board of Directors approved the final version in October 2002, with review and re-

vision scheduled for November 2007, unless new information warrants revision before then.

RESULTS

Forty-three articles were identified as having original data, including 9 prospective controlled trials. In the following subsections, data are reviewed according to the specific intervention studied.

BENZODIAZEPINES AND OTHER SEDATIVE-HYPNOTIC AGENTS

Mortality

No controlled trials comparing sedative-hypnotic agents with placebo in treating AWD were identified. However, 5 controlled trials[13-17] compared sedative-hypnotic agents and neuroleptic drugs in reducing mortality with AWD (**Table 3**). Meta-analysis indicated that sedative-hypnotic use is more effective than neuroleptic use in reducing mortality from AWD, with a summary relative risk of mortality with neuroleptic treatment compared with sedative-hypnotic treatment of 6.6 (95% confidence interval, 1.2-34.7).

The effectiveness of different sedative-hypnotic agents (diazepam, chlordiazepoxide, pentobarbital, paraldehyde, and barbital) in reducing mortality with AWD was evaluated in 5 controlled trials (Table 3).[15,17-20] Two deaths were reported (both patients were treated with paraldehyde); thus, overall, these trials do not demonstrate statistically significant differences among them. The small number of deaths in these trials, however, limits the power to detect differences in this outcome.

Table 3. Prospective Controlled Trials Reporting Mortality as an Outcome*

Source	Intervention	Route of Administration	Deaths, No./ Patients, Total No.
Friedhoff and Zitrin,[13] 1959	*Chlorpromazine*	IM/PO	0/15
	Paraldehyde	IM/PO	0/16
Thomas and Freedman,[14] 1964	*Promazine*	PO	6/17
	Paraldehyde	PO	1/22†
Chambers and Schultz,[15] 1965	*Promazine* plus chloral hydrate	PO	0/34
	Diazepam	PO	0/35
	Chlordiazepoxide	PO	0/34
Golbert et al,[16] 1967	*Promazine*	IM/PO	2/13
	Paraldehyde and chloral hydrate	IM/PO	0/12
Kaim and Klett,[17] 1972	*Perphenazine*	IM/PO	0/46
	Chlordiazepoxide	IM/PO	0/46
	Pentobarbital	IM/PO	0/41
	Paraldehyde	IM/PO	0/55
Brown et al,[18] 1972	Diazepam	IV	0/7
	Chlordiazepoxide	IV	0/7
Thompson et al,[19] 1975	Diazepam	IV	0/17
	Paraldehyde	Rectal	2/17
Kramp and Rafaelsen,[20] 1978	Diazepam	IM	0/13
	Barbital	PO	0/17
Present meta-analysis	*Neuroleptics* vs sedative-hypnotics		‡

Abbreviations: IM, intramuscular; IV, intravenous; PO, oral.
*Neuroleptic agents are shown in italic.
†$P<.05$.
‡The summary relative risk of neuroleptics vs sedative-hypnotics of the 2 studies with mortality is 6.6 (95% confidence interval, 1.2-34.7).

Duration of Delirium

Table 4 summarizes the results of prospective trials evaluating different agents in reducing the duration of AWD. Three of 4 trials[13,14,17] comparing sedative-hypnotic agents with neuroleptic agents demonstrated that the former are superior to the latter in reducing the duration of AWD. (In the fourth trial,[16] there was insufficient data in the original article to calculate *P* values.) Differences among sedative-hypnotic agents in reducing duration of AWD were not demonstrated.

Time Required to Control Agitation

Only 2 studies were identified that considered the time required to control agitation. In a study[19] comparing rectal paraldehyde use with intravenous (IV) diazepam use, the time to achieve adequate sedation, defined as the patient being quiet but awake, was significantly shorter with diazepam (1.1 vs 3.0 hours; $P=.02$). In contrast, in a study[20] comparing intramuscular diazepam use and oral barbital therapy, there was no significant difference in the mean number of hours to achieve adequate sedation, defined as a light sleep from which the patient could easily be aroused (11 hours for diazepam vs 8 hours for barbital; $P>.05$).

General pharmacokinetic studies have shown that oral diazepam has slightly shorter times to onset and to peak action than other benzodiazepines.[21] The onset of action of all benzodiazepines injected IV is rapid, ranging from 15 seconds to a few minutes. Peak action of IV benzodiazepines is 5 to 15 minutes.[21] Intramuscular injection of chlordiazepoxide and diazepam is associated with erratic absorption, which can lead to difficulty in rapid control of symptoms.[22,23] An exception is lorazepam, which has good intramuscular and sublingual absorption.[24] Continuous infusion of shorter-acting agents, such as midazolam and lorazepam, has also been used,[25] with the hypothesis that this may facilitate rapid titration of the dose. However, continuous infusion has not been directly compared with intermittent dosing in any study.

Adequate Control of Delirium

In the study[19] comparing rectal paraldehyde use and IV diazepam administration, satisfactory control of agitation was achieved in all 17 patients in the diazepam arm but in only 12 of 17 in the paraldehyde arm. In a large, multicenter Veterans Affairs study,[17] there were no significant differences in achieving adequate control of delirium, but the rate of failure was low. Two of 46 patients taking perphenazine and 1 of 41 taking pentobarbital were "unresponsive to treatment" with their assigned medication. Studies have demonstrated that the

Table 4. Prospective Controlled Trials Reporting Duration of Delirium*

Source	Intervention	Route of Administration	Patients, No.	Duration, h	*P* Value
Friedhoff and Zitrin,[13] 1959	*Chlorpromazine*	IM/PO	15	192	<.05
	Paraldehyde		16	144	
Thomas and Freedman,[14] 1964	*Promazine*	PO	17	96	.04†
	Paraldehyde	PO	22	74	
Golbert et al,[16] 1967	*Promazine*	PO	5	134	. . .‡
	Paraldehyde/chloral hydrate		11	<24	
Kaim and Klett,[17] 1972	*Perphenazine*	IM/PO	46	77.9	>.20
	Pentobarbital	IM/PO	41	80	
	Paraldehyde	IM/PO	55	78.4	
	Chlordiazepoxide	IM/PO	46	74	
Thompson et al,[19] 1975	Paraldehyde	Rectal	17	57	>.05
	Diazepam	IV	17	55	

Abbreviations: IM, intramuscular; IV, intravenous; PO, oral.
*Neuroleptic agents are shown in italic.
†Fisher exact test, 2-tailed.
‡Insufficient data provided in the original article to calculate *P* value.

required dose of medication can vary substantially among patients and within the same patient over time. In one study,[19] the doses for initial calming ranged from 15 to 215 mg of diazepam. Cumulative doses of more than 2000 mg of diazepam in 2 days,[26] more than 2000 mg of diazepam in 4 days, and more than 20 000 mg of oxazepam in 9 days[27] have been required for the management of AWD. In one published case,[28] the patient required 2850 mg of midazolam in a 50-day period. Another patient required 12 424.4 mg of diazepam, 121 mg of lorazepam, 3050 mg of chlordiazepoxide, and 2025 mg of midazolam in 8 weeks.[29]

Although studies have shown no difference in overall rates of achieving control of delirium among different sedative-hypnotic agents, case series describe patients whose agitation was refractory to even massive doses of benzodiazepines but then responded to pentobarbital[30] or IV infusions of propofol.[31] The authors hypothesized that the benzodiazepine receptors that mediate γ-aminobutyric acid–A activity became saturated with high doses of benzodiazepines and that further increases thus had little effect on control of delirium. Barbiturates and propofol act via a different set of receptors, and, thus, their addition could yield beneficial results. Furthermore, propofol has additional effects on *N*-methyl-D-aspartate and glutamate receptors that also are believed to play a role in alcohol withdrawal symptoms. Thus, propofol may be able to modify withdrawal symptoms by a different pathway than benzodiazepines.

Treatment Complications

In the study[19] comparing rectal paraldehyde use and IV diazepam use, 2 of 17 patients in the paraldehyde group developed respiratory arrest requiring resuscitation. In another study,[17] 1 patient treated with pentobarbital developed lethargy progressing to coma. In the remainder of the studies, significant complications related to treatment were not observed. It has also been demonstrated in patients undergoing alcohol withdrawal, but not in those with AWD, that shorter-acting agents have a higher incidence of rebound symptoms[32] and may be associated with the occurrence of withdrawal seizures if discontinued too rapidly.[30,33]

Several case series have reported on the use of other sedative-hypnotic agents in managing AWD, including chlormethiazole,[34-37] lorazepam,[38,39] flunitrazepam,[40] pentobarbital,[41] propofol,[31,42-45] and midazolam.[29] Chlormethiazole and flunitrazepam are not available in the United States. The shorter-acting agents—propofol, pentobarbital, lorazepam, and midazolam—were thought to be advantageous owing to ease of titration and lower risk of excess sedation. However, there are no controlled trials comparing short- and longer-acting agents in AWD.

Costs

Costs can vary greatly depending on the selected drug and the route of administration. For example, the average wholesale cost of different agents in oral form at approximately equivalent dosages are as follows: chlordiazepoxide, 25 mg, $0.07; diazepam, 5 mg, $0.10; and lorazepam, 1 mg, $0.80.[10,29] Intravenous medication, which is usually needed for adequate control of AWD, is often more than 3 times as expensive as oral medication. For example, the average wholesale cost of these agents in equivalent dosages are as follows: diazepam, 10 mg, $2.40; lorazepam, 2 mg, $2.74; pentobarbital, 350 mg, $4.90; and midazolam, 5 mg, $5.60. (Midazolam would need continuous infusion, with published doses at 0.75 to 10.0 μg/kg per minute, or $3.36 to $47.04 per hour for a 70-kg person, although prices are expected to decrease as the generic form becomes available.) Some practitioners[28,29,46] have described the use of continuous infusion of short-acting benzodiazepines, such as lorazepam or midazolam. Such infusions can require very large amounts of medication over several hours or days. Direct drug costs (excluding costs of preparation, administration, and monitoring) of $50 335 for a 25-hour infusion of midazolam were reported for 1 patient,[29] and a hospital stay costing $26 045 was reported for another patient.[46] Furthermore, there are no trials reporting comparative risks and benefits of intermittent vs continuous IV administra-

tions, and no evidence could be identified documenting an advantage for continuous infusion.[46]

NEUROLEPTIC AGENTS

No placebo-controlled trials of neuroleptic agents in AWD were identified. The trials reviewed earlier demonstrated that neuroleptic drug therapy is inferior to sedative-hypnotic drug use in reducing mortality and duration. Nevertheless, neuroleptic agents, especially haloperidol, are commonly used with sedative-hypnotic drugs to calm patients with AWD.[47-50] However, neuroleptic agents have the potential to cause a variety of serious adverse effects, particularly when used in very high doses, which may be required to control severe agitation. Chlorpromazine, promazine, and other low-potency typical antipsychotic agents have been reported[51] to have the greatest effect on lowering seizure threshold. Chlorpromazine and thioridazine are the most common offenders for causing hypotension, and thioridazine may also prolong the QTc interval, increasing risk for torsade de pointes and sudden death.[52] All neuroleptic agents are thought to have the potential for causing neuroleptic malignant syndrome,[53] and cases have been reported in patients with AWD who have received neuroleptic drugs. No studies were identified describing the use of newer "atypical" antipsychotic agents, such as risperidone, olanzapine, and quetiapine, for AWD. These agents are at least as efficacious as typical antipsychotic agents for other indications and have a preferable adverse effect profile.

β-ADRENERGIC ANTAGONISTS

The effect of β-adrenergic antagonists in patients with AWD has not been studied. However, delirium is a known adverse effect of β-adrenergic blocker therapy,[54] and in at least 1 controlled study[55] of propranolol in alcohol withdrawal syndrome, there was an increased incidence of delirium.

MAGNESIUM

Low serum magnesium levels have repeatedly been reported[56-59] in patients with AWD. It has been suggested that magnesium administration reduces neuromuscular activity. However, its use has not been evaluated in controlled trials in AWD.

ETHYL ALCOHOL

Although there have been small case series describing administration of alcohol for the prevention and treatment of withdrawal symptoms, there are no controlled trials evaluating its use in the prevention or treatment of AWD. Ethyl alcohol is known to have the potential for several adverse effects, including hepatic, gastrointestinal, hematologic, and neurologic toxic effects.

THIAMINE

Patients with alcohol dependence are often thiamine deficient, and it has been reported[57,59] that patients with AWD have even more substantial deficiencies. Thiamine deficiency is associated with Wernicke encephalopathy and Wernicke-Korsakoff syndrome. Thiamine administration has a low risk of adverse effects and can prevent the development of these conditions. In particular, thiamine should be given before administration of IV fluids containing glucose, as the IV administration of glucose may precipitate acute thiamine deficiency.[60]

OTHER AGENTS

Several articles describe the use of various other agents in managing AWD, including carbamazepine,[61] dexamethasone,[62] physostigmine,[63] 5-hydroxytrytophan,[64] and bromperidol.[65] However, these case series have been small and uncontrolled. In addition, although studies of other agents (antiepileptic agents, clonidine, etc) in managing alcohol withdrawal without delirium have been published, no evidence regarding their effectiveness in AWD has been identified.[5]

SUPPORTIVE CARE

No controlled studies of nonpharmacologic interventions were identified in the literature search. However, the literature includes recommendations from clinical experts on general management of AWD.

A comprehensive history, physical examination, and thorough diagnostic evaluation are always recommended in view of the known morbidity and mortality of AWD and the frequent occurrence of associated medical illnesses.[47,48,50,66-68] Patients usually need the standard diagnostic tests to evaluate new-onset delirium, including neuroimaging to rule out subdural hemorrhaging or other intracranial lesions. Lumbar punctures have been recommended in febrile patients when there are no contraindications.[67,68] Further diagnostic evaluation can be undertaken for any indication of commonly coexisting conditions, such as gastrointestinal hemorrhage, pancreatitis, and infectious diseases.[47,50,67,68] Most experts have recommended general supportive care that includes a quiet, well-lit room, reassurance and reorientation, frequent monitoring of vital signs, and restraints as needed.[47,49,50,67,68] Dehydration and metabolic abnormalities, such as magnesium and phosphorus deficiency, are common with AWD, and it is generally recommended that fluid status and electrolyte levels be monitored carefully and any abnormalities be corrected.[48-50,67,68]

RECOMMENDATIONS

CHOICE OF PHARMACOLOGIC AGENT

The initial therapeutic goal in patients with AWD is control of agitation, the symptom that should trigger use of the medication regimens described in this guideline. Rapid and adequate control of agitation reduces the incidence of clinically important adverse events. Sedative-hypnotic drugs are recommended as the primary agents for managing AWD (grade A recommendation). These drugs reduce mortality, reduce the duration of symptoms, and are associated with fewer complications compared with neuroleptic agents in controlled trials.

Examples of Medication Regimens

Several different benzodiazepines and dosing regimens have been used and recommended. The following are examples of medications and dosing regimens.

Benzodiazepines

Diazepam, 5 mg intravenously (2.5 mg/min). If the initial dose is not effective, repeat the dose in 5 to 10 minutes. If the second dose of 5 mg is not satisfactory, use 10 mg for the third and fourth doses every 5 to 10 minutes. If not effective, use 20 mg for the fifth and subsequent doses until sedation is achieved. Use 5 to 20 mg every hour as needed to maintain light somnolence.

Lorazepam, 1 to 4 mg intravenously every 5 to 15 minutes, or lorazepam, 1 to 40 mg intramuscularly every 30 to 60 minutes, until calm, then every hour as needed to maintain light somnolence.

Neuroleptics

Haloperidol, 0.5 to 5 mg intravenously/intramuscularly every 30 to 60 minutes as needed for severe agitation. (Only to be used as adjunctive therapy with sedative-hypnotic agents.)

Haloperidol, 0.5 to 5 mg orally every 4 hours as needed for agitation not controlled by sedative-hypnotic agents alone.

Current evidence does not clearly indicate that a specific sedative-hypnotic agent is superior to others or that switching from one to another is helpful. Benzodiazepines are most commonly used and recommended by addiction specialists because of a favorable therapeutic/toxic effect index. Examples of commonly used regimens are shown in the Box. However, reported clinical experience indicates that barbiturates may be considered an option. Owing to difficulties in administration and titration of dose, paraldehyde is not recommended (grade A recommendation). Choice among benzodiazepines may be guided by the following considerations: (1) agents with rapid onset control agitation more quickly, for example, oral or IV diazepam has a more rapid onset than other agents (level II evidence); (2) agents with long duration of action (eg, diazepam) provide a smooth treatment course with less breakthrough symptoms; (3) agents with shorter duration of activity (eg, lorazepam) may have lower risk when there is concern about prolonged sedation, such as in patients who are elderly or who have substantial liver disease or other serious concomitant medical illness (level III evidence); and (4) the cost of different benzodiazepines can vary considerably.

If a patient demonstrates agitation that is not controlled with extremely large doses of benzodiazepines, use of pentobarbital or propofol can be considered (grade C recommendation).

DETERMINATION OF DOSE AND ROUTE OF ADMINISTRATION

It is recommended that the dose be determined specifically for each individual patient and that medications be given in doses sufficient to achieve and maintain light somnolence as the recommended therapeutic end point (grade C recommendation). Light somnolence is characterized by a state in which the patient is awake but tends to fall asleep unless stimulated or is sleeping but easily aroused. The amount of medication required for adequate sedation varies greatly from patient to patient and over time in the same patient. Sedative-hypnotic drug doses needed to suppress AWD are commonly much higher than doses used to treat severe anxiety or to sedate patients presurgically. Tolerance, age, severity of signs and symptoms, and medical comorbidity affect the quantity of medication needed for adequate control. When using shorter-acting agents, medication should be tapered carefully even after AWD resolves to prevent the development of breakthrough symptoms or the occurrence of withdrawal seizures.

The medication should be administered by a route that supports achievement of rapid control of agitation and maintenance of appropriate sedation (light somnolence). Intravenous administration has the quickest onset compared with other routes. Intramuscular injection of most benzodiazepines is not recommended owing to erratic absorption (grade C). Lorazepam, however, is an option in patients with stable cardiovascular status, as it has good intramuscular absorption. Intermittent IV administrations of long-acting medications and continuous IV infusion of short-acting medications seem effective and thus are acceptable. However, continuous IV infusion is considerably more expensive, and there is no existing evidence of therapeutic superiority.

OTHER AGENTS

Neuroleptic agents are not recommended as the sole pharmacologic agents in the treatment of AWD because they are associated with higher mortality, longer duration of delirium, and more complications compared with sedative-hypnotic agents in controlled trials[13-17] (grade A recommendation). Neuroleptic agents may be considered for use in conjunction with benzodiazepines when agitation, perceptual disturbances, or disturbed thinking are not adequately controlled by benzodiazepine therapy (grade C recommendation).

β-Adrenergic antagonists may be considered for use in conjunction with benzodiazepines in selected patients for control of persistent hypertension or tachycardia (grade C recommendation). They are not recommended for routine use in all patients with AWD, however, as there is no evidence that they improve outcomes in AWD, and β-adrenergic antagonists, particularly propranolol, may worsen delirium (level V evidence).

Ethyl alcohol is not recommended because there are no controlled trials and there are well-known adverse effects (grade C recommendation).

There is no evidence that magnesium therapy specifically benefits the delirium in alcohol withdrawal. However, magnesium deficiency is common in patients with AWD. Magnesium should be provided for demonstrated hypomagnesemia, and it is also safe and reasonable to include it in IV fluids given for volume repletion provided renal function is normal and levels are monitored (grade C recommendation).

Parenteral administration of thiamine (100 mg daily for at least 3 days, IV or intramuscularly) is recommended to prevent or treat Wernicke-Korsakoff syndrome (grade C recommendation).

SETTING AND SERVICES

The following recommendations are based on the clinical experience of recognized experts; they have not been the subject of controlled studies (grade C recommendations).

EVALUATION

On admission or transfer of a patient from one setting to another, a thorough medical evaluation is needed to determine appropriate diagnostic tests, monitoring, and medication. Elderly patients and those with concurrent medical conditions, acute and chronic, are at higher risk of complications. Concurrent medical conditions are common and may include dehydration, unrecognized head trauma, electrolyte abnormalities, infections (including meningitis), gastrointestinal hemorrhage, pancreatitis, liver disease, and myocardial infarction. These conditions may not be obvious or self-reported in delirious patients.

MONITORING

- Close monitoring by nursing personnel is critical in providing protection for the patient and for maintaining accurate information to guide ongoing medical management. In many cases, continuous, one-to-one observation and monitoring may be required to ensure safe and adequate management of agitated and disoriented patients.
- Vital signs should be monitored regularly in all patients. The appropriate frequency of monitoring depends on the frequency of medication administration, concurrent medical conditions, and the degree of abnormality of the vital signs.

When high doses of benzodiazepines are needed, or when continuous infusions of medication are used, or when patients have significant concurrent medical conditions, cardiac monitoring and oximetry should be in place and resuscitative equipment should be readily available.

MANAGEMENT

- A quiet room with good lighting and environmental cues (eg, a clock and a calendar) may help reduce confusion.
- Physical restraints may be needed temporarily to protect agitated patients from injuring themselves and to protect staff. Guidelines have been formulated on the appropriate use of restraints to ensure patient safety.[69,70]

If patients cannot take oral medications or maintain adequate oral intake, or if more rapid sedation is needed, IV fluids and medications are recommended. Fluid and electrolyte balance should be maintained, and monitoring of fluid input and output and laboratory variables may be required. Occasionally, endotracheal intubation and ventilatory support may be required.

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This guideline is not a substitute for the experience and judgment of a physician. It has been developed to enhance the physician's ability to practice evidence-based medicine. Presented authors' opinions are not necessarily representative of the agencies for which they work.

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phosphodiesterase type 5 (PDE5) inhibitors in patients with cardiac disease. Until such trials become available, PDE5 inhibitors should be used with caution in patients with CHF.

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1. Webster LJ, Michelakis ED, Davis T, Archer SL. Use of sildenafil for safe improvement of erectile function and quality of life in men with New York Heart Association classes II and III congestive heart failure: a prospective, placebo-controlled, double-blind crossover trial. *Arch Intern Med.* 2004;164:514-520.
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Use of Sildenafil Is Safe in Men With Congestive Heart Failure

Webster et al[1] found that the PDE5 inhibitor sildenafil citrate can be safely used in the treatment of ED in men with NYHA classes II and III heart failure. The study by Webster and colleagues[1] may include additional data of further clinical importance. It is generally recognized that the concomitant use of nitrates and PDE5 inhibitors is strictly contraindicated. Caution in using PDE5 inhibitors in patients receiving treatment with α-blockers has also been warranted, and combination therapy cannot be recommended. In the product summary of the most recent commercial available PDE5 inhibitor vardenafil hydrochloride (launched in 2003), it is emphasized that clinical data addressing the safety of combination therapy with vardenafil and α-blockers are insufficient. Similar conclusions can most likely be drawn for therapy with sildenafil or tadalafil.

Cardiologists and other physicians treating patients with CHF therefore have to anticipate 1 more challenge. The prevalence of ED in these patients is high. Because of its prognostic superiority to β-blockers, the use of the αβ-blocker carvedilol in patients with reduced left ventricular ejection fraction has increased worldwide. The quantitative proportion of α-blocker in 1 carvedilol tablet is approximately one tenth. To the best of our knowledge, no study has so far assessed the safety of combination therapy with carvedilol and PDE5 inhibitors. However, Webster and colleagues[1] may be in the position of having data that can enlighten us on this important issue. In their study,[1] 33 (94%) of the 35 patients took β-blockers, and we would like to ask the authors if any of these patients actually were treated with the "modern β-blocker" carvedilol? If so, were there any differences in the blood pressure and heart rate response between patients taking carvedilol and patients being treated with the older β-blockers?

In their study, Webster et al[1] measured blood pressure and heart rate at 15-minute intervals after the ingestion of sildenafil. However, there appear to be no data telling the readers how often the 35 patients actually took sildenafil during the 12-week study period. We would appreciate if the authors could also inform us on the total number of 50-mg doses of sildenafil citrate that were taken by the 35 patients. These data are of importance in the overall evaluation of the scientific strength of the study and its potential clinical consequences.

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1. Webster LJ, Michelakis ED, Davis T, Archer SL. Use of sildenafil for safe improvement of erectile function and quality of life in men with New York Heart Association classes II and III congestive heart failure: a prospective, placebo-controlled, double-blind crossover trial. *Arch Intern Med.* 2004;164:514-520.

Correction

Error in Box. In the Original Investigation by Mayo-Smith et al published in the July 12 issue of the ARCHIVES (2004;164:1405-1412), titled "Management of Alcohol Withdrawal Delirium: An Evidence-Based Practice Guideline," there was an error in the box on page 1410. The example medication regimen for lorazepam should have read as follows: Lorazepam, 1 to 4 mg intravenously every 5 to 15 minutes, or lorazepam, 1 to 4 mg intramuscularly every 30 to 60 minutes, until calm, then every hour as needed to maintain light somnolence.