Complete Summary

GUIDELINE TITLE

Management of alcohol withdrawal delirium. An evidence-based practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Mayo-Smith MF, Beecher LH, Fischer TL, Gorelick DA, Guillaume JL, Hill A, Jara G, Kasser C, Melbourne J. Management of alcohol withdrawal delirium. An evidence-based practice guideline. Arch Intern Med 2004 Jul 12;164(13):1405-12. [70 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Alcohol withdrawal delirium (AWD)

GUIDELINE CATEGORY

Evaluation
Management
Treatment

CLINICAL SPECIALTY

Critical Care
Emergency Medicine

Family Practice
Internal Medicine
Neurology
Pharmacology
Psychiatry

INTENDED USERS

Advanced Practice Nurses
Nurses
Physician Assistants
Physicians
Substance Use Disorders Treatment Providers

GUIDELINE OBJECTIVE(S)

To assist physicians and other health care professionals in providing appropriate treatment for all patients with alcohol withdrawal delirium (AWD)

TARGET POPULATION

Patients with alcohol withdrawal delirium (AWD)

This guideline does *not* include patients with uncomplicated alcohol withdrawal syndrome.

INTERVENTIONS AND PRACTICES CONSIDERED

Pharmacologic Treatment

1. Benzodiazepines and other sedative-hypnotic agents as primary therapy
2. Neuroleptic agents in combination with benzodiazepines
3. Beta-adrenergic antagonists in combination with benzodiazepines
4. Magnesium
5. Thiamine
6. Neuroleptic agents as sole pharmacologic therapy, ethyl alcohol, and any other pharmacologic agent for which published data on its use in patients with alcohol withdrawal delirium (AWD) could be located.

Evaluation/Management

1. Medical evaluation
2. Close nursing monitoring
3. Vitals sign measurement
4. Cardiac monitoring and oximetry
5. Environmental cues
6. Physical restraints
7. Intravenous fluids and medications
8. Endotracheal intubation and ventilatory support as needed

MAJOR OUTCOMES CONSIDERED

- Mortality rate
- Duration of delirium
- Time required for control of agitation
- Adequate control of delirium
- Treatment complications
- Costs

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT 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 alcohol withdrawal delirium (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.

NUMBER OF SOURCE DOCUMENTS

Forty-three articles were reviewed

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

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

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

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 Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for alcohol withdrawal delirium (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.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Recommendations based on the evidence were drafted and graded according to a published system. 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. 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).

RATING SCHEME FOR THE STRENGTH OF THE 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

COST ANALYSIS

Acquisition costs were determined by averaging wholesale prices listed in the *2001 Red Book*.

Costs can vary greatly depending on the selected drug and the route of administration. For example, the average wholesale costs 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. Intravenous (IV) medication, which is usually needed for adequate control of alcohol withdrawal delirium (AWD), is often more than 3 times as expensive as oral medication. For example, the average wholesale costs 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 micrograms/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 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, and a hospital stay costing $26,045 was reported for another patient. Furthermore, there are no trials reporting comparative risks and benefits of intermittent vs. continuous IV administrations, and no evidence could be identified documenting an advantage for continuous infusion.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

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

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Levels of recommendation (A-C) and Levels of Evidence (I-V) are defined at the end of the "Major Recommendations" field.

Choice of Pharmacologic Agent

The initial therapeutic goal in patients with alcohol withdrawal delirium (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.

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 original guideline document. 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 intravenous (IV) diazepam has a more rapid onset than other agents (**level II evidence**); (2) agents with long duration of action (e.g., diazepam) provide a smooth treatment course with less breakthrough symptoms; (3) agents with shorter duration of activity (e.g., 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 recommendation**).

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 (**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**).

Beta-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 beta-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**).

Settings 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 (e.g., 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. 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.

Definitions:

Strength of the 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

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

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is stated for selected recommendations (see the "Major Recommendations" field).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Appropriate treatment for all patients with alcohol withdrawal delirium (AWD)
- Control of patient agitation
- Maintenance of light somnolence for the duration of the delirium
- Prevention of morbidity and mortality

Sedative-hypnotic drugs reduce mortality, reduce the duration of symptoms, and are associated with fewer complications compared with neuroleptic agents in controlled trials.

POTENTIAL HARMS

Overall Harms

Complications of treatment

Specific Harms

- *Benzodiazepines and other sedative-hypnotic agents*: In the study comparing rectal paraldehyde use and intravenous (IV) diazepam use, 2 of 17 patients in the paraldehyde group developed respiratory arrest requiring resuscitation. In another study, 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 alcohol withdrawal delirium (AWD), that shorter-acting agents have a higher incidence of rebound symptoms and may be associated with the occurrence of withdrawal seizures if discontinued too rapidly.

- Several case series have reported on the use of other sedative-hypnotic agents in managing AWD, including chlormethiazole, lorazepam, flunitrazepam, pentobarbital, propofol, and midazolam. 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.
- *Neuroleptic Agents*: 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 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. All neuroleptic agents are thought to have the potential for causing neuroleptic malignant syndrome, and cases have been reported in patients with alcohol withdrawal syndrome (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.
- *Beta-adrenergic Antagonists*: Delirium is a known adverse effect of beta-adrenergic blocker therapy, and in at least 1 controlled study of propranolol in alcohol withdrawal syndrome, there was an increased incidence of delirium.

Patients Most Likely to Experience Harm

Elderly patients and those with concurrent medical conditions, acute and chronic, are at higher risk of complications.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- 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.
- This guideline does not address the management of uncomplicated alcohol withdrawal syndrome or the prevention of alcohol withdrawal syndrome as these topics are covered in a previously published guideline.
- American Society of Addiction Medicine practice guidelines are intended to assist physicians in making clinical decisions. The ultimate judgment regarding any specific treatment must be made by the physician with

consideration of the pertinent scientific and patient information and in light of the diagnostic and treatment options available.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Mayo-Smith MF, Beecher LH, Fischer TL, Gorelick DA, Guillaume JL, Hill A, Jara G, Kasser C, Melbourne J. Management of alcohol withdrawal delirium. An evidence-based practice guideline. Arch Intern Med 2004 Jul 12;164(13):1405-12. [70 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 Jul 12

GUIDELINE DEVELOPER(S)

American Society of Addiction Medicine - Medical Specialty Society

SOURCE(S) OF FUNDING

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GUIDELINE COMMITTEE

Working Group on the Management of Alcohol Withdrawal Delirium

American Society of Addiction Medicine, Practice Guidelines Committee

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The guideline authors have no relevant financial interest in this article.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the American Society of Addiction Medicine (ASAM) Web site:

- HTML Format
- Portable Document Format (PDF)

Print copies: Available from ASAM, 4601 North Park Ave, Arcade Suite 101, Chevy Chase, MD 20815.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on April 26, 2005. The information was verified by the guideline developer on May 20, 2005.

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