REVIEW ARTICLE

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# Recognition and Management of Withdrawal Delirium (Delirium Tremens)

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At some time in their lives, 20% of men and 10% of women in most Western societies will have an alcohol-use disorder, which is defined as repetitive alcohol-related problems in at least 2 of 11 areas of life.[1,2] These conditions can decrease the life span by a decade and are associated with severe impairments in social functioning, as well as high rates of medical problems. Although alcohol-related conditions occur in persons from all social strata and affect more than 20% of patients in most medical settings,[2,3] few physicians have been adequately trained in identifying and treating these serious problems.

About 50% of persons with alcohol-use disorders have symptoms of alcohol withdrawal when they reduce or discontinue their alcohol consumption; in 3 to 5% of these persons, grand mal convulsions, severe confusion (a delirium), or both develop.[1] It is essential that clinicians know how to prevent, recognize, and treat these severe withdrawal states to minimize costly hospitalizations and avoidable deaths.

## States of Alcohol Withdrawal

### Mild and Moderate Withdrawal

Alcohol is a central nervous system depressant. Like benzodiazepines, barbiturates, and drugs that have similar action, it rapidly increases the release of γ-aminobutyric acid (GABA) in the brain, with prominent effects on GABA type A ($GABA_A$) receptors, and it inhibits postsynaptic *N*-methyl-D-aspartate glutamate-receptor activity.[4,5] With repeated exposure, the brain adapts to the effects of alcohol through changes in receptors and other proteins. These adaptations result in decreased effects of the depressant, with the result that higher doses of the agent are required to achieve similar results.[5,6] Subsequent reductions in blood alcohol levels lead to symptoms that are, in general, the opposite of the acute effects of the drug. Withdrawal symptoms associated with depressants such as alcohol include insomnia, anxiety, and increased pulse and respiration rates, body temperature, and blood pressure, as well as a hand tremor.[1,4] Because of the short action of ethanol (beverage alcohol), withdrawal symptoms usually begin within 8 hours after blood alcohol levels decrease, peak at about 72 hours, and are markedly reduced by day 5 through 7 of abstinence.[4,7]

The time course of alcohol withdrawal and the severity of symptoms associated with it must be closely monitored to identify the most effective treatments. Table 1 describes a withdrawal rating instrument that is commonly used by trained clinicians — the Clinical Institute Withdrawal Assessment of Alcohol Scale, revised (CIWA-Ar).[4,8] Scores on the CIWA-Ar range from 0 to 67; scores lower than 8 indicate mild withdrawal symptoms that rarely require the use of medications, scores from 8 to 15 indicate moderate withdrawal symptoms that are likely to respond to modest doses of benzodiazepines, and scores higher than 15 indicate severe syn-

**Table 1. Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised.***

| Components of Scale | Most Severe Manifestations |
|---|---|
| Nine items scored on a scale ranging from 0 (no symptoms) to 7 (most severe symptoms) | |
| Nausea or vomiting | Constant nausea with vomiting |
| Tremor | Severe tremor, even with arms extended |
| Paroxysmal sweats | Drenching sweats |
| Anxiety | Acute panic |
| Tactile disturbances (itching, numbness, sensation of bugs crawling on or under the skin) | Continuous hallucinations |
| Auditory disturbances (sensitivity to sound, hearing things that are not there) | Continuous hallucinations |
| Visual disturbances (sensitivity to brightness and color, seeing things that are not there) | Continuous hallucinations |
| Headache, sensation of a band around the head | Extremely severe headache |
| Agitation | Pacing during most of interview with clinician or thrashing about |
| One item scored on a scale ranging from 0 (no symptoms) to 4 (disoriented with respect to place or person) | |
| Orientation and clouding of sensorium | |

* Data are from Kosten and O'Connor.[4] Total scores on this clinician-rated, 10-item scale range from 0 to 67, with scores less than 8 indicating mild alcohol withdrawal that probably will not require the use of medications, 8 to 15 moderate withdrawal, and more than 15 severe withdrawal associated with a danger of grand mal seizures, delirium, or both. Some studies use a score of 10 as the cutoff point between mild and moderate withdrawal.

dromes that require close monitoring to avoid seizures and alcohol withdrawal delirium (delirium tremens).

### Withdrawal Delirium (Delirium Tremens)

The criteria for withdrawal delirium, described in Table 2, are delirium (a rapid-onset fluctuating disturbance of attention and cognition, sometimes with hallucinations) plus alcohol withdrawal.[1,7,9] Clinicians differ in how well they adhere to these criteria, so it is difficult to determine the prevalence of withdrawal delirium, and rates depend on whether persons with this condition were treated as outpatients, as general medical or psychiatric inpatients, or as patients in an intensive care unit (ICU). Most studies estimate that 3 to 5% of patients who are hospitalized for alcohol withdrawal meet the criteria for withdrawal delirium.[7,10,11] Retrospective chart reviews based on diagnoses made by general clinicians show higher but less reliable rates.

Withdrawal delirium usually begins about 3 days after the appearance of symptoms of alcohol withdrawal and lasts from 1 to 8 days or more (usually 2 or 3 days).[7,9,12] Approximately 1 to 4% of hospitalized patients who have withdrawal delirium die; this rate could be reduced if an appropriate and timely diagnosis were made and symptoms were adequately treated.[7,9,11,13] Death usually results from hyperthermia, cardiac arrhythmias, complications of withdrawal seizures, or concomitant medical disorders.[14,15]

Delirium during alcohol withdrawal is predicted by the following: CIWA-Ar scores above 15 (especially in association with a systolic blood pressure >150 mm Hg or a pulse rate >100 beats per minute), recent withdrawal seizures (seen in 20% of persons with delirium), prior withdrawal delirium or seizures, older age, recent misuse of other depressant agents, and concomitant medical problems.[7,10,11,13,16,17] The latter include electrolyte abnormalities (e.g., low levels of potassium, magnesium, or both), low platelet counts, and respiratory, cardiac, or gastrointestinal disease.[7,10,11,17]

## Treatment of Withdrawal Delirium

The best approach to the prevention of withdrawal delirium is the identification and treatment of

preexisting concomitant medical problems and withdrawal syndromes.[4] Perhaps because of the low prevalence of withdrawal delirium and the high treatment costs, and because pharmaceutical companies lack profit motives associated with research into new treatments for this condition, few double-blind, controlled, prospective trials of treatments exist. The best evidence is provided in a 2004 review of nine prospective, controlled trials that were conducted between 1959 and 1978[9] and in subsequent noncontrolled studies that were identified in a PubMed search.

The major treatment goals for withdrawal delirium are to control agitation, decrease the risk of seizures, and decrease the risk of injury and death with the use of the methods outlined in Table 3.[7,9,13,18-23] Because of the high prevalence of agitation among patients with withdrawal delirium and the potential lethal outcomes, treatment is best carried out in a locked inpatient ward or an ICU.

The approach to the management of withdrawal delirium includes a careful physical examination and appropriate blood tests to identify and treat medical problems that may have contributed to the severe withdrawal state.[9,17] The same general types of support needed for any patient with delirium should be used for the patient with withdrawal delirium, including helping to reorient the patient to time, date, and place, evaluating and treating the patient in a well-lit room, providing reassurance, performing frequent monitoring of vital signs, and ensuring adequate hydration. A functioning intravenous line should be established; care should be taken when administering glucose to avoid precipitating Wernicke's encephalopathy or thiamine-related cardiomyopathies and to circumvent overhydration in patients who have temporary, alcohol-related, compromised cardiac functioning.[18,23] Although thiamine (e.g., 500 mg infused intravenously over the course of 30 minutes once or twice daily for 3 days) and multivitamins are recommended, there is little support for routine administration of magnesium.[9,19,20,24] In patients in whom Wernicke's encephalopathy is suspected, recommended doses of thiamine are even higher (e.g., 500 mg intravenously three times daily for 5 days), in addition to daily parenteral multivitamins.[24]

The mainstay of the pharmacologic treatment of withdrawal delirium is depressants such as benzodiazepines.[7,9,12] No single drug of this class has been shown to be superior to another. Table 3 provides examples of regimens of a drug with a long half-life (diazepam) and of a shorter-acting drug (lorazepam).[9,13,18,21] The doses needed to control agitation and insomnia vary dramatically among patients and can be prodigious (e.g., >2000 mg of diazepam in the first 2 days in some patients); this underscores the advisability of providing treatment in a hospital, preferably in an ICU. The severity of symptoms requires that care be directed by clinicians who are well trained in the treatment of this disorder.

Alternative depressant-like drugs have been proposed for uncomplicated withdrawal, but data are lacking regarding their use in persons who have withdrawal delirium. These agents include phenobarbital (up to 1500 mg to 2000 mg administered orally or intravenously on day 1 in patients with delirium[13]); clomethiazole (not available intravenously, but for uncomplicated withdrawal, up to 2304 mg (12 capsules) can be administered orally in divided doses on day 1[7,25]); midazolam (one study indicated a dose of up to 2800 mg over 50 days); carbamazepine (approximately 800 mg

**Table 2. DSM-5 Criteria for Withdrawal Delirium (Delirium Tremens).***

| |
|---|
| **Criteria for alcohol withdrawal** |
| Cessation of or reduction in heavy and prolonged use of alcohol |
| At least two of eight possible symptoms after reduced use of alcohol: |
| Autonomic hyperactivity |
| Hand tremor |
| Insomnia |
| Nausea or vomiting |
| Transient hallucinations or illusions |
| Psychomotor agitation |
| Anxiety |
| Generalized tonic–clonic seizures |
| **Criteria for delirium** |
| Decreased attention and awareness |
| Disturbance in attention, awareness, memory, orientation, language, visuospatial ability, perception, or all of these abilities that is a change from the normal level and fluctuates in severity during the day |
| Disturbances in memory, orientation, language, visuospatial ability, or perception |
| No evidence of coma or other evolving neurocognitive disorders |

* The criteria are based on the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5).[1] A patient who meets the criteria for both alcohol withdrawal and delirium is considered to have withdrawal delirium.

**Table 3. Suggested Treatment of Alcohol Withdrawal Delirium (Delirium Tremens).**

Provide care in an inpatient setting, preferably an intensive care unit.

Perform a workup to rule out medical conditions and measure values such as the levels of electrolytes and pancreatic enzymes, hematocrit, and platelet counts; perform liver-function tests.

Provide supportive care by monitoring vital signs frequently (e.g., every 15–30 min) in a quiet, well-lit room. Reorient patient to time, place, and person.

Administer thiamine intravenously at a dose of 500 mg once or twice a day for 3 days; monitor patient for overhydration.[9,18-20]

Provide medications to control agitation, promote sleep, and raise the seizure threshold.

Administer primary pharmacotherapy with the use of benzodiazepines, preferably intravenously, in doses high enough to achieve a lightly dozing but still arousable state, while monitoring the patient's vital signs until delirium abates (approximately 3 days).[9] The dose on day 1 is the amount needed to control target symptoms (e.g., diazepam at a dose of 15 mg).

Examples of diazepam regimens[9,13,18,21]:

Regimen 1[21]: administer 10–20 mg intravenously or orally every 1–4 hr, as needed.

Regimen 2[9]:

Begin treatment with 5 mg intravenously (2.5 mg/min).[9]

If needed, repeat 10 min later.

If needed, administer 10 mg intravenously 10 min later.

If needed, administer 10 mg again 10 min later.

If needed, administer 20 mg 10 min later.

Continue to administer 5–20 mg/hr, as needed.

Examples of lorazepam regimens[9,18]:

Regimen 1[18]: administer 8 mg intravenously, intramuscularly, or orally every 15 min, as needed. After the patient has received 16 mg, if delirium is still severe, administer an 8-mg bolus intravenously. Then administer 10–30 mg/hr.

Regimen 2[9]:

Administer 1 to 4 mg intravenously every 5–15 min,[9] as needed.

Alternatively, administer 1–40 mg intramuscularly every 30–60 min, as needed.

Continue dosing every hr as needed to maintain somnolence.

In addition to benzodiazepines, administer adjunctive medications such as the antipsychotic agent haloperidol[9,21,22] for uncontrolled agitation or hallucinations (0.5–5.0 mg intravenously or intramuscularly every 30–60 min as needed for severe agitation or hallucinosis — not to exceed 20 mg; or 0.5–5.0 mg orally every 4 hr up to 30 mg).

per day); and oxcarbazepine (approximately 900 mg per day).[7,26-28]

In patients who do not have a response to high doses of benzodiazepines (especially patients who are intubated), propofol may be administered (e.g., 0.3 to 1.25 mg per kilogram of body weight, up to 4 mg per kilogram per hour, for up to 48 hours).[20,26] Another adjunctive medication is dexmedetomidine, an $\alpha_2$-adrenergic agonist that is used in ICUs to produce a state in which the patient is sedated but arousable, with decreased sympathetic tone. Doses up to 0.7 $\mu$g per kilogram per hour have been administered in patients who do not have a good response to benzodiazepines.[29,30] This drug cannot be used in patients with a heart block, and the patient's blood pressure and heart rate must be closely monitored. None of these regimens have been as well studied as the benzodiazepine regimen, and each has additional dangers and few advantages over benzodiazepines for most patients.[21,31-33] Table 3 also lists the potential adjunctive use of haloperidol for severe agitation or hallucinosis, but antipsychotic drugs can prolong the QT interval and can increase the likelihood of seizures.

## CONCLUSIONS

Withdrawal delirium is an uncommon, serious complication of alcohol withdrawal that is best treated with intravenous benzodiazepines. All the doses described in this review are approximations based on uncontrolled studies. Data on the most effective care for patients with withdrawal delirium are lacking. Since the low potential of profit from this research may undercut interest

from pharmaceutical companies, treatment trials sponsored by the National Institutes of Health are warranted.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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