# Individualized Treatment for Alcohol Withdrawal

## A Randomized Double-blind Controlled Trial

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**Objective.**—To assess the effect of an individualized treatment regimen on the intensity and duration of medication treatment for alcohol withdrawal.

**Design.**—A randomized double-blind, controlled trial.

**Setting.**—An inpatient detoxification unit in a Veterans Affairs medical center.

**Patients.**—One hundred one patients admitted for the treatment of alcohol withdrawal who could give informed consent and had no history of seizures or medication use that might alter the clinical course of withdrawal.

**Intervention.**—Patients were randomized to either a standard course of chlordiazepoxide four times daily with additional medication as needed (fixed-schedule therapy) or to a treatment regimen that provided chlordiazepoxide only in response to the development of the signs and symptoms of alcohol withdrawal (symptom-triggered therapy). The need for administration of "as-needed" medication was determined using a validated measure of the severity of alcohol withdrawal.

**Main Outcome Measures.**—Duration of medication treatment and total chlordiazepoxide administered.

**Results.**—The median duration of treatment in the symptom-triggered group was 9 hours compared with 68 hours in the fixed-schedule group ($P<.001$). The symptom-triggered group received 100 mg of chlordiazepoxide, and the fixed-schedule group received 425 mg ($P<.001$). There were no significant differences in the severity of withdrawal during treatment or in the incidence of seizures or delirium tremens.

**Conclusions.**—Symptom-triggered therapy individualizes treatment, decreases both treatment duration and the amount of benzodiazepine used, and is as efficacious as standard fixed-schedule therapy for alcohol withdrawal.

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THE ALCOHOL withdrawal syndrome and its complications are common in alcohol-dependent patients who reduce or discontinue their alcohol intake.[1] Although many of these patients develop only mild symptoms, a significant number experience more severe manifestations of withdrawal, including seizures, delirium tremens, and their associated morbidity and mortality.[2-4] Benzodiazepines ameliorate the symptoms of alcohol withdrawal and reduce the frequency of seizures and delirium tremens.[1,3,5,6] A report from the Institute of Medicine[7] notes the superiority of benzodiazepines over all other agents used for alcohol withdrawal and suggests that attention be focused on how to determine when pharmacotherapy is indicated and how to use it most effectively.

When used for alcohol withdrawal, benzodiazepines are generally administered on predetermined dosing schedules for several days, often in gradually tapering doses. This regimen is recommended by current textbooks of medicine,[8,9] is the one most commonly used to treat patients admitted for alcohol withdrawal,[10] and is the one with which new treatments are compared.[11-13]

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Predetermined, fixed benzodiazepine-dosing regimens may subject many patients to unnecessary medication and sedation and excessive hospital stays. In fact, many patients undergo alcohol withdrawal safely and comfortably without pharmacologic intervention.[14,15] Nonpharmacologic and outpatient regimens are treatment options that may decrease medical resource utilization and improve the efficiency of the treatment of alcohol withdrawal. However, studies of risk stratification to select appropriate candidates who might achieve similar outcomes with less intensive outpatient or nonpharmacologic intervention have not been performed.

Symptom-triggered therapy, which consists of monitoring patients and providing medication only when symptoms of alcohol withdrawal appear, is an alternative approach that could individualize and improve the management of alcohol withdrawal. Previous studies[16,17] have suggested that the introduction of a simple, objective, standardized scale

to monitor patients and to guide the administration of medication was feasible, appeared safe and effective, and might reduce benzodiazepine use and shorten treatment duration. However, these studies were retrospective and unblinded and used historical control subjects not receiving standardized treatment protocols. Although symptom-triggered therapy may have advantages, it may also be less effective at both preventing the development of symptoms and lessening the incidence of severe withdrawal and its complications, when compared with a standardized protocol of early scheduled benzodiazepines administration. These two approaches have not been directly compared. Therefore, we performed a randomized double-blind controlled trial to compare the efficacy and efficiency of the individualized symptom-triggered regimen with that of the standard fixed-schedule approach for the treatment of alcohol withdrawal.

## METHODS

### Subjects

The study protocol was reviewed and approved by the Research and Development Committee and the Human Subjects Subcommittee of the Department of Veterans Affairs Medical Center, Manchester, NH. All adults with alcohol abuse or dependence as defined in the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*,[18] who were admitted to the Manchester Veterans Affairs Medical Center Alcohol Detoxification Unit for the treatment of alcohol withdrawal from February through October 1992 were eligible to be considered for inclusion in the study. Although patients were allowed to reenter the trial for separate episodes of alcohol withdrawal, only first episodes were included in the analyses. Exclusion criteria included concurrent acute medical or psychiatric illness requiring acute care hospitalization, a history of seizures of any cause, an inability to take oral medication, current use of or withdrawal from opiates, benzodiazepines, barbiturates, clonidine, or β-blockers, and an inability or unwillingness to consent to participation in the study. The admitting physician determined the competence of the patient to give informed consent.

### Assessment and Data Collection

A history and physical examination, complete blood cell counts and liver function tests, and the Clinical Institute Withdrawal Assessment for Alcohol, revised (CIWA-Ar) scale[19] modified to include both a measurement of the pulse rate and sweating[20] were performed on admission and recorded on standardized forms. The CIWA-Ar is a validated, reliable measure of the current severity of alcohol withdrawal composed of 10 items: nausea, tremor, autonomic hyperactivity, anxiety, agitation, tactile, visual, and auditory disturbances, headache, and disorientation; the maximum score is 67. The Quantitative Inventory of Alcohol Disorders (QIAD),[21] a validated, reliable measure of the severity of alcoholism, and the Short Michigan Alcohol Screening Test (SMAST)[22] were administered to subjects during the study to describe and define the sample. To monitor the subjects' progress and response to therapy, vital signs, the CIWA-Ar, and level of alertness (a five-point scale including coma, stupor, lethargy, alertness, and hyperalertness) were assessed at baseline, every 8 hours, and 1 hour after every medication dose. Monitoring with the CIWA-Ar was done by nurses trained in its use by videotapes obtained from the Addiction Research Foundation Clinical Institute in Toronto, Ontario, where the scale was developed. Beginning on the day after admission, 10-cm line visual analogue scales measuring alcohol craving and degree of general discomfort were administered daily. Subjects were monitored prospectively for the development of hallucinations, seizures, and delirium tremens. A search of the hospital's computerized records covering 30 days after hospital discharge for each patient in the study documented subsequent rehabilitation, readmission for detoxification, and compliance with outpatient follow-up.

### Treatment Assignment

There were 280 admissions to the detoxification unit with alcohol withdrawal during the study period. One hundred twenty-eight admissions were excluded. Sixty admissions had a history of seizures of any cause, 28 were using or withdrawing from opiates, 19 were using or withdrawing from benzodiazepines, 13 were using β-blockers, one was using barbiturates, and one was using clonidine. Five patients were unable to give informed consent, and one patient refused to participate in the trial. In 41 admissions, therapy had been instituted before the investigators were notified, so they were not enrolled.

A pharmacist not involved in other aspects of the trial randomly assigned the 111 eligible patients in blocks of 10 to either symptom-triggered therapy or standard fixed-schedule therapy. One patient assigned to fixed-schedule therapy was excluded after randomization because he received neither study regimen due to a clerical error. Nine repeat episodes of withdrawal in eight patients were also excluded. Physicians, nurses, and subjects were blinded to treatment assignment throughout the trial.

### Treatment Regimens

Subjects in the fixed-schedule group received chlordiazepoxide every 6 hours for 12 doses (four doses of 50 mg followed by eight doses of 25 mg). In addition, they received 25 to 100 mg of chlordiazepoxide hourly when they achieved a CIWA-Ar score of 8 or greater ("as-needed" medication). Fixed-schedule doses were not administered if the patient was somnolent or refused the medication. The symptom-triggered group received 25 to 100 mg of chlordiazepoxide hourly when the CIWA-Ar score was 8 or greater. Patients in the symptom-triggered group received an identical-appearing placebo every 6 hours for 12 doses. Nurses who were blinded to treatment assignment determined the actual amount (between 25 and 100 mg) of chlordiazepoxide given in response to an increased CIWA-Ar score. Chlordiazepoxide was chosen because it is currently the most commonly administered drug treatment for alcohol withdrawal in the United States[10] and because of the evidence supporting the effectiveness of long-acting benzodiazepines as treatment for alcohol withdrawal.[1] The study protocol prohibited the use of β-blockers, clonidine, and barbiturates and the use of benzodiazepines, except for the aforementioned regimens. At the discretion of the physician, nine subjects, primarily those who developed an inability to take oral medication, received an as needed dose (defined herein according to CIWA-Ar scores) of benzodiazepine other than chlordiazepoxide, maintaining blinding to original treatment assignment. Also, subjects who developed delirium tremens were transferred to a medical intensive care unit, and their subsequent treatment was at the discretion of their physicians. Subjects were observed for symptoms for 24 hours after their last medication dose to assure that detoxification from alcohol had been completed.

### Outcomes

The primary outcome measures were duration of medication treatment from the time of admission to the last dose of benzodiazepine administered and the total amount of benzodiazepines administered. Secondary outcomes included the number and amount of as-needed benzodiazepine doses given in response to increased CIWA-Ar scores; the severity of alcohol withdrawal as measured by the CIWA-Ar; leaving the hospital against medical advice; the development

Table 1.—Baseline Characteristics by Treatment Group*

| | Symptom Triggered (n=51) | Fixed Schedule (n=50) |
|---|---|---|
| Age, y | 47±11 | 47±12 |
| Male, % | 100 | 98 |
| Gastrointestinal disease, %† | 31 | 46 |
| Current smoking, % | 84 | 85 |
| Recent cocaine use, % | 8 | 8 |
| Prior delirium tremens, % | 14 | 29 |
| Prior detoxification, % | 63 | 78 |
| Prior hallucinations, % | 20 | 35 |
| Hours since last alcoholic beverage | 9 (4-18) | 10 (4-15) |
| Heart rate, beats/min | 96±17 | 93±16 |
| CIWA-Ar score | 9±6 | 8±5 |
| SMAST score | 11 (7-13) | 11 (8-13) |
| QIAD score | 47±14 | 50±17 |
| Mean corpuscular volume, fL | 96±7 | 95±5 |
| Aspartate aminotransferase, U/L | 44 (26-92) | 47 (34-81) |
| Prothrombin time, s | 12±1 | 12±1 |

*$P>.05$ for all comparisons between groups. Plus-minus values are means and SDs, and interquartile ranges are in parentheses for medians. CIWA-Ar indicates Clinical Institute Withdrawal Assessment for Alcohol, revised; SMAST, Short Michigan Alcoholism Screening Test; and QIAD, Quantitative Inventory of Alcohol Disorders.

†Gastrointestinal disease included a history of pancreatitis, hepatitis, and/or gastrointestinal bleeding.

Table 2.—Treatment Outcomes*

| | Symptom Triggered | Fixed Schedule |
|---|---|---|
| Primary outcomes | | |
| Treatment duration, h† | 9 (0-43) | 68 (64-73) |
| Total chlordiazepoxide, mg† | 100 (0-400) | 425 (350-750) |
| Secondary outcomes | | |
| No. of "as-needed" doses | 2 (0-4) | 2 (1-7) |
| Fixed-schedule chlordiazepoxide, mg | . . . | 275 (225-325) |
| "As needed" chlordiazepoxide, mg | 100 (0-400) | 163 (75-450) |
| Highest CIWA-Ar score | 11±5 | 11±5 |
| Lethargy, % | 35 | 44 |
| Left the hospital against medical advice, % | 4 | 6 |
| Hallucinations, % | 2 | 4 |
| Delirium tremens, % | 2 | 6 |
| Rehabilitation, % | 69 | 50 |
| Readmission, % | 6 | 8 |

*Plus-minus values are means and SDs, and interquartile ranges are in parentheses for medians. "Treatment duration" is the time from admission to the last dose of benzodiazepine given for alcohol withdrawal. CIWA-Ar indicates Clinical Institute Withdrawal Assessment for Alcohol, revised.

†$P<.001$. There were no other statistically significant differences between groups.

of hallucinations, seizures, or delirium tremens; the level of alertness dichotomized as the presence or absence of lethargy; the degree of general discomfort and craving for alcohol; and rates of rehabilitation, readmission, and compliance with follow-up. Benzodiazepine amounts are reported as milligrams of oral chlordiazepoxide or its equivalent determined using published treatment recommendations for alcohol withdrawal; diazepam amounts were multiplied by 5, lorazepam amounts were multiplied by 25, and oxazepam amounts were multiplied by 1.66, regardless of route of administration.[1]

### Data Analysis

Analyses were performed using SAS software.[23] All analyses were performed on an intention-to-treat basis. Kaplan-Meier curves demonstrating the time to last medication received were generated, and these times were compared using the log rank test. The Wilcoxon test was used to compare duration of treatment, medication doses, and other continuous variables that were not normally distributed (medians are reported). Normally distributed variables were compared using the $t$ test (means±SDs are reported). Fisher's Exact Test was used to compare dichotomous variables. Two-tailed $P$ values were obtained from all tests, and .05 was chosen as the level of significance. The CIWA-Ar values and visual analogue scale results were inspected for graphical trends over time. Repeated measures analysis of covariance was not used to compare every 8-hour CIWA-Ar values and daily visual analogue scale results for subjects remaining in the study because results could have been biased by differential termination of the study protocol. Daily CIWA-Ar and visual analogue scale results were compared using $t$ tests.

The trial was designed to have 90% power, using a two-tailed $\alpha$ of .05, to detect a 12-hour decrease in treatment duration. To assess the effect on this analysis, the patients who left the trial against medical advice with withdrawal symptoms were reassigned a duration of medication treatment equal to that of the longest time in the trial. This conservative analysis would eliminate the bias that either censoring these subjects or using their shorter (although incomplete) treatment times could have introduced.

## RESULTS

The baseline characteristics of the 101 subjects studied are shown in Table 1. All subjects but one were men, 21% reported a history of delirium tremens, 27% had experienced hallucinations, and 70% had been through alcohol detoxification before. Subjects had consumed their most recent alcoholic beverage a median of 9 hours before study entry. All subjects had SMAST and QIAD scores consistent with alcoholism; median SMAST scores were 11 in both groups, and mean QIAD scores were 47 in the symptom-triggered group and 50 in the fixed-schedule group, all greater than minimum scores associated with alcoholism (SMAST≥3, and QIAD>23). The median first CIWA-Ar score was 8 (range, 0 to 26), indicating a spectrum of minimal to severe withdrawal symptoms. There were no statistically significant differences in baseline characteristics between the treatment groups.

Medication treatment duration was shorter in the symptom-triggered group than that in the fixed-schedule group (median, 9 hours vs 68 hours, respectively) (Wilcoxon $z=5.68$; $P<.001$) (Table 2). Kaplan-Meier curves in the Figure show the abbreviated treatment course in the symptom-triggered group (log rank test $P<.001$). The symptom-triggered group also received less chlordiazepoxide than did the fixed-schedule group (median, 100 mg vs 425 mg, respectively; Wilcoxon $z=5.30$; $P<.001$). Although the total amount of chlordiazepoxide administered during each 8-hour period was greater in the fixed-schedule group during the first 72 hours, there was no difference between groups in total medication administered after that time (Table 3). Each group received a median of one dose of 75 mg of chlordiazepoxide triggered by symptoms in the first 8 hours followed by a median of zero doses during each subsequent 8-hour period, with no significant differences between groups.

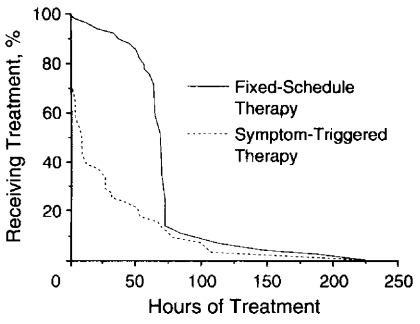
Three subjects (two in the fixed-schedule group) left against medical advice while still experiencing withdrawal symptoms, and two (one in the fixed-schedule group) left against medical advice after treatment for withdrawal had been completed. For the analysis of medication treatment duration, the three subjects who left before completing treatment were assigned times equal to the longest time in the data set (235 hours) with no change in the results; therefore, the actual times are shown (Table 2, Figure).

Even with shorter courses of treatment using less medication in the symptom-triggered group, the mean greatest severity of withdrawal as measured by the CIWA-Ar ($P=.73$), the incidence of delirium tremens ($P=.36$), hallucinations ($P=.62$), seizures (none), lethargy ($P=.42$), leaving the hospital against medical advice ($P=.68$), and readmission within 30 days ($P=.72$) did not differ

Table 3.—Amount of Chlordiazepoxide (Milligrams) Administered by Treatment Group*

| | Hours | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 0-8 | 9-16 | 17-24 | 25-32 | 33-40 | 41-48 | 49-56 | 57-64 | 65-72 |
| Symptom triggered | 75 (0-175) | 0 (0-75) | 0 | 0 (0-13) | 0 | 0 | 0 | 0 | 0 |
| Fixed schedule | 100 (50-150) | 50 (50-50) | 25 (50-100) | 25 (25-75) | 25 (0-50) | 25 (25-50) | 25 (25-50) | 25 (0-50) | 25 (0-25) |

*Values shown are medians and interquartile ranges in parentheses. $P$=.09 for the first 8 hours, and $P$<.001 for the remaining comparisons shown.




Time to completion of medication treatment of alcohol withdrawal. Kaplan-Meier curves illustrate treatment times for both groups. Treatment time was shorter in the patients receiving symptom-triggered therapy (log rank test $P$<.001).

between treatment groups (Table 2). Most patients (59%) entered a rehabilitation program: 69% in the symptom-triggered group vs 50% in the fixed-schedule group ($P$=.06). Few patients were readmitted (7%), with no significant difference between groups ($P$=.68). Among patients not entering rehabilitation but who were scheduled for outpatient follow-up, 73% (8/11) in the symptom-triggered group and 83% (10/12) in the fixed-schedule group were compliant ($P$=.54). One 69-year-old subject (in the fixed-schedule group) developed respiratory depression after receiving 200 mg of chlordiazepoxide during an 11-hour period.

Although less total chlordiazepoxide was administered in the symptom-triggered group, the median number (two in each group) and amount (100 mg in the symptom-triggered group vs 163 mg in the fixed-schedule group) of as-needed chlordiazepoxide doses administered in response to increased CIWA-Ar scores were not significantly different between groups, reflecting a similarity in the severity of withdrawal during treatment.

Severity of withdrawal as measured by the CIWA-Ar scores, craving scores, and general discomfort scores all decreased throughout the course of treatment. Mean CIWA-Ar values in the symptom-triggered group (4, 3, 2, and 2, at 24, 48, 72, and 96 hours, respectively) did not differ from daily values in the fixed-schedule group (5 [$P$=.29], 3 [$P$=.80], 1 [$P$=.50], and 1 [$P$=.32]). Similarly, on the 10-cm visual analogue scales, four daily mean values in the symptom-triggered group and the fixed-schedule group, respectively, for craving (3 vs 3, $P$=.83; 2 vs 3, $P$=.15; 1 vs 2, $P$=.15; and 1 vs 2, $P$=.09) and general discomfort (4 vs 4, $P$=.89; 3 vs 3, $P$=.92; 2 vs 3, $P$=.24; and 2 vs 2, $P$=.66) did not differ between treatment groups. Furthermore, the time from admission to achieving a CIWA-Ar score of less than 8 did not differ significantly between the symptom-triggered group (median, 7 hours) and the fixed-schedule group (median, 9 hours) ($P$=.66).

## COMMENT

This randomized double-blind controlled study demonstrates that patients with alcohol withdrawal treated with symptom-triggered therapy completed their treatment courses sooner and required less benzodiazepine than patients treated using the standard fixed-schedule approach. Moreover, the symptom-triggered approach was as efficacious as the standard regimen in managing alcohol withdrawal.

In previous studies,[16,17] because patients in the comparison groups were not assessed with a standardized scale measuring the severity of withdrawal, the selection of less symptomatic patients to receive symptom-triggered therapy could explain the treatment differences observed. Furthermore, in testing a new therapy it is particularly important to compare the intervention with a standard therapy, the fixed-schedule approach in this case.[10,24] Although it may appear that by virtue of the study design more medication would be used in the fixed-schedule group, waiting for symptoms to appear and trigger medication administration could have resulted in more severe withdrawal and prolonged treatment. This, however, was not the case. In fact, severity of withdrawal and use of as-needed medication were the same in both treatment groups, suggesting that fixed-schedule regimens may be unnecessarily intense and prolonged.

Our findings are consistent with prior preliminary observations,[16,17] yet our study had several methodological advantages. In our study, symptom-triggered therapy was compared with a standard treatment regimen. The severity of alcohol withdrawal was measured in all subjects. Randomization minimized confounding mainly by distributing the severity of alcohol withdrawal evenly between the two treatment groups. Blinding reduced biases that could have occurred in the assessment of withdrawal severity, the administration of therapy, and the decision to continue hospitalization.

We also recognize possible limitations in the study. Although no difference in major complications was found, the study was not designed to have sufficient power to detect small differences in the rates of uncommon complications, such as seizures and delirium tremens. In addition, although randomization was generally successful, there was a trend toward a more common history of hallucinations, delirium tremens, and prior detoxification in the fixed-schedule group. However, this trend did not result in increased severity of withdrawal or use of as-needed medications. The alternative drug regimens studied also were not designed to have an effect on long-term outcomes, yet it is reassuring that there were no differences in compliance with follow-up, rehabilitation, or readmission rates.

In addition, although these results may have wide applicability in treating patients withdrawing from alcohol, there are several limitations in the generalizability of the findings. First, the study was performed in an alcohol detoxification unit in which nurses were specifically trained to use the CIWA-Ar scale. It is possible that symptom-triggered therapy may not be as feasible in a setting in which withdrawal is not encountered as frequently. However, the CIWA-Ar scale is simple to learn and administer. Second, because the study was performed in a Veterans Affairs hospital, almost all participants were men. Although further studies are necessary to confirm these results in women, any differences in the clinical characteristics of alcohol withdrawal that might exist between men and women may underscore the advantages of individualized therapy. Third, this study excluded patients with any history of seizures. Withdrawal seizures are often unheralded by autonomic symptoms and signs that would be required for subjects to receive benzodiazepines as part of a symptom-triggered regimen.[1] We chose not to randomize patients at high risk for seizures to a strategy that might not include any medications.

Finally, we excluded patients with acute medical or psychiatric illnesses and

those with opiate or benzodiazepine withdrawal. Because the CIWA-Ar scale relies on a constellation of autonomic signs and subjective symptoms, the presence of other acute illnesses could lead to increased CIWA-Ar scores unrelated to alcohol withdrawal. Patients using clonidine and β-blockers were also excluded because these agents may reduce or mask the signs and symptoms of alcohol withdrawal. Although our study population was restricted as described herein for research purposes, others[25] have found a modified CIWA-A scale to be a valuable tool in the general hospital setting, even in acutely ill medical patients. The previously mentioned exclusions suggest that symptom-triggered therapy is useful in selected patients without seizures or acute concurrent medical illness, and who can be monitored appropriately for symptoms of withdrawal.

A recent survey[10] indicated that symptom-triggered regimens are not in widespread use and that fixed-schedule chlordiazepoxide for 3 days constituted the most commonly prescribed medication regimen for the treatment of alcohol withdrawal. Our study delineates the advantages of individualizing the treatment of alcohol withdrawal by using symptom-triggered therapy, and it suggests that patients currently treated for alcohol withdrawal with traditional regimens may be more efficiently treated with symptom-triggered regimens. In addition, many patients might be treated in less than 1 day and perhaps could be discharged earlier than with standard therapy, thereby providing significant cost savings. Symptom-triggered therapy is a reasonable alternative to other inpatient regimens that may be excessive and to outpatient treatment that is not appropriate for all patients.

Future studies should evaluate the effect of symptom-triggered therapy on the cost and duration of hospitalization for the treatment of alcohol withdrawal and should identify other patient populations for whom symptom-triggered therapy may be appropriate. The current study confirms that symptom-triggered therapy individualizes treatment, results in less benzodiazepine use and a shorter treatment course, and is as efficacious as standard fixed-schedule therapy for the management of alcohol withdrawal.

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