ORIGINAL INVESTIGATION

Symptom-Triggered vs Fixed-Schedule Doses of Benzodiazepine for Alcohol Withdrawal

A Randomized Treatment Trial

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Background: In alcohol withdrawal, fixed doses of benzodiazepine are generally recommended as a first-line pharmacologic approach. This study determines the benefits of an individualized treatment regimen on the quantity of benzodiazepine administered and the duration of its use during alcohol withdrawal treatment.

Methods: We conducted a prospective, randomized, double-blind, controlled trial including 117 consecutive patients with alcohol dependence, according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,* entering an alcohol treatment program at both the Lausanne and Geneva university hospitals, Switzerland. Patients were randomized into 2 groups: (1) 56 were treated with oxazepam in response to the development of signs of alcohol withdrawal (symptom-triggered); and (2) 61 were treated with oxazepam every 6 hours with additional doses as needed (fixed-schedule). The administration of oxazepam in group 1 and additional oxazepam in group 2 was determined using a standardized measure of alcohol withdrawal. The main outcome measures were the total amount and duration of treatment with oxazepam, the incidence of complications, and the comfort level.

Results: A total of 22 patients (39%) in the symptom-triggered group were treated with oxazepam vs 100% in the fixed-schedule group ($P<.001$). The mean oxazepam dose administered in the symptom-triggered group was 37.5 mg compared with 231.4 mg in the fixed-schedule group ($P<.001$). The mean duration of oxazepam treatment was 20.0 hours in the symptom-triggered group vs 62.7 hours in the fixed-schedule group ($P<.001$). Withdrawal complications were limited to a single episode of seizures in the symptom-triggered group. There were no differences in the measures of comfort between the 2 groups.

Conclusions: Symptom-triggered benzodiazepine treatment for alcohol withdrawal is safe, comfortable, and associated with a decrease in the quantity of medication and duration of treatment.

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AN IMPORTANT advance in the last 3 decades has been the use of benzodiazepines to treat alcohol withdrawal. In the late 1960s, the comparison of chlordiazepoxide with placebo and 3 other drugs established the therapeutic efficacy of benzodiazepines for alcohol withdrawal.[1] Recent meta-analyses concluded that benzodiazepines are recommended over most nonbenzodiazepine sedative-hypnotic agents because they have better efficacy, a greater margin of safety, and lower potential of abuse.[2,3]

Although withdrawal severity varies greatly, and the amount of medication needed to control symptoms can also vary significantly, benzodiazepines are generally administered on a predetermined dosing schedule for 3 to 5 days for all patients. This is in contrast with numerous observations indicating that the pharmacologic treatment of alcohol withdrawal should allow for a degree of individualization. A personal adaptation of medication dosage is now possible, using questionnaires that evaluate the occurrence and

For editorial comment see page 1093

intensity of alcohol withdrawal. One of these instruments, the revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar),[4] is a 10-item scoring system that measures the severity of alcohol withdrawal, monitors the clinical course, and identifies patients at risk of complications such as seizures and delirium.

METHODS

PARTICIPANTS

Between August 19, 1999, and October 3, 2000, consecutive patients admitted to the alcohol treatment inpatient program, the 12-bed clinic "Vallon" affiliated with the Lausanne University Hospital and the 10-bed clinic "Petit Beaulieu" of the Geneva University Hospital, were considered for study inclusion. On a weekly basis, staff organization required that study inclusion be interrupted when 2 patients from the given institution were included; thus, no more than 4 patients were included from any given week. Exclusion criteria were (1) last alcoholic beverage intake more than 72 hours prior to admission; (2) daily use of medication for treatment of alcohol withdrawal for the 30 days prior to admission (ie, benzodiazepines, barbiturates, or clomethiazole); (3) major cognitive, psychiatric, or medical comorbidity; (4) opiate or stimulant dependence; and/or (5) no fluency in French. The ethics committees of the departments of internal medicine at Lausanne and Geneva university medical schools approved the study protocol.

ASSESSMENTS

A history, physical examination, and blood tests for γ-glutamyltransferase, red blood cell volume, and blood alcohol concentration were done at admission. Levels of carbohydrate-deficient transferrin (CDT) were also checked, which is a biological marker suggestive of heavy alcohol use (>60 g of alcohol per day) for the past 15 days.[7] Eligible patients were personally interviewed by trained research assistants to assess their demographic characteristics, medical comorbidities (using the Charlson scale[8]), use of any prescribed drugs during the last 30 days, use of any illegal drugs, and *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria of alcohol dependence using questions adapted from the French version of the Diagnostic Interview for Genetic Studies (DIGS).[9] The interviewer also solicited a detailed history of alcohol use over the week, month, and year preceding admission[10] and a measure of alcohol dependence severity using the Severity of Alcohol Dependence Questionnaire.[11]

Finally, subjects' comfort level during the first 3 days of treatment was estimated retrospectively at treatment day 3: well-being was assessed using 4 questions adapted from the well-being schedule[12] and 3 dimensions adapted from the health-related, quality-of-life, Medical Outcomes Study 36-Item Short-Form Health Survey (MOS-SF-36)[13] questionnaire. Alcohol withdrawal was assessed using the CIWA-Ar, a validated, reliable measure of the current severity of alcohol withdrawal consisting of 10 items, scored from 0 (no withdrawal) to 67 (maximum withdrawal severity).[4] The fixed-schedule regimen of oxazepam was determined according to the guidelines of the American Society of Addiction Medicine (30 mg every 6 hours for 4 doses, then 15 mg every 6 hours for 8 doses).[2] We used 15-mg oxazepam tablets in our study regimen because they are frequently used for the oral treatment of alcohol withdrawal in Europe. We could have used 10-mg diazepam or 25-mg chlordiazepoxide instead.

INTERVENTION GROUPS

A pharmacist not involved in other aspects of the trial randomly assigned eligible patients in clusters of 10 subjects to either the symptom-triggered group or the fixed-schedule group. The allocation was generated using a program running on Excel (Microsoft Inc, Redmond, Wash). Oxazepam and placebo (mannitol) were manufactured in capsules of similar appearance. During the trial, each patient was allocated an identification number. A safety-sealed envelope labeled with the patient's identification number contained the code of randomization for each individual. Physicians, nurses, research assistants, and patients were blinded to treatment assignment throughout the trial. The evidence of successful blinding among the staff was assessed on the third day of the protocol by asking the nurse in charge to guess whether the patient was assigned to the symptom-triggered group or the fixed-schedule group. Data analyses indicated that 65 of 117 patients (55.5%) were attributed to the wrong group, with a similar rate of incorrect guesses in both groups. Subjects in the fixed-schedule group received oxazepam every 6 hours, 4 doses of 30 mg each, and then 8 doses of 15 mg each. Half an hour after taking each capsule, subjects with CIWA-Ar scores between 8 and 15 received 15 mg of oxazepam, and those with CIWA-Ar score higher than 15 received 30 mg of oxazepam. The CIWA-Ar scores were monitored, and additional oxazepam doses were administered every half hour as long as CIWA-Ar scores remained at 8 or higher ("as-needed" medication). Fixed-schedule doses were not administered when subjects were sleeping or were somnolent. The symptom-triggered group received placebo every 6 hours, 4 doses of 30 mg each followed by 8 doses of 15 mg each. Half an hour after taking each capsule, subjects with CIWA-Ar scores between 8 and 15 received 15 mg of oxazepam, while those with CIWA-Ar scores higher than 15 received 30 mg of oxazepam. The CIWA-Ar scores were monitored, and additional oxazepam doses were administered every half hour as long as CIWA-Ar scores remained at 8 or higher (as-needed medication). Subjects were observed for symptoms of withdrawal for 48 hours after study completion.

STATISTICAL ANALYSIS

Analyses were performed using SPSS (Chicago, Ill) for Windows. The Mann-Whitney test was used to compare duration of treatment and medication doses that were not normally distributed. Independent-sample *t* tests were used to compare normally distributed continuous variables, and χ^2 tests were used to compare categorical variables. Two-tailed *P* values were obtained from all tests. With the hypothesis of a medium effect size d (d=0.5 SE), where d illustrates the difference in the total quantity of oxazepam between the symptom-triggered group and the fixed-schedule group, the trial was designed to have a 90% probability obtaining significant differences between groups with an α (type I error) of 5%.

Since an individual monitoring system of alcohol withdrawal has become available, the characteristics of pharmacologic treatments adapted to each individual have been evaluated. Retrospective evaluation of admissions in a general hospital suggests that monitoring withdrawal symptoms using the CIWA-Ar allows for a reduction in duration and intensity of benzodiazepine treatment.[5] A single controlled trial demonstrated an important

Table 1. Comparison of Demographic Characteristics and Alcohol Use History by Treatment Group*

Characteristic	Treatment Group: Symptom-Triggered (n = 56)	Treatment Group: Fixed-Schedule (n = 61)	Statistical Test: t or χ^2
Demographic Characteristics			
Age at interview, y	46.1 ± 9.87	46.9 ± 9.23	0.41
Male, %	80.0	74.2	0.55
Ethnic group, %			0.53
White	96.4	93.4	. . .
Other	3.6	6.6	. . .
Current marital status, %			1.05
Married	30.4	39.3	. . .
Separated/divorced/widowed	50.0	44.3	. . .
Never married	19.6	16.4	. . .
Currently employed, %	55.4	49.2	0.44
Charlson Index (comorbidity)	0.6 ± 0.87	0.9 ± 1.37	1.49
Alcohol Use History at Intake			
Alcohol consumption (last 7 d)			
Time since last drink, h	13.8 ± 11.66	19.0 ± 15.56	2.09†
Total No. of drinks	87.9 ± 61.23	88.9 ± 83.82	0.08
Alcohol consumption (last 30 d)			
Mean drinking, d/wk	5.9 ± 1.53	5.4 ± 2.19	1.44
Mean No. of drinks per occasion	12.0 ± 10.60	11.2 ± 11.18	0.44
Maximum drinking, d/wk	6.7 ± 0.77	6.4 ± 1.79	0.26
Maximum No. of drinks per occasion	21.2 ± 18.30	20.9 ± 18.56	0.08
Blood alcohol concentration, g/L	0.5 ± 0.57	0.4 ± 0.63	0.88
Biological markers (reference values)			
GGT (15-85 U/L)	210.4 ± 335.06	220.8 ± 300.67	0.17
CDT (<6%)	8.1 ± 3.89	8.2 ± 4.07	0.10
MCV (81-99 fL)	96.4 ± 7.95	96.8 ± 10.15	0.23
Alcohol dependence			
DSM-IV dependence criteria	5.1 ± 1.42	5.1 ± 1.56	0.21
Withdrawal history			
DSM-IV withdrawal criteria, %	76.8	63.9	2.30
SADQ score (0-60)	29.2 ± 17.41	26.5 ± 18.03	0.84
SADQ score ≥35, %	32.1	29.5	0.09
History of seizures and/or delirium, %	19.6	13.1	0.91

*All data that include plus/minus signs are means ± SDs. Ellipses indicate not applicable; GGT, γ-glutamyltransferase; CDT, carbohydrate-deficient transferrin; MCV, mean corpuscular (red blood cell) volume; *DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition;* and SADQ, Severity of Alcohol Dependence Questionnaire.

†P = .04.

reduction in the duration of treatment and quantity of benzodiazepines administered during alcohol withdrawal. Saitz and colleagues[6] randomized 101 alcohol-dependent patients admitted to a treatment unit to either symptom-triggered or fixed-schedule chlordiazepoxide treatment. The individualized regimen was associated with a reduction in the duration (68 hours vs 9 hours) and intensity (425 mg vs 100 mg of chlordiazepoxide) of treatment without difference in the incidence of complications.[6]

However, as Mayo-Smith[2] notes, only 1 controlled trial confirms the reduction in medication use associated with individualized doses of benzodiazepines for treatment of alcohol withdrawal. The major aim of the present study is to reassess the extent of the benefits of an individualized regimen of benzodiazepines for treatment of alcohol withdrawal. Secondary objectives are to verify that the benefits of individualized benzodiazepine therapy persist even in patients with severe alcohol-withdrawal histories and individuals at elevated risk of alcohol withdrawal because of recent alcohol use at the time of admission in treatment.

RESULTS

Eight of the 251 consecutive patients admitted in the treatment program who were asked to participate declined the offer, resulting in 243 individuals evaluated for study inclusion. Forty-four subjects (18.1%) who did not have any alcoholic beverage within 72 hours preceding admission were excluded, as were 42 (17.3%) who had used benzodiazepines daily for the last 30 days. Another 31 (12.7%) were excluded because 12 were undergoing methadone maintenance therapy, 4 had used barbiturates on a regular basis, 13 had major psychiatric or medical comorbidity, and 2 did not speak French. Among the 126 patients randomized, 4 exited the program within the first 3 days, 3 had exclusion criteria apparent only after randomization, 1 had somnolence, and 1 had several falls. These exclusions left valid data for 117 patients. The mean±SD age of these subjects was 46.6±9.52 years; 90 (76.9%) were men; 40 (34.2%) were married; 21 (17.9%) were single; 56 (47.9%) were separated, divorced, or widowed; and 111 (94.9%) were white, while 6 (5.1%) were from other ethnic groups.

Table 2. Comparison of Treatment Outcomes by Treatment Group*

Characteristic	Treatment Group: Symptom-Triggered (n = 56)	Treatment Group: Fixed-Schedule (n = 61)	Statistical Test: Mann-Whitney, *t*, or χ^2
Oxazepam Treatment			
No. (%) treated with oxazepam	22 (39.3)	61 (100)	52.21‡
Fixed-schedule oxazepam, mg (range)	0.0	224.5 ± 27.95 (180-240)	10.05‡
"As-needed" oxazepam, mg (range)	37.5 ± 81.70 (0-375)	6.9 ± 20.41 (0-135)	2.52§
Total oxazepam, mg (range)	37.5 ± 81.70 (0-375)	231.4 ± 29.43 (180-375)	8.17‡
Treatment duration, h	20.0 ± 24.45	62.7 ± 5.44	5.88‡
CIWA-Ar Scores			
Highest, day 1	8.1 ± 5.76	5.5 ± 3.69	2.90‖
≥8, day 1, %	44.6	27.9	3.57
Highest, day 2	5.3 ± 4.41	3.2 ± 2.67	3.06‖
≥8, day 2, %	21.4	6.6	5.47§
Highest, day 3	4.2 ± 3.92	2.7 ± 2.71	2.46‖
≥8, day 3, %	17.9	3.3	6.74‖
Major Complications			
No. of seizures	1	0	1.10
No. of hallucinations	0	0	0.00
No. of delirium tremens	0	0	0.00
Well-being Schedule (Assessed at Day 3), 0-10			
Health concerns last 3 d	3.7 ± 3.08	3.9 ± 3.46	0.34
Anxiety last 3 d	3.8 ± 2.62	3.8 ± 2.71	0.11
Depressed last 3 d	6.0 ± 1.98	6.2 ± 2.41	0.40
Energy last 3 d	5.7 ± 2.26	5.2 ± 2.43	1.03
Health-Related Quality of Life (Assessment at Day 3),† 0-100			
Physical functioning last 3 d	91.9 ± 11.32	84.2 ± 19.04	2.64‖
Vitality last 3 d	59.6 ± 19.03	55.2 ± 21.51	1.16
Energy last 3 d	67.0 ± 17.37	66.3 ± 21.94	0.20

*All data that include plus/minus signs are means ± SDs. CIWA-Ar indicates revised Clinical Institute Withdrawal Assessment for Alcohol scale.
†Adapted from the Medical Outcomes Study 36-Item Short-Form Health Survey.
‡$P<.001$.
§$P<.05$.
‖$P<.01$.

Patients were randomized into 2 groups: symptom-triggered (n=56) and fixed-schedule (n=61) oxazepam administration. To verify that the withdrawal treatment characteristics did not reflect preexisting group differences, we compared demographic characteristics and alcohol use history between the groups (**Table 1**), which were similar at intake in age, sex ratio, ethnic makeup, marital status, and employment. There was no group difference in medical comorbidity assessed with the Charlson scale. Table 1 underscores group similarities in (1) alcohol use over the 7-day and 30-day periods preceding admission, (2) blood alcohol concentration, (3) biological markers of recent heavy alcohol intake (γ-glutamyltransferase, carbohydrate-deficient transferrin, and red blood cell volume), (4) severity of alcohol dependence (assessed by the number of *DSM-IV* dependence criteria endorsed), and (5) withdrawal history (the number of *DSM-IV* alcohol withdrawal criteria, findings of the Severity of Alcohol Dependence Questionnaire, and the proportion of patients reporting a former history of major alcohol withdrawal [seizures, hallucinations, or delirium tremens]).

Considering group similarities in demography, alcohol use, and alcohol withdrawal history, we found that the symptom-triggered treatment approach resulted in a significant reduction in duration and quantity of oxazepam used during alcohol withdrawal (**Table 2**). The symptom-triggered group used 6 times less oxazepam than the fixed-schedule group and also experienced markedly shorter duration of treatment. This important difference between groups resulted in part from the fact that only 22 (39%) of the patients in the symptom-triggered group used oxazepam at all, compared with 100% in the fixed-schedule group. However, it is important to note that the group differences persisted after excluding individuals who did not require any oxazepam in the symptom-triggered group. Indeed, although not reported in the tables, after excluding individuals who did not require any oxazepam treatment (CIWA-Ar score was always lower than 8 in 34 [61%] patients in the symptom-triggered group), we found that the mean±SD quantity of oxazepam administered to the 22 treated patients was 95.4±107.7 mg, which was significantly less than the 231.4±29.4 mg registered in the fixed-schedule group (Mann-Whitney, $z=5.84$; $P<.001$).

To explore whether the individualized benzodiazepine regimen also offered benefits in the subgroup with a history of severe alcohol withdrawal (seizures, hallucinations, or delirium tremens), analyses were repeated in the 19 subjects with such history (not reported in the tables). The results indicated a trend toward less total ox-

azepam used (94.1±137.2 mg vs 240.0±34.95 mg; Mann-Whitney, $z=1.83$; $P=.07$) and a reduction in treatment duration (22.7±26.68 hours vs 62.1±6.18 hours; Mann-Whitney, $z=2.87$; $P=.004$) in the symptom-triggered group compared with the fixed-schedule group.

While the symptom-triggered regimen was associated with a reduction in the intensity and duration of oxazepam use, it is important to examine whether treatment reduction was associated with a change in safety, withdrawal intensity, and/or comfort. Regarding safety, Table 2 indicates that a single patient experienced an episode of seizure, while no hallucinations or delirium tremens were registered. The intensity of the withdrawal symptoms assessed by the CIWA-Ar indicated that symptom-triggered group mean scores were generally higher at days 1, 2, and 3, with a larger proportion of patients with CIWA-Ar scores of 8 or higher than in the fixed-schedule group. Higher CIWA-Ar scores might have been associated with more anxiety, nervousness, and a decrease in comfort. Therefore, to explore whether the symptom-triggered regimen might be detrimental to comfort, at day 3 we evaluated well-being and health-related quality of life over the 3 days of detoxification (Table 2). There were no treatment group differences in health concerns, anxiety, energy, or depression (well-being schedule), similar findings of vitality and energy, and a higher level of physical functioning during detoxification in the symptom-triggered group than in the fixed-schedule group (adapted from the MOS-SF-36). To verify that the measures of well-being and health-related quality of life did not reflect preexisting group differences, we conducted further analyses (not reported) that indicated similar scores between groups for the 4 questions of the well-being schedule and the 3 dimensions of the MOS-SF-36 evaluated over the 30 days preceding admission.

COMMENT

The data reported offer strong support to the hypothesis that for many patients withdrawing from alcohol, symptom-triggered therapy can shorten detoxification time and avoid unnecessary medications without decrease in safety or comfort. Anecdotally, the nursing staff involved in the study preferred to have an objective scale to guide their medication dosing and decided to pursue the symptom-triggered regimen after completion of the study. While the results presented confirm an important reduction in the duration and intensity of benzodiazepine treatment, the study by Saitz and colleagues[6] and the present data differed in the magnitude of the reduction (7 times vs 3 times for treatment duration and 4 times vs 6 times for medication quantity, respectively). Differences between the 2 studies' results were probably due to variations in the protocol of administration of "as-needed" medication. By excluding patients without recent alcohol intake and focusing on subjects at risk to develop alcohol withdrawal symptoms, the present study adds precision to the importance of the benefits of the symptom-triggered regimen. Including patients with seizures or severe withdrawal histories adds potential for generalizing from the results reported by Saitz and colleagues, confirming the benefit of a symptom-triggered regimen for the numerous patients with these complications.

In the present study, 60.3% of the patients withdrawing from alcohol did not require any oxazepam (symptom-triggered group), suggesting that, even in a sample of individuals with severe alcohol problems, most patients did not require any pharmacologic treatment for alcohol withdrawal. This result extends over prior research demonstrating that among 203 problem drinkers admitted to a general hospital, 46% demonstrated no significant withdrawal symptoms requiring pharmacologic treatment.[14]

Although these results may have wide applicability in treating patients withdrawing from alcohol, it is important to recognize some limitations in the generalizablity of the findings. First, these subjects were in alcohol detoxification units, and the results may not hold true for other settings, such as general hospitals, where withdrawal occurs less frequently. Second, the sample consisted mostly of white men; the findings might not apply to women or nonwhites. Finally, although efforts were made to optimize the accuracy of the data, information on quantity and frequency of alcohol use and severity of alcohol use disorders relied solely on the subjects' estimates and recollections.

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