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A Comparative Study of Fixed Tapering Dose Regimen versus Symptom-triggered Regimen of Lorazepam for Alcohol Detoxification

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Abstract — **Aims:** The study aimed at comparing the fixed tapering dose and the symptom-triggered regimens of lorazepam for alcohol detoxification. **Methods:** We carried out a prospective, randomized, double blind controlled trial involving 63 consecutive consenting male patients admitted with diagnosis of uncomplicated alcohol withdrawal. The patients were randomized into two groups based on the type of lorazepam dosage: symptom-triggered ($n = 33$) and fixed tapering dose regimens ($n = 30$). Alcohol withdrawal symptoms were rated on CIWA-Ar (Clinical Institute Withdrawal Assessment – Alcohol revised). The main outcome measures were the total amount and duration of lorazepam treatment and the incidence of adverse events or complications. **Results:** The mean lorazepam dose administered in the symptom-triggered group was significantly lower than in the fixed tapering dose group (9.5 versus 19.9 mg, $P < 0.001$) and for a significantly shorter duration of time (47.8 versus 146 h, $P < 0.001$) with more significant results for higher initial CIWA-Ar scores. There were no significant differences between both the groups in terms of the incidence of complications like seizures or delirium tremens. **Conclusion:** Symptom-triggered lorazepam treatment for alcohol withdrawal resulted in administration of lower total doses of medication for a shorter duration of treatment and was as safe as the fixed tapering dose.

INTRODUCTION

Alcohol use disorders cause pervasive public health concern. According to the World Development Report (1993), alcohol-related disorders affect 5–10% of the world population each year and account for 2% of the global burden of disease. The most severe manifestations of alcohol withdrawal syndrome (AWS) include delirium tremens and seizures. These manifestations result from alcohol-induced imbalances in the brain chemistry that causes excessive neuronal activity if alcohol is withheld (Saitz, 1998).

AWS is managed by various drugs among which Benzodiazepines are preferred for safety and efficacy (Rosenbloom, 1988; Mayo-Smith, 1997). The most commonly used are chlordiazepoxide, diazepam (long acting) and lorazepam, oxazepam (short/intermediate acting). Two regimens, fixed tapering dose (FTDR) and symptom-triggered (STR) are commonly employed for treatment of AWS with benzodiazepines. In FTDR, medication doses are given at fixed specified intervals, tapered off gradually and additional doses are given as required. In STR, medications are dosed based on the patient's cross-sectional manifestations of withdrawal symptoms, which can be evaluated by different rating scales such as CIWA-Ar (Clinical Institute Withdrawal Assessment – Alcohol revised) (Holbrook *et al.*, 1999).

A symptom-triggered regimen may be preferred in most cases of AWS because it results in the administration of less dosages of medication and shorter duration of treatment (Saitz *et al.*, 1994; Daeppen *et al.*, 2002) and reduces the risk of under medicating or overmedicating a patient since the drug is dosed and administered depending upon the severity of withdrawal symptoms as assessed by the rating scales (Sullivan *et al.*, 1991). However, a fixed tapering dose regimen is usually preferred if monitoring of withdrawal symptoms cannot be accurately performed which may be due to inadequate staffing, lack of training of staff and professionals, outpatient setting, co-morbid medical or psychiatric illnesses or use of medications that may affect CIWA-Ar measurements (Mayo-Smith, 1997). CIWA-Ar rating can help individualize treatment for alcohol detoxification depending upon the severity of AWS and reduce the risk of seizures and delirium tremens (DT) (Saitz and O'Malley, 1997).

We conducted this study in a tertiary care de-addiction center in India to compare the fixed tapering dose and the symptom-triggered regimens using lorazepam. Lorazepam is a short acting benzodiazepine available at our hospital and used commonly for AWS. Lorazepam undergoes direct glucuronidation without prior cytochrome p450 metabolism and thus is preferred in patients with hepatic or renal dysfunction (Griffin *et al.*, 2013). The advantage of using such a medication is that it can be immediately started in a patient presenting with AWS without waiting for the liver enzyme profile, which is beneficial in patients with severe withdrawal symptoms. Our literature search did not reveal any study comparing these regimens using lorazepam and no relevant literature is available for Indian subcontinent.

METHODOLOGY

This study was conducted on patients admitted via the Out Patient Department (OPD) of Psychiatry and De-Addiction at Post Graduate Institute of Medical Education and Research, Dr. Ram Manohar Lohia Hospital (RMLH), a free, tertiary care government medical teaching institution in New Delhi. All successive male patients between 18 and 60 years of age with a diagnosis of alcohol dependence and uncomplicated alcohol withdrawal as per International Classification of Diseases, Diagnostic Criteria for Research (World Health Organization, 1993), undergoing in-patient detoxification between November 2010 and November 2011 who provided written informed consent to participate in the study were included. The exclusion criteria included Alcohol Use Disorders Identification Test (AUDIT) (Saunders *et al.*, 1993) score <10, comorbid major Axis-I psychiatric disorders (excluded after assessing on Mini International Neuropsychiatric Inventory; Sheehan *et al.*, 1998), severe medical illnesses e.g. hepatic encephalopathy, delirium (using Delirium Rating Scale;

Trzepacz *et al.*, 1988), dependence on other substance excluding nicotine, mini mental state examination (MMSE; Folstein *et al.*, 1975) score <23, history of head injury and mental retardation. The protocol was approved by the Institutional Ethics Committee, RMLH.

The AUDIT is routinely administered to all patients presenting to this OPD for screening of alcohol dependence for several years now. For this study, those with AUDIT score >10 were consented for the study, assessed clinically and diagnosed using ICD-10 criteria, then rated on MINI. Severity of addiction was assessed using Addiction Severity Index. Comprehensive clinical and neurological examination was carried out after admission. To detect co-morbid medical illnesses laboratory investigations were conducted: haemogram with mean corpuscular volume, liver function tests, kidney function tests, serum electrolytes (S.E), serum proteins and random blood sugar. If required, ultra sonogram whole abdomen was conducted. No specific scales or criteria were used to diagnose any medical illness.

Subjects were assessed on CIWA-Ar for severity of alcohol withdrawal at baseline. CIWA-Ar scale is a validated 10-item assessment tool with high inter-rater reliability and construct validity (Sullivan *et al.*, 1989). Our scoring of subsequent CIWA-Ar ratings was as follows: (a) CIWA-Ar >15; Severe Withdrawal, CIWA-Ar to be applied 2 hourly till the score comes below 15, (b) CIWA-Ar 8–15; Moderate Withdrawal, CIWA-Ar to be applied 6 hourly till the score comes below 8, (c) CIWA-Ar <8; Mild Withdrawal, CIWA-Ar to be applied 8 hourly and (d) Stop CIWA-Ar assessment when the score is <8 for three consecutive readings (viz: Mayo-Smith, 1997; Asplund *et al.*, 2004; Mee-Lee, 2005).

Subjects were randomized into either fixed tapering dose (FTDR) or symptom-triggered (STR) lorazepam regimen by the designated senior resident using a random numbers table. Generic lorazepam (1 mg) tablets available as a part of free hospital supply were used. The first author (who was also the investigator-rater) and the patients were blind to the allocation of the study group. Treatment was started by the treating psychiatrist and nursing staff, based upon the randomization informed to them, and the initial CIWA-Ar ratings conveyed by the first author. Depending upon the initial CIWA-Ar ratings, the first author would repeat the rating at fixed times and report them to the nurse on duty who would give the medicines to the patient as per the treatment chart available to them. The first author, who did not know to which group a patient belonged, made an assessment from time to time using CIWA-Ar ratings only.

The treatment regimen in the two groups was as follows: Regimen 1—fixed tapering dose regimen (FTDR), the dose of lorazepam, given as bid/tid dosing, was tapered off as pre-determined (Table 1). Regimen 2—symptom-triggered regimen (STR), the dose of lorazepam was decided according to the CIWA-Ar scores each time, CIWA-Ar score <8—no drug required, CIWA-Ar score >8—2 mg lorazepam orally (Mayo-Smith, 1997; Asplund *et al.*, 2004; Taylor *et al.*, 2009).

In case of any adverse event or exacerbation of CIWA-Ar score, the psychiatrist was free to prescribe additional dosages according to the clinical judgment, which were also recorded in the evaluation sheet. The blinding was unmasked at the time of discharge and the outcome measures (dose of the lorazepam, duration of detoxification, adverse events such as seizures, delirium, hallucinations, increased severity of withdrawal symptoms, excessive sedation and insomnia) were recorded. Insomnia and excessive sedation were recorded based on patient's, caregiver's report and nurses observation. Increased severity of withdrawal symptoms was documented by an increase in consecutive CIWA-Ar ratings.

Table 1. Drug dosage in FTDR

CIWA-Ar scores	<8	8–15	>15
Severity of withdrawal	Mild	Moderate	Severe
Drug dosage (in mg)	mg/day (bid/tid)	mg/day (bid/tid)	mg/day (bid/tid)
Day 1	2 (tid dosing)	4 (tid dosing)	8 (tid dosing)
Day 2	1.5 (bid dosing)	3 (tid dosing)	6 (tid dosing)
Day 3	1 (bid dosing)	2 (tid dosing)	4.5 (tid dosing)
Day 4	0	1.5 (bid dosing)	3 (tid dosing)
Day 5		1 (bid dosing)	2 (tid dosing)
Day 6		0	1.5 (bid dosing)
Day 7			1 (bid dosing)

FTDR, fixed tapering dose regimen; bid, twice per day; tid, thrice per day.

The statistical analyses were performed using SPSS (17.0) for Windows. Independent-sample *t*-tests were used to compare normally distributed continuous variables, and chi-square 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 lorazepam between the symptom-triggered group and the fixed tapering group, the trial was designed to have a 95% probability of obtaining significant differences between groups with an alpha (type I error) of 5%.

RESULTS

Out of 72 inpatients with alcohol dependence and uncomplicated alcohol withdrawal meeting the inclusion and the exclusion criteria, 67 consented to inclusion in the study. One patient left against medical advice on the first day. Two patients were found to have co-morbid medical complications (ECG abnormalities, liver cirrhosis and deranged laboratory investigations) after admission and were excluded from the study. One patient consumed alcohol after admission on the second day and was excluded. Finally 63 patients were included in the study, 30 in Group FTDR and 33 in Group STR.

The two groups were comparable as to socio-demographic characteristics (age, education, family income, type of family, marital status and employment status), alcohol use history and baseline assessment (AUDIT, MINI, DRS and CIWA-Ar) and laboratory investigations. CIWA-Ar ratings at admission of the two groups (FTDR = 15.5, STR = 13.4) were comparable with no significant statistical difference (Table 2).

The groups were similar with respect to the severity of alcohol withdrawal. A majority ($N = 60$) suffered from moderate (54%) or severe withdrawal (41%) while only a few ($N = 3$, 5%) had mild withdrawal (Table 3). In the symptom-triggered group, 2 (6.66%) patients had mild withdrawal, 20 (60.61%) had moderate and 11 (33.33%) had severe withdrawal compared with the fixed tapering group where only 1 (3.33%) patient had mild withdrawal, 14 (46.67%) had moderate and 15 (50%) had severe withdrawal.

We found that the STR resulted in a significant reduction in the quantity of lorazepam used during alcohol withdrawal

Table 2. Socio-demographic variables, alcohol use parameters and baseline assessment of the two study groups

Socio-demographic variables and alcohol use parameters	Regimen		*P*-value
	FTDR (*N* = 30)	STR (*N* = 33)	
Age in Years (mean ± SD)	39.5 (±9)	37.8 (±10.2)	0.476
Duration of intake (years) Mean (±SD)	18.6 (±8.3)	15.5 (±8.3)	0.161
Last alcohol intake before baseline assessment (hours) Mean (±SD)	24.3 (±14.7)	21.4 (±12.6)	0.395
Amount of last intake (ml) (mean ± SD)[a]	294 (±166.77)	276 (±139.35)	0.644
MMSE (mean ± SD)	26.8 (±2.0)	27.5 (±1.8)	0.109
DRS (mean ± SD)	2.73 (±1.39)	2.5 (±1.9)	0.608
CIWA-AR at admission (mean ± SD)	15.5 (±4.5)	13.4 (±5.9)	0.115
Audit score (mean ± SD)	31.8 (±3.0)	31.3 (±4.3)	0.574

FTDR, fixed tapering dose regimen; STR, symptom-triggered regimen; MMSE, mini mental state examination; DRS, Delirium Rating Scale; CIWA-Ar, Clinical Institute Withdrawal Assessment – Alcohol revised.
[a]Assuming 1 peg of standard drink = 30 ml of whisky/vodka.

Table 3. Comparison of outcome parameters of the two study groups

Primary outcome measures	Regimen		*P*-value
	FTDR (*N* = 30)	STR (*N* = 33)	
Total dose of lorazepam (mean/mg ± SD)	19.9 (±9.9)	9.5 (±9.2)	<0.001[a]
Duration of detoxification (mean/h ± SD)	146.0 (±43.4)	47.8 (±45.8)	<0.001[a]
Mild withdrawal			
No of observations, *n* (%)	1 (3.33)	2 (6.66)	–
Total dose of lorazepam (mean/mg ± SD)	4.5	0.0	–
Duration of detoxification (mean/h ± SD)	72.0	0.0	–
Moderate withdrawal			
No of observations, *n* (%)	14 (46.67)	20 (60.61)	
Total dose of lorazepam (mean/mg ± SD)	12.6 (±4.9)	6.1 (±7.8)	0.005[a]
Duration of detoxification (mean/h ± SD)	119.1 (±30.7)	40.8 (±47.9)	<0.001[a]
Severe withdrawal			
No. of observations, *n* (%)	15 (50.00)	11 (33.33)	
Total dose of lorazepam (mean/mg ± SD)	27.7 (±6.7)	17.3 (±6.8)	<0.001[a]
Duration of detoxification (mean/h ± SD)	176.0 (±31)	69.1 (±36)	<0.001[a]
Days taken for 3 consecutive CIWA-Ar scores <8 Mean (± SD)	2.7 (±0.7)	2.7 (±1.3)	0.481
Additional hours of drug received after 3 consecutive CIWA-Ar ratings <8 Mean (± SD)	80 (±29.11)	4.36 (±25.1)[b]	–

FTDR, fixed tapering dose regimen; STR, symptom-triggered regimen.
[a]Cannot be rejected at a 5% significance level.
[b]Only 1 patient in the STR group received additional drug after 3 consecutive CIWA-Ar ratings <8.

Table 4. Adverse events in the two study groups

Adverse events	FTDR (*N* = 30)	STR (*N* = 33)	Total
Seizures	1	0	1
Delirium	1	1	2
Hallucinations	0	1	1
Increased severity of withdrawal symptoms	1	2	3
Excessive sedation	0	0	0
Insomnia	1	2	3

FTDR, fixed tapering dose regimen; STR, symptom-triggered regimen.

(Table 3) compared with FTDR (9.5 mg versus 19.9 mg, *P*-value <0.0001). Two patients in the STR did not receive the drug as per the protocol as they had mild withdrawal with CIWA-Ar <8. Patients randomized to STR had significantly lower duration of detoxification than FTDR (47.8 h versus 146 h, *P*-value <0.0001).

With comparable monitoring in both groups, the study subjects in FTDR group received the drug for ~80 more hours. Their lorazepam continued even after three consecutive CIWA-Ar became <8, while only one study subject in STR group received the drug after three consecutive CIWA-Ar became <8, which represents the excessive duration of detoxification the subjects in FTDR were exposed to.

While the symptom-triggered regimen was associated with a reduction in the dose and duration of lorazepam use, it was important to examine whether treatment reduction was associated with a change in safety and withdrawal intensity. Table 4 shows that in spite of receiving less drug for a significantly shorter duration of time, the study subjects in the STR did not develop significantly higher rates of adverse events. Four patients in FTDR suffered adverse events when

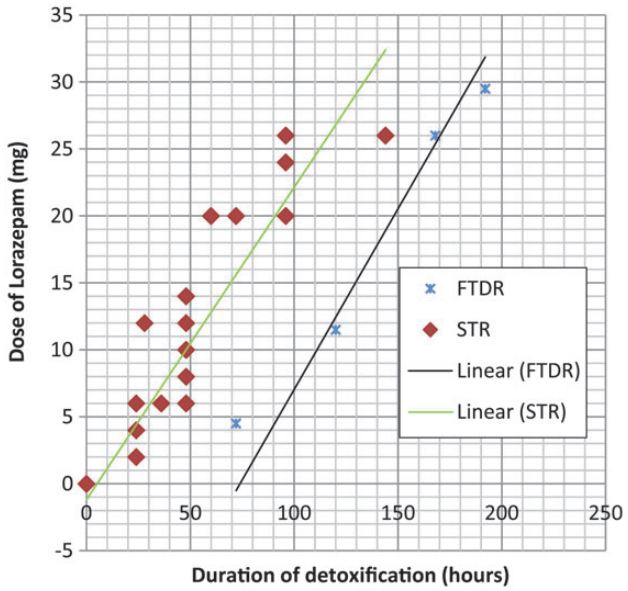

Fig. 1. Scatter diagram showing distribution of variables. FTDR, fixed tapering dose regimen; STR, symptom-triggered regimen. Note—Observations of patients who developed seizures and delirium were excluded. A single point in the graph may denote multiple subjects who had received same dosages for similar duration of time.

compared with five patients in STR during detoxification. One patient had a seizure in FTDR group and none in STR. One patient in each group developed delirium. Visual and auditory hallucinations developed in one patient in STR increased severity of withdrawal symptoms like increased anxiety, tremors, sweating developed in three patients, one patient in FTDR and two patients in STR. No patient in either group complained of excessive sedation. Sleep disturbances developed in three patients when detoxification was completed, one in group FTDR and two in group STR. The same patient in STR developed problems of insomnia as well as increased severity of withdrawal symptoms. All the adverse events were appropriately identified, reported and managed successfully.

To assess the efficacy of STR across all degrees of withdrawal, we compared the two treatment regimens according to the severity of withdrawal. STR was more efficacious than FTDR across all degrees of alcohol withdrawal. The level of significance of the results increased with increasing severity of alcohol withdrawal (Table 3).

Perhaps inclusion of the patients who developed complications during alcohol detoxification and received additional drug dosages could have resulted in such significant results and probably caused a bias in the assessment .When we excluded three patients who developed seizures and delirium during detoxification from the assessment, we found that STR was still associated with a significant reduction in dose (8.5 versus 19.1 mg, *P*-value <0.0001) and duration (41.7 versus 144.8 h., *P*-value <0.0001) of lorazepam use (Fig. 1).

DISCUSSION

This randomized double-blind study with two comparable groups demonstrates that patients with AWS treated with symptom-triggered therapy completed their detoxification courses sooner and required less lorazepam than the patients treated using fixed tapering doses. The symptom-triggered approach was as efficacious as the fixed dose in managing alcohol withdrawal in terms of the efficacy and incidence of adverse events. Since this study is one of the first such in the Indian subcontinent, it may add to the clinical armamentarium. It reiterates the advantages of symptom-triggered regimen over fixed tapering dose regimen of benzodiazepines in alcohol detoxification considering the short duration of detoxification and early road to recovery.

The STR group received significantly less lorazepam (mean total 9.5 mg) than the FTDR group (mean total 19.9 mg) ($P < 0.0001$). The results are consonant with Saitz *et al.* (1994) (100 versus 425 mg of chlordiazepoxide) and Daeppen *et al.* (2002) (37.5 versus 231.4 mg of oxazepam). In the present study, the patients in the STR group had significantly shorter duration of detoxification (47.8 h) when compared with the patients in the FTDR group (146 h)($P < 0.0001$). The findings are consonant with Daeppen *et al.* (2002) (20 versus 62.7 h) and Saitz *et al.* (1994) (9 versus 68 h).

Most patients (94%) in the STR group received the drug as our cohort consisted primarily of the patients in moderate to severe withdrawal. Approximate 60% of patients in the STR group studies by Daeppen *et al.* (2002) did not receive the drug as the majority of cohort had mild degree of withdrawal. Most patients in Saitz *et al.* (1994) were in mild to moderate withdrawal and required fewer doses of the given drugs. This difference may also be because in our study the decision for admission was voluntary and was made by the patient alone. The investigator did not influence the admission process. Patients with mild withdrawal wanted outpatient management and they did not feel the need for indoor detoxification as opposed to the patients having moderate to severe withdrawal symptoms and with past history of complicated withdrawal who may have wanted the admission. The difference may also be due to the different benzodiazepines used, as well as differing protocols of drug administration.

Reoux and Miller (2000) concluded that patients detoxified using a Clinical Institute Withdrawal Assessment – Alcohol revised (CIWA-Ar) based protocol in the addiction unit received significantly fewer chlordiazepoxide milligram equivalents over shorter durations. STR also results in decreased occurrence of delirium tremens, the most severe and life-threatening complication of AWS in medical inpatients (Jaeger *et al.*, 2001).

The advantage of the STR lies in the fact that detoxification is monitored through a standardized scale that results in administration of less benzodiazepines for a significantly shorter duration thereby reducing the cost to the patient as well as to the hospital. An early road to discharge and recovery could promote productivity which is particularly relevant for developing countries. However, the symptom-triggered regimen requires a vigorous, scale-based periodic monitoring of withdrawal, requiring trained and committed staff of residents and nurses. The training of involved personnel in applying withdrawal severity scales like CIWA-Ar may be carried out by holding small workshops within the department. Once trained, the same personnel can carry out assessment as a part of their clinical work.

Day *et al.* (2004) concluded that STR is acceptable to both patients and staff and is potentially a useful technique for busy acute psychiatric wards. Cassidy *et al.* (2012) reported that symptom-triggered approach reduced cumulative benzodiazepine dose and length of stay in an emergency department

clinical decision unit. Hence, it may be concluded that STR is an effective, safe and acceptable regimen in both standard and emergency care units managing AWS.

Although these results may have wide clinical applicability in treating patients with AWS, it is important to recognize the limitations of the study. The study was conducted at the tertiary care psychiatry and deaddiction center. This accounts for the smaller numbers of subjects with mild withdrawal. The decision to include only male subjects in the study reflects on the trend of alcohol consumption in Indian population wherein significant stigma is attached to females consuming alcohol as well as to female subjects seeking treatment for alcohol dependence or withdrawal (Benegal *et al.*, 2003). The results are limited to the male subjects presenting with uncomplicated moderate to severe alcohol withdrawal and without any significant medical co-morbidity. Insomnia and excessive sedation were recorded based on patients' and caregivers' report and nurses' observations. However, no objective measurement of sleep duration and quality was done, which is a limitation of this study.

Future studies need to include subjects with complicated alcohol withdrawal and/or the patients presenting with medical and/or psychiatric co-morbidity. There is a need to develop generally acceptable guidelines for detoxification using CIWA-Ar in the symptom-triggered regimen.

CONCLUSION

It may be concluded that the symptom-triggered regimen is more efficacious and cost effective than the fixed tapering dose regimen in managing AWS. The symptom-triggered regimen should be followed more widely for its advantages, especially in the established de-addiction centers with adequate resources for regular monitoring and managing alcohol withdrawal symptoms through the reliable scales like the CIWA-Ar. The benefits of the symptom-triggered regimen could be further extended to the general hospital units and emergency units admitting patients of alcohol dependence as it reduces the duration of detoxification, thereby reducing the duration of hospitalization that may prove helpful in managing the heavy inflow of the patients in the general hospitals. If practiced and implemented in most hospital settings, this might result in effective utilization of resources including drugs, manpower, hospital beds and time which would be more beneficial for resource sparse developing countries.

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