

Battle of the Benzodiazepines: Comparison of Treatment Outcomes for Alcohol Withdrawal Syndrome: Lorazepam vs Chlordiazepoxide - A Literature Review

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Abstract Alcohol use disorder is a frequent occurrence within the United States, accounting for approximately 18% of the general population. Statistically, 50% of these people experience Alcohol Withdrawal Syndrome (AWS); a clinical diagnosis characterized by autonomic hyperactivity, following abrupt abstinence from heavy alcohol consumption. AWS is a life-threatening disorder that for many years has been treated with tapering doses of benzodiazepines— mostly chlordiazepoxide (CDE) and lorazepam (LOR). This paper seeks to answer the question “Are there better clinical outcomes when treating acute Alcohol Withdrawal Syndrome symptoms with chlordiazepoxide or lorazepam?”. A literature review was conducted to compile and analyze data from Randomized Clinical Trials (RCTs), and peer reviewed journal articles. These sources were carefully critiqued and compared for an overview to support the use of one benzodiazepine therapy over the other in AWS treatment. The revised Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) scale of alcohol withdrawal is the primary measure used to quantify and monitor improvement of AWS and treatment used. CIWA-Ar scalings, dosing regimens (length, doses, number of doses), days to resolution of symptoms, and adverse effects were compared across multiple studies to reach a conclusion. This paper concludes that the use of lorazepam can be more advantageous than traditionally accepted treatments due to its safety profile among patients with liver disease, promising abilities to decrease the time to complete resolution of symptoms, and a potentially easier transfer to sobriety.

Keywords: alcohol withdrawal syndrome, benzodiazepines, Mendenhall, Suppan

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1. Introduction & Background

Alcohol Use Disorder has a high disease burden in the US adult population, affecting up to 18% of the general population. As much as 50% of that population will experience symptoms of Alcohol Withdrawal Syndrome (AWS) [1]. AWS is a clinical diagnosis that manifests as autonomic hyperactivity (tremors, agitation, irritability, anxiety, hypertension, tachycardia, and diaphoresis) occurring within 6-24 hours of abrupt alcohol cessation in an alcohol dependent individual. Some patients will experience more life-threatening symptoms of alcohol withdrawal including delirium tremens, seizures, and coma.

In the human central nervous system, GABA is the main inhibitory neurotransmitter while Glutamate is the main excitatory neurotransmitter. Acute alcohol intoxication causes CNS depression via increased GABA-ergic transmission while decreasing glutamatergic transmission. Subjects who chronically consume alcohol develop an adaptive tolerance caused by a reduction in number,

functionality, and sensitivity of GABA-a to GABA (down regulation) with an increase (up regulation) of NMDA receptors of glutamate. Abrupt abstinence from alcohol causes an acute imbalance of neurotransmitter activity with consequential hyperactivity due to the weakly opposed glutamatergic action [2].

AWS and its sequelae are a very preventable cause of morbidity and mortality in the US adult population. It is important for clinicians to not only rapidly recognize symptoms but treat appropriately. The Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar) is the formal measure of the severity of withdrawal and treatment. This scale consists of a cumulative score covering: Nausea and Vomiting, Tremor, Paroxysmal Sweating, Anxiety, Tactile Disturbances, Auditory Disturbances, Visual Disturbance, Headache/Sensation of Head Fullness, Agitation and Orientation/Clouding of Sensorium. Each category is given 0-7 points, with the exception of Orientation/Clouding of Sensorium which is assigned 0-4 points. The CIWA-Ar scale is primarily subjective at the report of the patient but may be subjective at the evaluation of the clinician. There are a total of 67 points, being the most severe presentation of AWS.

The mainstay treatment of AWS has been benzodiazepines due to their GABA agonist activity, mainly chlordiazepoxide (CDE) and lorazepam (LOR). Each of the benzodiazepines have their advantages and disadvantages. Both act on the frequency of depolarization of GABA channels by allosteric modification of the receptor, allowing chloride to pass through. CDE has an increased half-life of 24-48 hours, versus LOR which has a half-life of 10-20 hours. LOR often requires the clinician to more actively titrate the drug's administration.

LOR undergoes phase II drug metabolism, becoming conjugated which forms glucuronides, causing less stress to the liver. Clinically this is important due to the large number of patients being treated for AWS also presenting with alcoholic liver disease/liver comorbidities. If screening for liver disease is not actively available, LOR can be a safer alternative than CDE, with less fluctuations in the drug's steady state. In contrast, CDE primarily undergoes phase I drug metabolism leaving the drug dependent upon the liver's CYP4A3 Cytochrome P450 enzyme for metabolism. This oxidative process leaves the active metabolite desmethyldiazepam in the blood for up to 40 hours before it can be renally cleared [3,4].

There is limited research directly comparing the two drugs head-to-head in treatment of AWS. This paper seeks to answer the question "Are there better clinical outcomes when treating acute Alcohol Withdrawal Syndrome symptoms with chlordiazepoxide or lorazepam?"

2. Methods & Materials

A literature search for studies comparing the use of chlordiazepoxide and lorazepam in the treatment of acute alcohol withdrawal syndrome was performed using Pubmed. Articles were found, analyzed and data from them was compiled for an objective comparison of results across studies. Data from previous RCTs, peer-reviewed journals, and texts covering the subject are compiled, and carefully critiqued for an overview to support the use of one benzodiazepine therapy over the other in AWS treatment. The metrics used to compare treatment choices were total number of doses, days of treatment, adverse events (including breakthrough seizures, delirium tremens), reduction in CIWA-Ar, and as needed dosing used with treatment scheduling. The majority of studies used reduction in CIWA-Ar scoring as the primary metric to determine superiority using one drug over another. One study conducted by March et. al. [5], did not utilize CIWA-Ar scale reduction but rather other metrics like days of treatment, adjuvant therapy, doses, and percentage of adverse effects. It is important to make note of this when making comparisons between results as it provides more rounded insights when coming to a conclusion.

3. Results & Discussion

The primary objective of this study is to review and analyze existing clinical trials directly comparing the treatment of Alcohol Withdrawal symptoms with lorazepam or chlordiazepoxide to answer the question, "Are there better clinical outcomes when treating acute Alcohol Withdrawal Syndrome symptoms with chlordiazepoxide or lorazepam?". There is not much literature that compiles the data across multiple studies to compare and address this question.

Three of the studies reviewed (Kumar [3], Rajmohan [6], Ramunojam [7]) utilized the CIWA-Ar scale and its reduction as the primary method of comparison between drugs. The studies by Kumar [3] and Ramanujam [6] showed that over the duration of their trials, there was a significant improvement in CIWA-Ar scores within the treatment groups as a whole. Rajmohan then went on to conclude a statistically significant difference between treatment groups, each containing 54 subjects, at the 48-hour mark. This was determined by ANOVA statistical evaluation, producing a $p < 0.001$. The LOR group had a mean improvement of 70.4%, while the CDE group had a mean improvement of 54.8%. Additionally, the difference in treatment length favored LOR (5.6 days) over CDE (6.7 days) with $p < .001$. A stepwise regression was conducted to confirm the statistical significance, which found a 63% variance in the initial improvement of patient's CIWA-Ar scores between the drugs administered. Because of this improvement the study favored the use of LOR for treatment purposes.

Kumar et al [3]. also showed that CIWA-Ar scores stabilized earlier in the LOR treatment group (LOR Day 4, CDE Day 5), but this observation was not statistically evaluated in depth. Patients in both treatment groups stabilized at an average CIWA-Ar of 0.3. At day 4, CDE group average reached 0.4, with a standard deviation of 1.6. This puts the CDE patient group very close to LOR, despite the slightly longer time to reach 0.3.

In the Rajmohan study [6], a ratio of 1mg of LOR was given for every 25mg of CDE that was used in the other treatment group. Initial doses of each drug were contingent on the initial CIWA-Ar score. A number >15 warranted a dose of 8mg of LOR or 200mg of CDE, whereas a CIWA-Ar number of <15 warranted an initial dose of 6mg LOR or 150mg of CDE. Doses were tapered by 20% per day, for 5 days. This is important to note, because studies by Kumar expressed problems within the LOR group due to underdosing the patients. Those patients were placed on initial doses of 6mg of LOR, regardless of CIWA-Ar score. Dosing of CDE in the Kumar study was also begun at a lower dose of 80mg/day but continued for a longer period of time.

Table 1. CIWA-Ar Reduction

	Treatment Duration of LOR (days)	Treatment Duration of CDE (days)	Reduction in CIWA of LOR at 48 hours	Reduction in CIWA of CDE at 48 hours
Rajmohan	5.6	6.7	70.4%	54.8%
Kumar	8	8	87.5%	87.5%

The study conducted by March et al. [5], measured the incidence delirium tremens as their main comparison. They concluded there was no statistical difference between treatment groups (LOR 7% vs CDE 9% $p=.76$). However, the study also noted that more patients required prn dosing of LOR in the CDE group versus the LOR group itself (LOR 3.2 ± 4 mg vs. CDE 6.6 ± 13 mg; $p=0.03$). This occurrence caused the CDE group to require significantly higher amounts of benzodiazepines for control of symptoms (LOR 17.7 ± 10 mg vs. CDE 21.9 ± 14 mg; $p=0.04$). Additionally, the patients within their CDE group required more frequent use of adjuvant therapy (73% LOR vs. 90% CDE; $p=0.02$). The primary adjuvant was lorazepam, with some patients also warranting prn doses of clonidine. Though the outcomes were basically similar between groups, one could speculate that the more frequent incidences of intervention in the CDE group would make LOR a more favorable overall drug.

March et al. [5] found a non-statistical difference in their duration of treatment (LOR 3.6 vs CDE 2.1 $p=.3$). However, two studies, Kumar [3] and Ramanujam [6], utilized a fixed duration dosing schedule of 8 days regardless of whether or not a patient showed improvement. Thus, these studies did not compare this metric. Rajmohan also used a standard dosing schedule of 5 days with a 20% titration and focused on resolution of symptoms.

4. Conclusion

When picking the optimal treatment agent for a patient, it is important to take into consideration other factors that impact clinical outcomes, other than improvement of symptoms. In addition to comparing CIWA-Ar improvement, length of treatment protocols, side effect profiles, and time to onset were considered to reach a conclusion. These aspects are essential to take into acknowledge because they are directly related to patient comfort and satisfaction. If objective outcomes are similar, like CIWA-Ar reduction, then other clinical metrics need to become the deciding factors. The analysis conducted for this paper showed some minor statistical differences in CIWA-Ar improvement between LOR and CDE. Although small sample sizes and variation between metrics is a point of weakness that convolutes a clear winner between the outcome of each drug. However, the advantages of using LOR over CDE when comparing patient comfort was evident. In addition, the use of LOR

for patients who have alcohol liver disease or other liver comorbidities (i.e. chronic hepatitis, alcoholic cirrhosis), can be advantageous. If liver function testing is not available, LOR can be a quality empiric treatment for AWS.

The existing studies have numerous drawbacks across them including variability of metrics used and limited patient sample sizes conferring decreased statistical power. The limitations of these studies leave the desire for a larger, more homogenous study to be conducted and compared to previous small scale RCTs. The current head-to-head comparisons of chlordiazepoxide and lorazepam in the treatment of alcohol withdrawal syndrome suggest that lorazepam is the superior single agent when considering a full clinical picture.

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