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CURRENT OPINION

Diazepam in the Treatment of Moderate to Severe Alcohol Withdrawal

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Abstract Benzodiazepines ameliorate or prevent the symptoms and complications of moderate to severe alcohol withdrawal, which can include autonomic hyperactivity, agitation, combativeness, hallucinations, seizures, delirium, and death. The benzodiazepines most commonly used for this purpose are lorazepam, chlordiazepoxide, oxazepam, and diazepam. It is widely asserted that no member of this group is superior to the others for treatment of alcohol withdrawal. However, of these, diazepam has the shortest time to peak effect, which facilitates both rapid control of symptoms and accurate titration to avoid over-sedation. Furthermore, diazepam and its active metabolite, desmethyldiazepam, have the longest elimination half-lives, so their levels decrease in a gradual, self-tapering manner, resulting in a smoother withdrawal, i.e., a lower incidence and severity of both breakthrough symptoms and rebound phenomena, including a possibly decreased seizure risk. Importantly, the fear of increased risk of over-sedation with diazepam compared with other benzodiazepines is based on a misunderstanding of its pharmacokinetics and is unfounded. Similarly, the notion that diazepam should be avoided in patients with liver disease and elderly patients to avoid prolonged over-sedation is based on no more than conjecture. In fact, there is clinical evidence that diazepam is safe for the treatment of alcohol withdrawal in these patients when administered using a simple symptom-based approach. There is one instance in which diazepam should not be used: when intramuscular administration is the only option, the lipophilicity of diazepam can result in slow absorption—either lorazepam or, when rapid control of symptoms is required, midazolam should be used. The comparative pharmacokinetics of the benzodiazepines used in the treatment of alcohol withdrawal together with a comprehensive review of the literature on their use strongly suggest that diazepam should be the preferred benzodiazepine for the treatment of patients experiencing moderate to severe alcohol withdrawal under most circumstances.

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Key Points

Intravenous diazepam has a significantly shorter time to onset of action and peak effect than intravenous lorazepam, which suggests that intravenous diazepam should be the preferred agent when the rapid suppression of alcohol withdrawal syndrome is indicated.

When attempting to control severe alcohol withdrawal, excessive dosing leading to over-sedation is less likely with intravenous diazepam than with intravenous lorazepam because the shorter time to peak effect of diazepam allows rapid assessment of the need for additional dosing such that inadvertent dose stacking is avoided.

Prolonged over-sedation is avoided when diazepam is used for the treatment of alcohol withdrawal, even in elderly patients and patients with liver disease, if dosing is symptom based.

Inter-dose alcohol withdrawal symptoms and rebound phenomena are more likely with lorazepam and oxazepam treatment than with diazepam treatment.

Oral diazepam has a shorter time to peak effect than oral chlordiazepoxide, lorazepam, and oxazepam, which facilitates more rapid treatment and accurate titration to avoid under- or over-treatment when an oral benzodiazepine is used to treat alcohol withdrawal.

1 Introduction

Alcohol acts as a central nervous system (CNS) depressant primarily by enhancing the activity of the major CNS inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), and antagonizing the activity of the major CNS excitatory neurotransmitter, glutamate [1, 2].

Compensatory adaptations to these depressant effects develop in the CNS when alcohol intake is chronic: GABA-mediated inhibition is decreased and glutamate-mediated excitation is increased. These adaptations underlie a latent hyperexcited neurophysiologic state that is kept in check by the depressant effects of the alcohol. However, if alcohol intake is abruptly discontinued, the adaptations are unbridled, resulting in an overt hyperexcited state that is manifested clinically by the spectrum of symptoms and complications of the alcohol withdrawal syndrome, which can range from mild tremors and anxiety to seizures, delirium tremens, and death [1, 2].

Benzodiazepines have been used for the treatment of alcohol withdrawal for over 50 years since it was first reported that chlordiazepoxide reduces the incidence of alcohol withdrawal seizures more effectively than placebo or promazine [3, 4], a phenothiazine that was commonly used for the treatment of alcohol withdrawal at the time. It was subsequently shown that diazepam is more efficacious in calming patients experiencing delirium tremens than paraldehyde, another agent that was en vogue for the treatment of alcohol withdrawal [5]. Although there is evidence that certain non-benzodiazepine agents such as carbamazepine, gabapentin, topiramate, and baclofen are effective in the treatment of alcohol withdrawal [6], from a time soon after the reports outlined above were published, benzodiazepines have been recommended as the primary pharmacologic treatment for those experiencing alcohol withdrawal syndrome [7–12].

Benzodiazepines are effective because they, like alcohol, stimulate the inhibitory GABA-signaling pathways [2, 12, 13]. They both suppress alcohol withdrawal symptoms and shorten the course of withdrawal, and they are the only agents that have been shown to prevent withdrawal-associated seizures, delirium tremens, and death in patients undergoing alcohol withdrawal [12–15]. Dosing of benzodiazepines in a manner that results in a gradual tapering of levels allows the neurophysiology of the CNS to recover to its alcohol-free state while the clinical manifestations of alcohol withdrawal remain suppressed.

Although many different benzodiazepines have been shown to be effective [8], lorazepam, chlordiazepoxide, oxazepam, and diazepam are the benzodiazepines most commonly used to treat alcohol withdrawal [12]. It is widely stated that no single agent among these is superior to the others [2, 12, 15, 16]. However, the comparative studies have generally focused on patients experiencing the less severe manifestations of alcohol withdrawal [17–22]. In fact, patients with a history of alcohol withdrawal-related seizures were excluded from most of these studies [17–19, 22]. Furthermore, all of the studies compared the efficacy of the benzodiazepines using the same scheduled fixed-dose protocol, in which the same dose of a benzodiazepine was given at fixed intervals to all patients. This is in contrast to one of the individualized symptom-based approaches that are currently recommended for treatment of patients undergoing moderate to severe alcohol withdrawal, in which the benzodiazepine is dosed in response to a defined set of clinical parameters [12–16, 23]. Finally, none of the comparative studies utilized dosing protocols that were optimized for the unique pharmacokinetic profile of each of the individual benzodiazepines, nor did they use intravenous benzodiazepines,

which are preferable for the initial treatment of moderate to severe alcohol withdrawal [2, 12–15, 23–25], which would include the treatment of patients experiencing any more than mild anxiety or agitation, moderately severe headache, nausea with dry heaves or vomiting, tactile, auditory, or visual hallucinations, seizures, clouded sensorium, or any other signs or symptoms of alcohol withdrawal that warrant rapid treatment.

Therefore, a comprehensive examination of the literature on benzodiazepines and their use in the treatment of alcohol withdrawal was undertaken to determine whether evidence supports the superiority in regard to efficacy and safety of any one benzodiazepine over the others for the treatment of moderate to severe alcohol withdrawal. Studies for inclusion in this narrative review were identified by searching PubMed for articles through July 2016 using the keywords alcohol, alcohol withdrawal, benzodiazepine, chlordiazepoxide, oxazepam, lorazepam, diazepam, midazolam, delirium tremens, and diazepam loading, either alone or in combination. The reference lists of identified articles were also searched. In all instances, the primary source of information was sought.

2 Initiation of Therapy

Patients undergoing moderate to severe alcohol withdrawal can suffer from tremulousness, diaphoresis, insomnia, autonomic hyperactivity, nausea, vomiting, anorexia, intense anxiety, agitation, combativeness, hallucinations, seizures, and delirium. These patients are in severe distress, they may harm themselves or their healthcare providers, and they can deteriorate rapidly. Initial treatment with an intravenous benzodiazepine is indicated to rapidly alleviate symptoms, control behavior, and thwart progression to even more severe symptoms and complications, such as seizures, delirium tremens, and death [2, 12–15, 23–25]. Notably, intravenous benzodiazepine treatment has even been recommended for the initial management of most patients who are tremulous to ensure rapid effective treatment [26].

Diazepam and lorazepam are the benzodiazepines most frequently used for intravenous treatment of alcohol withdrawal. However, diazepam is more lipophilic; therefore, it diffuses across the blood–brain barrier more readily than lorazepam [27–29] and consequently eases symptoms, controls behavior, and prevents progression much more rapidly. Whereas the peak effects of intravenous lorazepam occur 30 min after administration [29–32], they occur within 5 min of intravenous diazepam administration [29, 31–33] (Table 1). Although these comparative studies were not performed in patients undergoing alcohol withdrawal, the rapidity with which diazepam is effective in treating alcohol withdrawal is demonstrated by the observation that in patients experiencing delirium tremens, the "drowsiness and muscular relaxation" brought about by intravenous diazepam, "reaching its maximum within a minute or two of injection, is so obvious during administration that any attempt to set up a 'blind' trial is vitiated … [33]." These findings suggest that intravenous diazepam should be favored over intravenous lorazepam when rapid control of symptoms is necessary.

The benzodiazepine dosing required to control the symptoms of moderate to severe alcohol withdrawal varies widely between patients [2, 15, 16, 24, 34]. A conservative dosing strategy is typically initially used to avoid oversedation, so it may take several doses to control symptoms. In this regard, the rapid time to peak effect of intravenous diazepam is advantageous because it allows a prompt

Table 1 Diazepam vs. lorazepam—comparative studies of time to peak effect

Study design	Authors' conclusions	References
Six healthy volunteers were given intravenous lorazepam 0.025 mg/kg, lorazepam 0.045 mg/kg, or placebo by 1-min infusion in a double-blind three-way cross-over study. Five of these subjects were given intravenous diazepam 0.15 mg/kg in a companion study of identical design. Activity in the 13–30 Hz band of EEG, which is increased by benzodiazepine treatment, was assessed at defined intervals after drug administration	"For both lorazepam doses, effects were of relatively slow onset, reaching their maximum at 30 min after the end of the infusion … Effects of diazepam were maximal immediately after the 1-min infusion"	[29]
Four groups of 30 preoperative patients each were given intravenous diazepam 10 mg, diazepam 20 mg, lorazepam 2 mg, or lorazepam 4 mg as a pre-anaesthetic agent before surgery in a double-blind manner and then assessed for level of sedation at defined intervals	"The clinical effects of intravenous diazepam peak in 2–3 min… Intravenous lorazepam has a latent period of 8–15 min, with increasing effects at 15–30 min"	[31]
Three groups of approximately ten preoperative patients each were given intravenous diazepam 10 mg, diazepam 20 mg, or lorazepam 4 mg as a pre-anaesthetic agent before surgery and then assessed for level of sedation at defined intervals	"The peak sedative action of diazepam was reached within 5 min of injection, whereas that of lorazepam was still increasing at 30 min"	[32]

assessment of the maximal effect of each dose [14]. This facilitates rapid titration to levels that quell symptoms while minimizing the risk of over-sedation due to dose stacking. The rapidity with which repeated intravenous diazepam doses can safely be administered is underscored by the statement "it is possible to 'titrate' the dose of diazepam by monitoring its effect while injecting it slowly [33]." This statement is supported by the finding that the peak effect of a 1-min intravenous diazepam infusion occurs immediately at the end of the infusion when assessed by electroencephalogram [29]. In contrast, a fully informed assessment of the necessity and safety of additional lorazepam dosing cannot be made until 30 min after each dose is given, the time at which its peak effect occurs [29–32]. This could lead to a prolonged interval before symptoms of severe alcohol withdrawal are controlled when using lorazepam, and it also increases the risk of progression to more serious symptoms and complications of alcohol withdrawal. Conversely, in the rush to control symptoms, lorazepam doses may be inadvertently stacked, leading to over-sedation.

The clinical benefit of the rapidity with which diazepam reaches peak effect in the treatment of alcohol withdrawal was first illustrated by a study of its use to treat a group of patients with such severe delirium tremens that they all required mechanical restraint [5]. The patients were initially loaded with intravenous diazepam 10 mg and then given intravenous diazepam 5 mg every 5 min until they were calm. Every patient was calmed without adverse effects from the diazepam. This demonstrated that rapidly repeated doses of intravenous diazepam for the treatment of severe alcohol withdrawal are safe when an individualized symptom-based approach to dosing is followed. In fact, the authors and others have since recommended even more aggressive intravenous diazepam dosing protocols [15, 24].

Indeed, the same authors described treatment with intravenous diazepam 40 mg repeated every 5 min for seven doses to calm a patient undergoing alcohol withdrawal [5], and, in a recent study of the treatment of alcohol withdrawal in critically ill patients, diazepam was administered intravenously in gradually escalating doses from 10 mg up to as high as 120 mg as frequently as every 15 min until light sedation was achieved [35]. Such seemingly aggressive strategies are safe because the rapid time to peak effect of diazepam allows for the full evaluation of the maximal sedating effect of each dose before a subsequent dose is given [14]. In contrast, repeated dosing of lorazepam at such short intervals would not be safe because it does not reach its peak effect until 30 min after each dose [29–32].

Strikingly, instead of resulting in over-sedation, protocols that incorporate aggressive individualized symptom-based administration of intravenous diazepam early in the course of treatment have reduced the need for mechanical ventilation of patients experiencing severe alcohol withdrawal [35, 36]. This has been attributed to the effective reduction in psychomotor agitation achieved with these protocols [36]. Indeed, one group noted that patients who required mechanical ventilation had been treated with significantly less diazepam during the first 24 h than those who did not require mechanical ventilation [36]. Furthermore, only one of the 129 patients in the two studies required mechanical ventilation because of over-sedation [35, 36], and that patient had been treated with both phenobarbital and intermittent boluses of propofol in addition to the diazepam (J.A. Gold, personal communication) [36]. Finally, an exhaustive search of PubMed failed to reveal a single report of clinically significant over-sedation when diazepam was used as the sole sedating agent for the treatment of alcohol withdrawal. These findings underscore the efficacy and safety of diazepam in the treatment of moderate to severe alcohol withdrawal.

Many clinicians prefer lorazepam over diazepam for the treatment of alcohol withdrawal because lorazepam is thought to carry a decreased risk of prolonged over-sedation due to its shorter elimination half-life, but this reflects an incomplete and misleading understanding of the comparative pharmacokinetics of the two [37]. It is true that the elimination half-life of lorazepam is only 10–20 h, whereas the elimination half-life of diazepam is 30 h and diazepam is converted into desmethyldiazepam, an active metabolite that has an elimination half-life of 90 h [38]. However, the duration of clinical action of a single dose of intravenous lorazepam is considerably longer than that of an equivalent single dose of intravenous diazepam [32, 39, 40].

This apparent paradox is resolved by the fact that the volume of distribution of diazepam is more than ten times that of lorazepam because of the much higher lipophilicity of diazepam [40]. When a single dose of intravenous diazepam is given, it rapidly crosses the blood–brain barrier to exert its effect, but circulating and CNS levels soon decline as it is redistributed throughout the peripheral tissue [29, 37, 40, 41]. It is then slowly released, accounting for its prolonged elimination half-life [37]. Because the volume of distribution of diazepam is so large, it is only present in the CNS at low concentrations during this phase and, consequently, there are only low level or no clinical effects [29, 37, 41].

With successive doses, diazepam and desmethyldiazepam accumulate such that clinically effective CNS levels are maintained for incrementally longer periods [23, 34, 37]. This would appear to increase the risk of prolonged over-sedation. However, because the peak sedating effect of each dose of diazepam occurs within just a few minutes after administration, and the level of sedation then steadily decreases as the dose is redistributed, the

risk of prolonged over-sedation is avoided as long as an individualized symptom-based approach to dosing is used [14, 23, 34, 42]. There is only a risk if diazepam is repeatedly administered heedless of the patient's level of sedation [43].

Finally, intravenous diazepam can have a localized irritant effect at the injection site, but this is minimized by avoiding the use of small veins, such as those on the back of the hand, and by avoiding rapid injection.

3 Continuation of Treatment

With ongoing diazepam treatment and consequent accumulation, the circulating and CNS levels of diazepam and desmethyldiazepam decline in a gradual, smooth, self-tapering manner between doses [34]. This underlies a significant therapeutic advantage over the use of lorazepam. Because of its shorter elimination half-life, the levels of lorazepam fluctuate to a greater extent and decline more rapidly between doses than do the levels of diazepam and desmethyldiazepam. Therefore, inter-dose breakthrough symptoms and rebound phenomena occur more frequently and more abruptly and increase in severity more rapidly when lorazepam is used [27, 37, 44–51]. Indeed, during treatment for alcohol withdrawal, patients treated with lorazepam experience more pronounced reemergence of withdrawal symptoms, anxiety, and depression, and their mean daily pulse rate is significantly elevated compared with patients treated with diazepam [23, 52].

Furthermore, there is evidence that patients treated for alcohol withdrawal with lorazepam or oxazepam, which also has a relatively short elimination half-life, experience a higher incidence of seizures than patients treated with the long elimination half-life benzodiazepines diazepam or chlordiazepoxide [16, 53, 54]. In this context, it is particularly striking that the use of diazepam for the treatment of alcohol withdrawal in a group of patients who were at high risk for withdrawal seizures completely prevented the occurrence of seizures [55]. The increased seizure incidence that occurs with lorazepam and oxazepam treatment has been postulated to be a consequence of the rapid fall of benzodiazepine levels that can occur with these drugs [54].

Once the more severe symptoms of alcohol withdrawal are controlled with an intravenous benzodiazepine, an oral benzodiazepine is frequently used to continue treatment. The continuation of treatment with a long elimination half-life oral agent maintains a gradual taper, facilitating a smooth transition to a non-drug state. Chlordiazepoxide is commonly used for this purpose. However, compared with oral diazepam, chlordiazepoxide has a slower time to peak plasma concentration [46], crosses the blood–brain barrier more slowly [56], and has a more complicated metabolism in that it is oxidized in the liver to form two or more active metabolites that accumulate after multiple doses in a manner that varies between patients [57, 58]. Furthermore, there is evidence that at least one of these metabolites has more sedating activity than chlordiazepoxide itself [59–61], which could result in an even more delayed and less predictable time to maximal sedating effect. Hence, oral chlordiazepoxide becomes effective in treating alcohol withdrawal more slowly and is more difficult to titrate to clinical response than oral diazepam.

Indeed, there is no clinical rationale for use of oral chlordiazepoxide instead of oral diazepam for the inpatient treatment of alcohol withdrawal. The widespread use of chlordiazepoxide for this purpose seems to be primarily based on tradition, as it was the first benzodiazepine shown to be effective in the treatment of alcohol withdrawal [3, 4]. Additionally, even though diazepam and other benzodiazepines were available at the time, the use of chlordiazepoxide for the treatment of alcohol withdrawal was likely reinforced when it was the only benzodiazepine listed in some hospital formularies for many years because it was the only one available in an inexpensive generic form [46]. This was because its US patent expired in late 1975, whereas the patents for the other available benzodiazepines did not expire until 1984 and later [62, 63].

Nevertheless, chlordiazepoxide may have a clinical advantage in the treatment of milder forms of alcohol withdrawal in the outpatient setting because its slower onset of action is thought to give the patient less of a 'rush' or 'buzz' than diazepam. This makes chlordiazepoxide less prone to abuse [16, 64].

4 Diazepam Loading

As outlined above, alcohol withdrawal treatment in which intravenous diazepam is rapidly titrated until the patient is calm or mildly sedated has proven to be efficacious and safe [5, 35, 36]. An analogous treatment approach, known as diazepam loading, in which doses of oral diazepam 10–20 mg are repeatedly administered at intervals of 1–2 h until the patient is either calm or mildly sedated, has been studied extensively [23]. Oral diazepam is used for this approach because it has a shorter time to peak than oral chlordiazepoxide, lorazepam, and oxazepam [12], so it can be titrated relatively rapidly while avoiding over-sedation, and because its long half-life facilitates a smooth taper [23].

Across the six published studies of oral diazepam loading to treat alcohol withdrawal, 244 patients, including at least 96 who were experiencing delirium, were treated with oral diazepam until their symptoms resolved (some of the patients were in control groups that were treated with

scheduled fixed doses of diazepam) [34, 65–69]. Diazepam loading was found to provide rapid relief of symptoms, reduce seizure incidence, and shorten the course of delirium tremens [23]. Strikingly, the authors of all six studies uniformly reported that none of the patients experienced significant adverse effects from the diazepam treatment (adverse effects were not addressed in the report of a seventh study of diazepam loading [55]). Together with the studies that used intravenous diazepam [5, 35, 36], these studies underscore the efficacy and safety of diazepam for the treatment of alcohol withdrawal when a symptom-based approach is used.

5 Elderly Patients and Patients with Liver Disease

In elderly patients and patients with decreased hepatic function, the elimination half-lives of diazepam and desmethyldiazepam are prolonged whereas those of lorazepam and oxazepam are unchanged [12]. On this basis, it is frequently asserted that the risk of prolonged over-sedation with diazepam treatment is unacceptable in these patients and that lorazepam or oxazepam should be used [12]. However, diazepam should be considered the same as any other drug for which dosing is adjusted based on patient-specific alterations in pharmacokinetics [27, 70–72], such as when vancomycin is used in patients with renal impairment. In fact, when an individualized symptom-based approach is used to dose diazepam intravenously for the treatment of alcohol withdrawal, optimal dosing is facilitated because diazepam is titrated to a rapidly achieved and readily apparent clinical response. Indeed, the authors of a report on diazepam loading commented, "The loading dose method offers a distinct advantage in the treatment of the elderly and patients with impaired liver function, since dosing is adjusted according to individual response, and therefore, the risk of overdosage is avoided [34]."

The safety of diazepam in these patients is underscored by the aforementioned study in which patients with severe delirium tremens were treated with rapidly repeated doses of diazepam until calm [5]. More than 75% of the patients in this study had liver disease, yet no adverse events were reported despite the patients being treated with a mean total diazepam dose of over 200 mg. Furthermore, in a study of 51 hospitalized patients with cirrhosis who were treated with diazepam, only one experienced an adverse event that was thought to be related to the diazepam (the indication for diazepam, the nature of the adverse effect, and the patient's comorbid conditions and other medications were not reported) [73]. As long as the approach is symptom-based, there is no reason to avoid the use of diazepam to treat alcohol withdrawal in elderly patients and those with liver disease, and the advantages of its use in moderate to severe alcohol withdrawal suggest that it should be the preferred benzodiazepine for this purpose.

6 Intramuscular Benzodiazepines

Patients undergoing alcohol withdrawal can become severely agitated and combative. Intramuscular administration of benzodiazepines may be necessary in these instances if intravenous access cannot be obtained or maintained. The use of an intramuscular benzodiazepine with a rapid onset of action is essential under these circumstances. The intramuscular form of chlordiazepoxide is uniformly slowly absorbed [74, 75], so it should not be used in the treatment of alcohol withdrawal. The rate of systemic absorption of intramuscular diazepam is relatively slow in some patients and is unpredictable, so it should be avoided [37, 76]. The systemic absorption of intramuscular lorazepam is rapid and complete in all individuals [77, 78], but the onset of its activity is somewhat delayed because, as noted above, it does not cross the blood–brain barrier as rapidly as more lipophilic benzodiazepines [27–29].

Midazolam is a very short-acting benzodiazepine that is effective in the treatment of alcohol withdrawal [79–81]. Midazolam is unique among benzodiazepines in that it is water soluble at the low pH of its carrier, so it is rapidly absorbed after intramuscular injection, but also crosses the blood–brain barrier rapidly because it becomes highly lipophilic at plasma pH [82]. Therefore, intramuscular midazolam consistently has a rapid onset of action, which suggests it should be the benzodiazepine of choice for the treatment of alcohol withdrawal when intravenous access cannot be obtained and the use of a rapidly acting benzodiazepine is indicated. Importantly, however, the duration of action of midazolam is relatively short, so intravenous access should be established for the administration of a longer acting agent once the patient is calmed by the midazolam.

7 Conclusion

There are clinically meaningful differences in the pharmacokinetics of the various benzodiazepines. When an individualized symptom-based approach is used to treat severe alcohol withdrawal syndrome, the advantages afforded by the pharmacokinetic profile of diazepam are self-evident. When dosing is optimized based on its pharmacokinetics, the use of diazepam should result in a more rapid and safer control of symptoms and a smoother withdrawal than is achievable with any of the other benzodiazepines commonly used to treat alcohol withdrawal

syndrome. Furthermore, there is evidence that the widespread preference for the use of lorazepam or oxazepam instead of diazepam for the treatment of alcohol withdrawal in elderly patients and patients with liver disease is unfounded as long as a symptom-based approach is used, and diazepam should be preferred because of the advantages it affords. Finally, the one instance in which diazepam should be avoided is when intramuscular administration is necessary because of its unpredictable systemic absorption—either lorazepam or, when rapid control of symptoms is required, midazolam should be used.

Compliance with Ethical Standards

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Conflict of interest Steven J. Weintraub has no conflicts of interest.

References

1. Erdozain AM, Callado LF. Neurobiological alterations in alcohol addiction: a review. Adicciones. 2014;26(4):360–70.
2. Schuckit MA. Recognition and management of withdrawal delirium (Delirium Tremens). N Engl J Med. 2014;371(22):2109–13.
3. Sereny G, Kalant H. Comparative clinical evaluation of chlordiazepoxide and promazine in treatment of alcohol-withdrawal syndrome. Br Med J. 1965;1(5427):92–7.
4. Kaim SC, Kaim SC, Klett CJ, Klett CJ, Rothfeld B, Rothfeld B. Treatment of the acute alcohol withdrawal state: a comparison of four drugs. Am J Psychiatry. 1969;125(12):1640–6.
5. Thompson WL, Johnson AD, Maddrey WL. Diazepam and paraldehyde for treatment of severe delirium tremens. A controlled trial. Ann Intern Med. 1975;82(2):175–80.
6. Amato L, Minozzi S, Davoli M. Efficacy and safety of pharmacological interventions for the treatment of the alcohol withdrawal syndrome. Cochrane Database Syst Rev. 2011;6:CD008537. doi:10.1002/14651858.CD008537.pub2.
7. Greenblatt DJ, Greenblatt M. Which drug for alcohol withdrawal? J Clin Pharmacol New Drugs. 1972;12(11):429–31.
8. Sellers EM, Kalant H. Alcohol intoxication and withdrawal. N Engl J Med. 1976;294(14):757–62.
9. Romach MK, Sellers EM. Management of the alcohol withdrawal syndrome. Annu Rev Med. 1991;42:323–40.
10. Holbrook AM, Crowther R, Lotter A, Cheng C, King D. Meta-analysis of benzodiazepine use in the treatment of acute alcohol withdrawal. Can Med Assoc J. 1999;160(5):649–55.
11. Amato L, Minozzi S, Vecchi S, Davoli M. Benzodiazepines for alcohol withdrawal. Cochrane Database Syst Rev. 2010;3:CD005063. doi:10.1002/14651858.CD005063.pub3.
12. Perry EC. Inpatient management of acute alcohol withdrawal syndrome. CNS Drugs. 2014;28(5):401–10.
13. Mirijello A, D'Angelo C, Ferrulli A, Vassallo G, Antonelli M, Caputo F, et al. Identification and management of alcohol withdrawal syndrome. Drugs. 2015;75(4):353–65.
14. Lejoyeux M, Solomon J, Adès J. Benzodiazepine treatment for alcohol-dependent patients. Alcohol Alcohol. 1998;33(6):563–75.
15. Mayo-Smith MF, Beecher LH, Fischer TL, Gorelick DA, Guillaume JL, Hill A, et al. Management of alcohol withdrawal delirium. An evidence-based practice guideline. Arch Intern Med. 2004;164(13):1405–12.
16. Mayo-Smith MF. Pharmacological management of alcohol withdrawal. A meta-analysis and evidence-based practice guideline. American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. JAMA. 1997;278(2):144–51.
17. Solomon J, Rouck LA, Koepke HH. Double-blind comparison of lorazepam and chlordiazepoxide in the treatment of the acute alcohol abstinence syndrome. Clin Ther. 1983;6(1):52–8.
18. ÓBrien JE, Meyer RE, Thoms DC. Double-blind comparison of lorazepam and diazepam in the treatment of the acute alcohol abstinence syndrome. Curr Ther Res Clin Exp. 1983;34(5):825–31.
19. Miller WC, McCurdy L. A double-blind comparison of the efficacy and safety of lorazepam and diazepam in the treatment of the acute alcohol withdrawal syndrome. Clin Ther. 1984;6(3):364–71.
20. Kumar CN, Andrade C, Murthy P. A randomized, double-blind comparison of lorazepam and chlordiazepoxide in patients with uncomplicated alcohol withdrawal. J Stud Alcohol Drugs. 2009;70(3):467–74.
21. Rajmohan V, Sushil K, Mohandas E. A double blind randomised comparison of chlordiazepoxide and lorazepam in alcohol withdrawal. Asian J Psychiatr. 2013;6(5):401–3.
22. Ramanujam R, Padma L, Swaminath G, Thimmaiah RS. A comparative study of the clinical efficacy and safety of lorazepam and chlordiazepoxide in alcohol dependence syndrome. J Clin Diagn Res. 2015;9(3):FC10-3.
23. Muzyk AJ, Leung JG, Nelson S, Embury ER, Jones SR. The role of diazepam loading for the treatment of alcohol withdrawal syndrome in hospitalized patients. Am J Addict. 2013;22(2):113–8.
24. Thompson WL. Management of alcohol withdrawal syndromes. Arch Intern Med. 1978;138(2):278–83.
25. Stehman CR, Mycyk MB. A rational approach to the treatment of alcohol withdrawal in the ED. Am J Emerg Med. 2013;31(4):734–42. doi:10.1016/j.ajem.2012.12.029.
26. Hoffman RS, Weinhousec GL. Management of moderate and severe alcohol withdrawal syndromes. Waltham, MA: UpToDate. http://www.uptodate.com/contents/management-of-moderate-and-severe-alcohol-withdrawal-syndromes. Accessed 27 July 2016.
27. Hollister LE. Benzodiazepines—an overview. Br J Clin Pharmacol. 1981;11:117S–9S.
28. Arendt RM, Greenblatt DJ, Liebisch DC, Luu MD, Paul SM. Determinants of benzodiazepine brain uptake: lipophilicity versus binding affinity. Psychopharmacology (Berl). 1987;93(1):72–6.
29. Greenblatt DJ, Ehrenberg BL, Gunderman J, Scavone JM, Tai NT, Harmatz JS, et al. Kinetic and dynamic study of intravenous lorazepam: comparison with intravenous diazepam. J Pharmacol Exp Ther. 1989;250(1):134–40.
30. Elliott HW. Metabolism of lorazepam. Br J Anaesth. 1976;48(10):1017–23.
31. Conner JT, Katz RL, Bellville JW, Graham C, Pagano R, Dorey F. Diazepam and lorazepam for intravenous surgical premedication. J Clin Pharmacol. 1978;18(5–6):285–92.
32. Dundee JW, McGowan WA, Lilburn JK, McKay AC, Hegarty JE. Comparison of the actions of diazepam and lorazepam. Br J Anaesth. 1979;51(5):439–46.
33. Brown JH, Moggey DE, Shane FH. Delirium tremens: a comparison of intravenous treatment with diazepam and chlordiazepoxide. Scott Med J. 1972;17(1):9–12.
34. Heinälä P, Piepponen T, Heikkinen H. Diazepam loading in alcohol withdrawal: clinical pharmacokinetics. Int J Clin Pharmacol Ther Toxicol. 1990;28(5):211–7.

35. Duby JJ, Berry AJ, Ghayyem P, Wilson MD, Cocanour CS. Alcohol withdrawal syndrome in critically ill patients: protocolized versus nonprotocolized management. J Trauma Acute Care Surg. 2014;77(6):938–43.
36. Gold JA, Rimal B, Nolan A, Nelson LS. A strategy of escalating doses of benzodiazepines and phenobarbital administration reduces the need for mechanical ventilation in delirium tremens. Crit Care Med. 2007;35(3):724–30.
37. Teboul E, Chouinard G. A guide to benzodiazepine selection. Part I: Pharmacological aspects. Can J Psychiatry. 1990;35(8):700–10.
38. Griffin CE 3rd, Kaye AM, Bueno FR, Kaye AD. Benzodiazepine pharmacology and central nervous system-mediated effects. Ochsner J. 2013;13(2):214–23.
39. George KA, Dundee JW. Relative amnesic actions of diazepam, flunitrazepam and lorazepam in man. Br J Clin Pharmacol. 1977;4(1):45–50.
40. Greenblatt DJ, Divoll M. Diazepam versus lorazepam: relationship of drug distribution to duration of clinical action. Adv Neurol. 1983;34:487–91.
41. Greenblatt DJ, Friedman HL, Shader RI. Correlating pharmacokinetics and pharmacodynamics of benzodiazepines: problems and assumptions. Psychopharmacol Ser. 1987;3:62–71.
42. Bird RD, Makela EH. Alcohol withdrawal: what is the benzodiazepine of choice? Ann Pharmacother. 1994;28(1):67–71.
43. Kendall MJ, Clarke SW. Prolonged coma after tetanus. Br Med J. 1972;1(5796):354–5.
44. Kales A, Scharf MB, Kales JD, Soldatos CR. Rebound insomnia. A potential hazard following withdrawal of certain benzodiazepines. JAMA. 1979;241(16):1692–5.
45. Scharf MB, Kales A, Bixler EO, Jacoby JA, Schweitzer PK. Lorazepam-efficacy, side effects, and rebound phenomena. Clin Pharmacol Ther. 1982;31(2):175–9.
46. Greenblatt DJ, Shader RI, Abernethy DR. Drug therapy. Current status of benzodiazepines. N Engl J Med. 1983;309(6):354–8.
47. Kales A, Soldatos CR, Bixler EO, Kales JD, Vela-Bueno A. Diazepam: effects on sleep and withdrawal phenomena. J Clin Psychopharmacol. 1988;8(5):340–6.
48. Hallfors DD, Saxe L. The dependence potential of short half-life benzodiazepines: a meta-analysis. Am J Public Health. 1993;83(9):1300–4.
49. Hoey LL, Nahum A, Vance-Bryan K. A prospective evaluation of benzodiazepine guidelines in the management of patients hospitalized for alcohol withdrawal. Pharmacotherapy. 1994;14(5):579–85.
50. Chouinard G. Issues in the clinical use of benzodiazepines: potency, withdrawal, and rebound. J Clin Psychiatry. 2004;65(Suppl 5):7–12.
51. Ashton H. The diagnosis and management of benzodiazepine dependence. Curr Opin Psychiatry. 2005;18(3):249–55.
52. Ritson B, Chick J. Comparison of two benzodiazepines in the treatment of alcohol withdrawal: effects on symptoms and cognitive recovery. Drug Alcohol Depend. 1986;18(4):329–34.
53. Hill A, Williams D. Hazards associated with the use of benzodiazepines in alcohol detoxification. J Subst Abuse Treat. 1993;10(5):449–51.
54. Mayo-Smith MF, Bernard D. Late-onset seizures in alcohol withdrawal. Alcohol Clin Exp Res. 1995;19(3):656–9.
55. Devenyi P, Harrison ML. Prevention of alcohol withdrawal seizures with oral diazepam loading. Can Med Assoc J. 1985;132(7):798–800.
56. Stanski DR, Greenblatt DJ, Selwyn A, Shader RI, Franke K, Koch-Weser J. Plasma and cerebrospinal fluid concentrations of chlordiazepoxide and its metabolites in surgical patients. Clin Pharmacol Ther. 1976;20(5):571–8.
57. Greenblatt DJ, Shader RI, Franke K, Harmatz JS. Pharmacokinetics of chlordiazepoxide and metabolites following single and multiple oral doses. Int J Clin Pharmacol Biopharm. 1978;16(10):486–93.
58. Greenblatt DJ, Shader RI, MacLeod SM, Sellers EM. Clinical pharmacokinetics of chlordiazepoxide. Clin Pharmacokinet. 1978;3(5):381–94.
59. Lin KM, Friedel RO. Relationship of plasma levels of chlordiazepoxide and metabolites to clinical response. Am J Psychiatry. 1979;136(1):18–23.
60. Minder EI. Toxicity in a case of acute and massive overdose of chlordiazepoxide and its correlation to blood concentration. J Toxicol Clin Toxicol. 1989;27(1–2):117–27.
61. Sainati SM, Lorens SA. Intra-raphe benzodiazepines enhance rat locomotor activity: interactions with GABA. Pharmacol Biochem Behav. 1983;18(3):407–14.
62. DrugPatentWatch [database on the Internet]. http://www.drugpatentwatch.com. Accessed 27 July 2016.
63. Frew B, Frew JR, Swift CF. Competition Between Original Brands and Generics in Pharmaceuticals: Analysis and Policy Implications. In: Bellur VV, editor. The 1980's: A Decade of Marketing Challenges. Cham: Springer International Publishing; 2015. p. 282–5.
64. Shader RI, Greenblatt DJ. Benzodiazepines: some aspects of their clinical pharmacology. Ciba Found Symp. 1979;74:141–55.
65. Sellers EM, Naranjo CA, Harrison M, Devenyi P, Roach C, Sykora K. Diazepam loading: simplified treatment of alcohol withdrawal. Clin Pharmacol Ther. 1983;34(6):822–6.
66. Manikant S, Tripathi BM, Chavan BS. Loading dose diazepam therapy for alcohol withdrawal state. Indian J Med Res. 1993;98:170–3.
67. Salloum IM, Cornelius JR, Daley DC, Thase ME. The utility of diazepam loading in the treatment of alcohol withdrawal among psychiatric inpatients. Psychopharmacol Bull. 1995;31(2):305–10.
68. Wasilewski D, Matsumoto H, Kur E, Dziklinska A, Wozny E, Stencka K, et al. Assessment of diazepam loading dose therapy of delirium tremens. Alcohol Alcohol. 1996;31(3):273–8.
69. Hyatt M, Cheever T, Eldot R. Diazepam Loading for Alcohol Detoxification. Am J Addict. 1996;5(4):354–8.
70. Sellers EM. Clinical pharmacology and therapeutics of benzodiazepines. Can Med Assoc J. 1978;118(12):1533–8.
71. Schenker S. Effects of liver disease and of aging on the disposition and elimination of sedatives. Trans Am Clin Climatol Assoc. 1978;89:91–9.
72. Ochs HR, Greenblatt DJ, Eckardt B, Harmatz JS, Shader RI. Repeated diazepam dosing in cirrhotic patients: cumulation and sedation. Clin Pharmacol Ther. 1983;33(4):471–6.
73. Naranjo CA, Busto U, Janecek E, Ruiz I, Roach CA, Kaplan K. An intensive drug monitoring study suggesting possible clinical irrelevance of impaired drug disposition in liver disease. Br J Clin Pharmacol. 1983;15(4):451–8.
74. Perry PJ, Wilding DC, Fowler RC, Hepler CD, Caputo JF. Absorption of oral intramuscular chlordiazepoxide by alcoholics. Clin Pharmacol Ther. 1978;23(5):535–41.
75. Greenblatt DJ, Shader RI, Koch-Weser J. Slow absorption of intramuscular chlordiazepoxide. N Engl J Med. 1974;291(21):1116–8.
76. Divoll M, Greenblatt DJ, Ochs HR, Shader RI. Absolute bioavailability of oral and intramuscular diazepam: effects of age and sex. Anesth Analg. 1983;62(1):1–8.
77. Greenblatt DJ, Shader RI, Franke K, MacLaughlin DS, Harmatz JS, Allen MD, et al. Pharmacokinetics and bioavailability of intravenous, intramuscular, and oral lorazepam in humans. J Pharm Sci. 1979;68(1):57–63.

78. Greenblatt DJ, Divoll M, Harmatz JS, Shader RI. Pharmacokinetic comparison of sublingual lorazepam with intravenous, intramuscular, and oral lorazepam. J Pharm Sci. 1982;71(2):248–52.
79. Galvin GM, Jelinek GA. Midazolam: an effective intravenous agent for seizure control. Arch Emerg Med. 1987;4(3):169–72.
80. Lineaweaver WC, Anderson K, Hing DN. Massive doses of midazolam infusion for delirium tremens without respiratory depression. Crit Care Med. 1988;16(3):294–5.
81. Newman JP, Terris DJ, Moore M. Trends in the management of alcohol withdrawal syndrome. Laryngoscope. 1995;105(1):1–7.
82. Reves JG, Fragen RJ, Vinik HR, Greenblatt DJ. Midazolam: pharmacology and uses. Anesthesiology. 1985;62(3):310–24.