Meta-analysis of benzodiazepine use in the treatment of acute alcohol withdrawal

Evidence

Études

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? An overview of the diagnosis and management of acute alcohol withdrawal appears on page 675

Abstract

Objective: To analyse the evidence for the efficacy and potential harmful effects of benzodiazepines compared with other therapies in the treatment of acute alcohol withdrawal.

Data sources: MEDLINE and the Cochrane Controlled Trials Registry were searched for English-language articles published from 1966 to December 1997 that described randomized controlled trials (RCTs) of benzodiazepines in the treatment of acute alcohol withdrawal. Key words included "benzodiazepines" (exploded) and "randomized controlled trial." Bibliographies of relevant articles were reviewed for additional RCTs, and manufacturers of benzodiazepines were asked to submit additional RCT reports not in the literature.

Study selection: Articles were considered for the meta-analysis if they were RCTs involving patients experiencing acute alcohol withdrawal and comparing a benzodiazepine available in Canada with placebo or an active control drug. Of the original 23 trials identified, 11 met these criteria, representing a total of 1286 patients.

Data extraction: Data were extracted regarding the participants, the setting, details of the intervention, the outcomes (including adverse effects) and the methodologic quality of the studies.

Data synthesis: The meta-analysis of benefit (therapeutic success within 2 days) showed that benzodiazepines were superior to placebo (common odds ratio [OR] 3.28, 95% confidence interval [CI] 1.30–8.28). Data on comparisons between benzodiazepines and other drugs, including β-blockers, carbamazepine and clonidine, could not be pooled, but none of the alternative drugs was found to be clearly more beneficial than the benzodiazepines. The meta-analysis of harm revealed no significant difference between benzodiazepines and alternative drugs in terms of adverse events (common OR 0.67, 95% CI 0.34–1.32) or dropout rates (common OR 0.68, 95% CI 0.47–0.97).

Interpretation: Benzodiazepines should remain the drugs of choice for the treatment of acute alcohol withdrawal.

Résumé

Objectif : Analyser les données probantes relatives à l'efficacité et aux effets nocifs possibles des benzodiazépines comparativement à d'autres thérapies utilisées pour traiter le sevrage alcoolique aigu.

Sources de données : On a effectué, dans MEDLINE et le registre des études contrôlées Cochrane, une recherche d'articles en anglais publiés de 1966 à décembre 1997 où l'on décrit des études contrôlées randomisées (ECR) portant sur l'utilisation des benzodiazépines dans le traitement du sevrage alcoolique aigu. On a utilisé comme mots clés «benzodiazepines» (développé) et «randomized controlled trial». On a passé en revue les bibliographies d'articles pertinents pour y trouver d'autres ECR et l'on a demandé aux fabricants de benzo-

diazépines de produire d'autres rapports d'ECR ne figurant pas dans les écrits.

Sélection d'études : On a envisagé d'utiliser pour la méta-analyse les articles qui constituaient des ECR portant sur des patients vivant un sevrage alcoolique aigu et comparant une benzodiazépine disponible au Canada à un placebo ou à un médicament de contrôle actif. Sur les 23 études repérées à l'origine, 11 satisfaisaient aux critères et représentaient au total 1286 patients.

Extraction des données : On a extrait des données portant sur les participants, le contexte, les détails de l'intervention, les résultats (y compris les effets indésirables) et la qualité méthodologique des études.

Synthèse des données : La méta-analyse des avantages (réussite du traitement dans les deux jours) a montré que les benzodiazépines donnaient de meilleurs résultats que le placebo (coefficient de probabilité[CP] ordinaire de 3,28, intervalle de confiance [IC] à 95 % de 1,30 à 8,28). On a pu regrouper des données portant sur des comparaisons entre les benzodiazépines et d'autres médicaments, y compris les β-bloquants, la carbamazépine et la clonidine, mais aucun des autres médicaments ne présentait d'avantage clair sur les benzodiazépines. La méta-analyse des préjudices n'a révélé aucune différence importante entre les benzodiazépines et d'autres médicaments en ce qui concerne les effets indésirables (CP ordinaire de 0,67, IC à 95 % de 0,34 à 1,32) ou les taux d'abandon (CP ordinaire de 0,68, IC à 95 % de 0,47 à 0,97).

Interprétation : Les benzodiazépines devraient demeurer les médicaments de choix pour le traitement du sevrage alcoolique aigu.

Benzodiazepines have been available for use in Canada since 1960.[1] Few medications have been as controversial in their clinical application.[2–11] To address a perceived lack of summary data and to provide a background paper for a practice guidelines initiative sponsored by the Canadian Pharmaceutical Association and the Canadian Medical Association, we prepared a series of meta-analyses of the benefits and harms of benzodiazepines for their common indications. In this article we review studies of benzodiazepine use in the treatment of acute alcohol withdrawal. Benzodiazepine use for anxiety and insomnia will be addressed in future issues of *CMAJ*. In an accompanying article in this issue (page 675) we review the diagnosis and management of acute alcohol withdrawal.[12]

Methods

A comprehensive search of MEDLINE was conducted for articles of randomized controlled trials published from 1966 to December 1997 on the use of benzodiazepines in the treatment of alcohol withdrawal. The search terms used were "benzodiazepine" (exploded) or "benzodiazepine tranquillizers" (exploded) or "clonazepam"; "drug therapy"; "randomized controlled trial" or "random allocation" or "all random"; "human" and "English language." A similar search was carried out in the Cochrane Controlled Trials Registry. Relevant articles were retrieved and appraised for original data comparing therapies for alcohol withdrawal. Bibliographies of retrieved articles were scanned for additional articles, and each manufacturer of a brand-name benzodiazepine was asked to contribute reports of early trials not published in the medical literature.

Reports of randomized controlled trials of benzodiazepine therapy for alcohol withdrawal were considered for the meta-analysis if they compared the benzodiazepine with a placebo or an alternative drug or mode of therapy available in Canada; they involved actual patients rather than healthy volunteers; and they measured at least one relevant clinical endpoint. Studies in which a benzodiazepine was combined with another drug were not included unless there was also a benzodiazepine-alone group.

Individual reports were rated for quality with the use of a scale from 0 to 5; for therapeutic efficacy, this meant taking into account the quality of randomization, blinding and follow-up, and for harmful effects, it meant examining randomization, blinding and control for baseline differences between groups.[13]

Descriptive data were recorded on the conditions treated, patient exclusion criteria, major coexisting disorders and concurrent interventions, patient age and sex, setting and duration of the study, and side effects encountered during treatment and follow-up. The study design (crossover, parallel group or *n* of 1), the outcome measures and study day on which they were measured, and the results (numbers of patients, outcome means and measures of variability or numbers of patients with events in each group, and the study investigators' estimated *p* values for differences between the groups) were recorded. Interrater reliability was checked through duplicate, independent abstraction of the first 21 articles. Overall agreement on classification and descriptive data extracted from the studies was 98% (κ value 0.95). Agreement that all 5 validity criteria were met for a study of therapy was 95% (κ value 0.90) and for a study of harmful effects was 76% (κ value 0.51). Disagreement was resolved by consensus, and subsequent abstraction was carried out by one of us (A.L.).

The meta-analysis of the endpoints from the selected studies was necessarily limited to those presented in a comparable way. Fixed-effects modelling was used, and heterogeneous results were checked with a random-effects model.[14,15] Mantel–Haenszel common odds ratios, along with 95% confidence intervals (CIs, calculated by the method of Cornfield[16]) were obtained for discrete data (e.g., number of patients with an outcome) with the use of the Metanal software program (MS-DOS version 2.0; J. Julian, McMaster University, Hamilton, Ont., 1993). The Breslow–Day test for homogeneity was applied; if study results were heterogeneous, the studies were subdivided into predefined groups and the common odds ratios recalculated. Since the null hypothesis is homogeneity among effect sizes, a significant *p* value suggests that heterogeneity exists among individual studies. Heterogeneity indicates that a single, overall analysis of effect size may not be valid and that previously identified important subgroups should possibly be analysed separately. The subdivisions examined included individual benzodiazepine, dosage levels (e.g., high versus low), type of patient (e.g., primary care versus tertiary care) and quality of methodology. For continuous variables (e.g., alcohol withdrawal assessment scales), effect sizes were calculated for each study as the difference between the outcome means of the groups divided by the pooled standard deviations. An overall weighted effect size was obtained and converted into natural units for the overall difference (along with the 95% CI) in outcome between the benzodiazepine groups and the control groups with the use of the Metanal software program. Results were tested for homogeneity using the Breslow–Day test as outlined above. If a measure of variability was not reported for study results, standard deviations were calculated by means of substitution in the formula for the coefficient of variation, using the study results most similar in outcome means and numbers of patients to the study with missing data.[17] In studies with a crossover desgn, the number of patients was counted once for each arm in which they were included.

Results

Of the 23 randomized controlled trials we identified, 9 were rejected: in 5 the alternative drug or drug formulation was not available in Canada,[18–22] in 3 a random allocation of participants was not confirmed,[23–25] and in 1 benzodiazepines were included only as part of combination therapy.[26] Of the remaining 14 studies, 13 examined acute alcohol withdrawal[27–39] and 1 looked at long-term maintenance of abstinence after alcohol withdrawal.[40] Two of the 13 studies of acute withdrawal[36,37] compared 2 benzodiazepines and therefore were not considered further. The remaining 11 studies (representing a total of 1286 patients) compared a benzodiazepine with a placebo, active control drug or both. Details of these studies are summarized in Table 1.

Most of the 11 trials involved small samples. The mean age of patients ranged from 35 to 45 years. In half of the trials, patients with concomitant medical conditions were excluded. Five of the studies involved chlordiazepoxide, 3 used diazepam, 2 involved oxazepam and 1 used lorazepam. Doses varied greatly once adjusted for equivalent potency, from 2 to 18 diazepam dose equivalents per day (a single dose equivalent = 5 mg of diazepam). Nine of the trials followed patients for a week or less. Outcome measures were different in virtually every study, rendering meta-analysis of all studies impossible. The methodologic quality of the trials was generally reasonable except for 2 trials.[33,34]

Meta-analysis of the 3 studies of benzodiazepine versus placebo that had a similar outcome measure yielded a common odds ratio of 3.28 (95% CI 1.30–8.28) (Fig. 1).[27–29] This meant that the benzodiazepine studied was rated as superior to placebo in relieving the symptoms of alcohol withdrawal within the first 2 days of withdrawal. Review of the individual benzodiazepines (diazepam, chlordiazepoxide and lorazepam) used in these placebo-controlled trials did not suggest differences in efficacy among them. The 2 studies that specifically compared benzodiazepines directly (chlordiazepoxide v. clobazam[36] and diazepam v. lorazepam[37]) did not show significant differences in efficacy.

Nine of the trials compared benzodiazepines with other drugs (bromocriptine,[28] carbamazepine,[31,32] chlorpromazine,[39] clonidine,[30] doxepin,[35] ethanol,[34] hydroxyzine,[39] paraldehyde,[33] propranolol[38] and thiamine[39]). The heterogeneity of efficacy outcomes measured in these trials precluded the combination of data, but there was no evidence of overall superiority of any alternative agent over benzodiazepines in these small trials. Propranolol, as would be expected of β-blockers, lowered heart rate, blood pressure and tremor more than placebo but was less effective in the management of other symptoms such as anxiety, difficulty sleeping and nausea within the first 2 days. Carbamazepine appeared as efficacious as relatively low doses of oxazepam.

Data could be pooled for meta-analysis of harm (adverse effects and dropout rates). Three studies (representing a total 148 patients) reported on the number of patients who had an adverse event (Fig. 2).[28,31,35] The common odds ratio (0.67, 95% CI 0.34–1.32) suggested no difference between benzodiazepines and the alternative drugs examined. Data on study dropout rates could be combined from 5 trials (representing a total 633 patients) (Fig. 3).[30–33,39] The common odds ratio (0.68, 95% CI 0.47–0.97) indicated that fewer patients in the benzodiazepine group than in the alternative drug group dropped out within the first 7 days of treatment. Inclusion of trials of alternative drugs not available in Canada, such as chlormethiazole, tetrabamate and transdermal clonidine,[18–20,22] resulted in virtually identical results.

One study followed patients long enough (6 months) to be able to comment on therapy for maintenance of abstinence from alcohol.[40] This study involved 78 patients and compared chlordiazepoxide and metronidazole. The authors found that both drugs were equally ineffective for abstinence maintenance, as judged by dropout rates of 80% at 6 months.

A recent study of note compared different methods of administration of benzodiazepine for acute alcohol withdrawal.[41] This study was conducted in an alcohol detoxification unit with staff trained in the management of alcohol withdrawal who used the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) scale every 8 hours routinely and after each dose of benzodiazepine. (The CIWA-Ar scale is reproduced in Appendix 2 of the accompanying article on the diagnosis and management of acute alcohol withdrawal[12] [page 680 of this issue].) The authors found that a fixed dosage schedule of benzodi-

Table 1: Summary of randomized controlled trials of efficacy of benzodiazepines in the treatment of acute alcohol withdrawal

Study	Study quality*	Drugs compared (and mean daily dose)	No. of subjects (male/female)	Treatment duration	Main results
Sellers et al, 1983[26]	T 4 H 4	Diazepam (73 mg) v. placebo	43/7	12–15 h	Significant improvement in withdrawal symptoms with diazepam than with placebo ($p < 0.05$). Therapeutic success (CIWA-Ar score of ≤ 10) did not differ significantly between groups
Burroughs et al, 1985[27]	T 5 H 5	Chlordiazepoxide (250 mg tapered to 25 mg) v. bromocriptine (7.5 mg tapered to 2.5 mg) v. placebo	40/31	7 d	Significant improvement in withdrawal symptoms and therapeutic success at 2 d with chlordiazepoxide than with bromocriptine or placebo ($p < 0.05$). Number of patients reporting adverse events did not differ significantly
Naranjo et al, 1983[28]	T 4 H 4	Lorazepam (6 mg) v. placebo	35/6	7 h	At 7 h, therapeutic success (CIWA-Ar score ≤ 10) was significantly greater with lorazepam than with placebo ($p < 0.05$)
Baumgartner et al, 1987[29]	T 3 H 3	Chlordiazepoxide (100 mg) v. clonidine (0.4 mg)	61/0	60 h	Anxiety, cognitive capacity, self-rated severity of withdrawal symptoms, adverse effects and dropout rates did not differ significantly between groups. Blood pressure and heart rate significantly reduced with clonidine than with chlordiazepoxide ($p < 0.05$)
Tuppaeck et al, 1992[30]	T 4 H 4	Oxazepam (≤ 120 mg) v. carbamazepine (≤ 800 mg)	11/47	7 d	Improvement in withdrawal symptoms, complications, adverse effect rates and dropout rates did not differ significantly between groups. Continued improvement over 7 d
Malcolm et al, 1989[31]	T 4	Oxazepam (120 mg) v. carbamazepine (800 mg)	86/0	7 d	Severe withdrawal. CIWA-Ar score and dropout rates did not differ significantly between groups. Stable improvement by 5 d
Thompson et al, 1975[32]	T 1 H 2	Cumulative dose to endpoint: diazepam (mean dose 46 mg) (DTs only) v. paraldehyde (mean dose 36 mL) (DTs only)	26/8	160 h	Severe withdrawal – all patients had DTs. Time to calm and number of patients experiencing apnea, agitation or death significantly reduced with diazepam than with paraldehyde ($p < 0.05$)
Funderburk et al, 1978[33]	T 1 H 1	Chlordiazepoxide (99.7 mg) v. ethanol (358.8 mL)	18/0	4–6 d	Improvement in withdrawal symptoms did not differ significantly between groups
Gallant et al, 1969[34]	T 4 H 4	Diazepam (15 mg) v. doxepin (75 or 150 mg) v. placebo	100/0	21 d	Clinical improvement and adverse effect rates did not differ significantly between groups
Sellers et al, 1977[37]	T 3 H 3	Chlordiazepoxide (100 mg) v. propranolol (40 or 160 mg) v. placebo	30/0	4 d	Withdrawal symptoms at 2 d significantly improved with chlordiazepoxide than with propranolol or placebo ($p < 0.05$). Propranolol 160 mg decreased tremor, heart rate and blood pressure
Kaim et al, 1969[38]	T 4 H 4	Chlordiazepoxide (200 mg) v. chlorpromazine (400 mg) v. hydroxyzine (400 mg) v. thiamine (400 mg) v. placebo	537	10 d	Incidence rates of delirium and seizures significantly reduced with chlordiazepoxide than with chlorpromazine or placebo

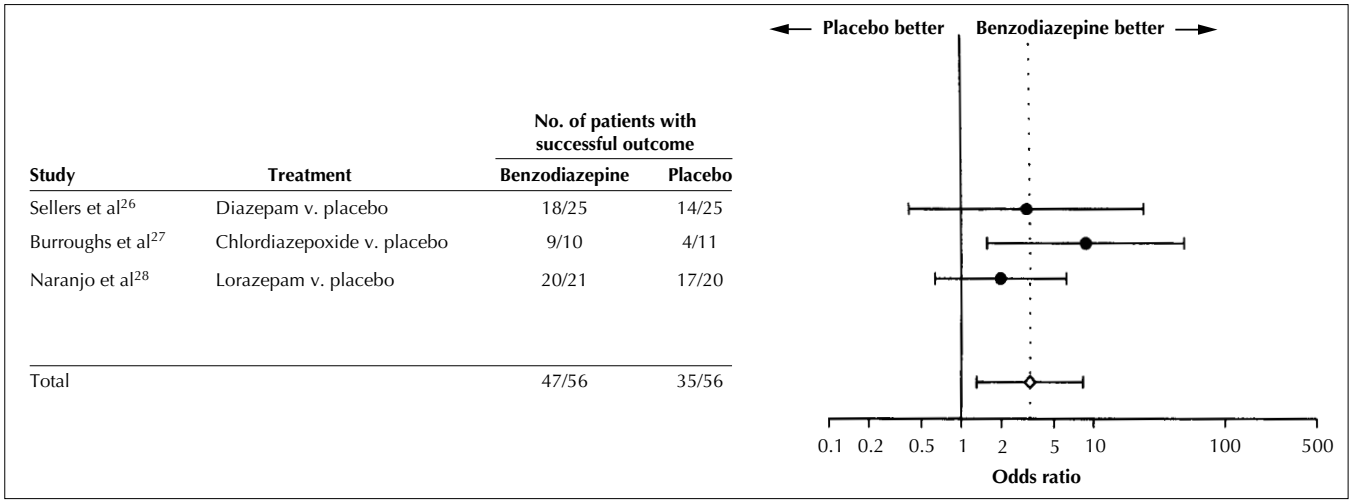
Note: CIWA-Ar = Clinical Institute Withdrawal Assessment for Alcohol, DTs = delirium tremens.
*T = therapy (maximum score 5), H = harm (maximum score 5); see Methods.

azepines over 48 hours was less successful than a regimen in which the benzodiazepine was administered as needed on the basis of the CIWA-Ar score; this was true for both the duration of benzodiazepine treatment and the total number of milligrams given.

Interpretation

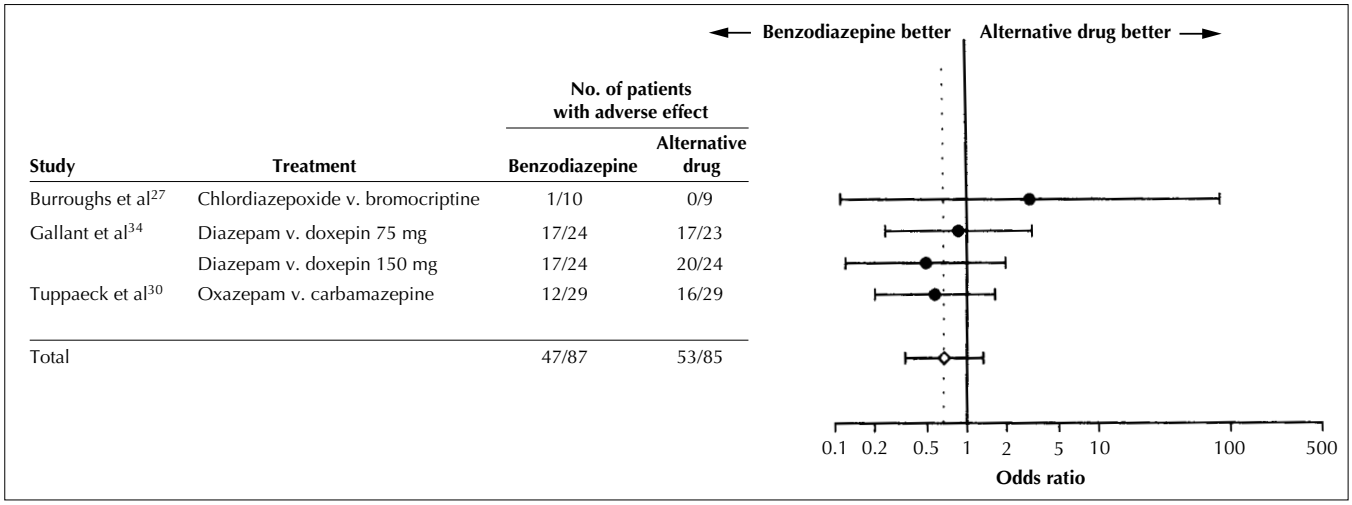
Our confirmation of the superiority of benzodiazepines over placebo in the treatment of acute alcohol withdrawal would probably not surprise most clinicians. However, alternatives to benzodiazepines have attracted interest primarily because of initial concerns about central nervous system depression at high doses of benzodiazepines plus the risk of benzodiazepine dependence. The former concern was not borne out in the trials, and the latter should not be an issue because of the short-term use recommended in the treatment of alcohol withdrawal. Although β-blockers may decrease the peripheral autonomic manifestations of alcohol withdrawal, they have no anti-epileptic effect. Clonidine and carbamazepine remain second-line or adjunctive choices if high doses of benzodiazepine cannot be given.[42] Their impact on delirium and seizures is unknown, given the small samples of the relevant studies. Carbamazepine has broader intuitive appeal than clonidine because of its anticonvulsant activity. The additional alternatives studied that are not available in Canada (chlormethiazole,[19,22] tetrabamate[20] and transdermal clonidine[18]) were not found to be superior to benzodiazepines.

Our analysis revealed no evidence of superiority of one



Study	Treatment	No. of patients with successful outcome: Benzodiazepine	Placebo
Sellers et al[26]	Diazepam v. placebo	18/25	14/25
Burroughs et al[27]	Chlordiazepoxide v. placebo	9/10	4/11
Naranjo et al[28]	Lorazepam v. placebo	20/21	17/20
Total		47/56	35/56

Fig. 1: Odds ratio of trials analysing effect of benzodiazepine versus placebo in treatment of acute alcohol withdrawal. Success was measured as reduction in Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) score within 2 days. Overall odds ratio 3.28 (95% confidence interval [CI] 1.30 to 8.28; test for homogeneity, $p > 0.05$).



Study	Treatment	No. of patients with adverse effect: Benzodiazepine	Alternative drug
Burroughs et al[27]	Chlordiazepoxide v. bromocriptine	1/10	0/9
Gallant et al[34]	Diazepam v. doxepin 75 mg	17/24	17/23
	Diazepam v. doxepin 150 mg	17/24	20/24
Tuppaeck et al[30]	Oxazepam v. carbamazepine	12/29	16/29
Total		47/87	53/85

Fig. 2: Odds ratio of trials analysing effect of benzodiazepine versus alternative drug treatment in terms of adverse effects among patients with acute alcohol withdrawal. Overall odds ratio 0.67 (95% CI 0.34 to 1.32; test for homogeneity, $p > 0.05$).

benzodiazepine over another. All benzodiazepines available orally in Canada are relatively long acting (effective half-life over 12 hours[12]) except for triazolam. The advantage of a benzodiazepine with a longer half-life in promoting a smoother withdrawal from alcohol[43,44] may be partially offset by accumulation of the drug in patients who have significant hepatic impairment or who are given prolonged treatment with inadequate doses.[44–46]

We are unaware of other meta-analyses of benzodiazepines for their common uses. Recent evidence-based guidelines from the American Society for Addiction Medicine support the use of benzodiazepines as first-line drug therapy for alcohol withdrawal, with therapy individualized according to the CIWA-Ar scores.[43] The guidelines incorporated a meta-analysis, but nonrandomized trials had been included.

This first article in our series of meta-analyses illustrates a number of deficiencies with the benzodiazepine literature. Given that members of this family of drugs began appearing on the market in 1960,[1] there are surprisingly few randomized controlled trials of their use in the treatment of alcohol withdrawal. As with many areas of therapeutics, the great variety of ways that benefit and harm of therapies were expressed rendered the pooling of data from different trials difficult. We were able to standardize dosing to a common measurement, the diazepam dose equivalent,[12] but there were insufficient trials to examine dose–response relationships.

A potential limitation to our methodology was the restriction of our search to studies published in English.[47] Another potential limitation was our adoption of the fixed-effects model, recommended by the Cochrane Collaboration.[14] Meta-analyses are undertaken using one of 2 main models, fixed effects or random effects.[48–50] Various arguments have been put forth supporting one or the other model. Although we used the fixed-effects model, our results were virtually identical when we repeated the analyses using a standard random-effects model.

Most of the studies included in our meta-analysis had been conducted in inpatient alcohol detoxification units, and the participants tended to be younger men with little or no comorbidity. In contrast, comorbidity, particularly lung and heart disease, is common in hospital patients, and competing comorbidities may prevent the recognition of symptoms and signs of alcohol withdrawal at an early stage. Furthermore, elderly patients or those with known hepatic, cardiac or respiratory impairment tend to be routinely excluded from trials; however, they may be more sensitive to various adverse effects of benzodiazepines including respiratory suppression. Nonetheless, the generalizability of the trial results to these individuals at higher risk is cautiously recommended,[41,51,52] although these patients must be closely monitored, particularly for respiratory status.

Conclusions

Benzodiazepines appear to deserve a key role as first-line drug therapy for the management of acute alcohol withdrawal. The most important consideration is not which benzodiazepine to use, but to ensure that adequate doses are administered early in the course of withdrawal. Early treatment coupled with close and regular monitoring appears to be effective in avoiding prolonged withdrawal, sedation-related morbidity and extra resource utilization.

Study	Treatment	No. of patients who dropped out: Benzodiazepine	No. of patients who dropped out: Alternative drug
Baumgartner et al[29]	Chlordiazepoxide v. clonidine	9/30	5/31
Malcolm et al[31]	Oxazepam v. carbamazepine	4/30	4/30
Tuppaeck et al[30]	Oxazepam v. carbamazepine	9/34	11/32
Thompson et al[32]	Diazepam v. paraldehyde	0/17	0/17
Kaim et al[38]	Chlordiazepoxide v. hydroxyzine	14/103	17/103
	Chlordiazepoxide v. chlorpromazine	14/103	25/103
	Chlordiazepoxide v. thiamine	14/103	24/103
Total		36/214	86/419

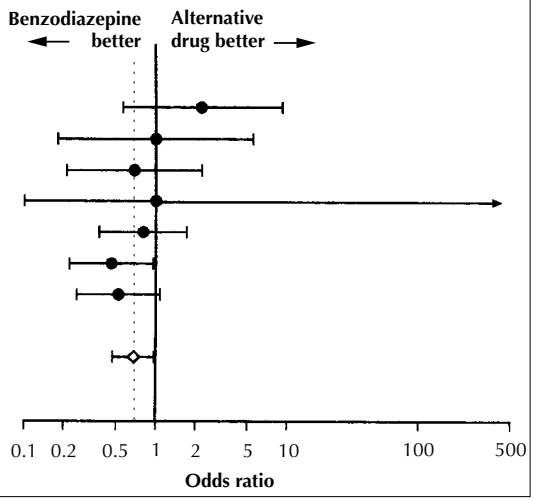


Fig. 3: Odds ratio of trials analysing effect of benzodiazepine versus alternative drug treatment in terms of dropout rates within 7 days after randomization among patients with acute alcohol withdrawal. Overall odds ratio 0.68 (95% CI 0.47 to 0.97; test for homogeneity, $p > 0.05$).

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Competing interests: None declared.

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