Pharmacological interventions for benzodiazepine mono-dependence management in outpatient settings (Review)

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[Intervention Review]

Pharmacological interventions for benzodiazepine mono-dependence management in outpatient settings

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ABSTRACT

Background

The improved safety profile of benzodiazepines compared to barbiturates has contributed to a high rate of prescription since the seventies. Although benzodiazepines are highly effective for some disorders, they are potentially addictive drugs and they can provide reinforcement in some individuals.

Objectives

To evaluate the effectiveness of pharmacological interventions for benzodiazepine mono-dependence.

Search strategy

We searched the Cochrane Drugs and Alcohol Group' Register of Trials (October 2004), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 4, 2004), MEDLINE (January 1966 to October 2004), EMBASE (January 1988 to October 2004), PsycInfo (1985 to October 2004), CINAHL (1982 to October 2004), Pascal, Toxibase, reference lists of articles.

Selection criteria

Randomized trials of benzodiazepines dependence management regardless of type, dose (daily and total) and duration of f therapy and type of therapy.

Data collection and analysis

Reviewers independently assessed trials for inclusion, rated their methodological quality and extracted data.

Main results

753 references were selected and 35 were eligible. Eight met the inclusion criteria for a total of 458 participants. The studies included could not be analysed cumulatively because of heterogeneity of interventions and participants' characteristics. Results support the policy of gradual rather than abrupt withdrawal of benzodiazepine. Progressive withdrawal (over 10 weeks) appeared preferable if compared to abrupt since the number of drop-outs was lower and the procedure judged more favourable by the participants. Short half-life

benzodiazepine, associated with higher drop-out rates, did not have higher withdrawal symptoms scores. Switching from short half-life benzodiazepine to long half-life benzodiazepine before gradual taper withdrawal did not receive much support from this review. No benefits of Propanolol, Dothiepin, Buspirone, Progesterone or Hydroxyzine were found for managing benzodiazepine withdrawal or improving benzodiazepine abstinence. Carbamazepine might have promise as an adjunctive medication for benzodiazepine withdrawal, particularly in patients receiving benzodiazepines in daily dosages of 20 mg/d or more of diazepam (or equivalents).

Authors' conclusions

All included studies showed that gradual taper was preferable to abrupt discontinuation. The results of this systematic review point to the potential value of carbamazepine as an effective intervention for benzodiazepine gradual taper discontinuation. But, larger controlled studies are needed to confirm carbamazepine's potential benefit, to assess adverse effects and to identify when its clinical use might be most indicated. Other treatment approaches to benzodiazepine discontinuation management should be explored (antidepressants, benzodiazepine receptors modulator).

PLAIN LANGUAGE SUMMARY

Pharmacological interventions for benzodiazepine mono-dependence management in outpatient settings

The improved safety profile of benzodiazepines compared to barbiturates has contributed to a high rate of prescription since the seventies. Prevalence of benzodiazepines use remains important worldwide. Although benzodiazepines are highly effective as short-term treatments for some disorders, they also are potentially addictive drugs. This review has shown that a gradual taper is preferable to abrupt discontinuation of benzodiazepines, and that carbamazepine may be an effective intervention for benzodiazepine gradual taper discontinuation. But, larger controlled studies are needed to confirm carbamazepine's potential benefit, to assess adverse effects and to identify when its clinical use might be most indicated.

BACKGROUND

The improved safety profile of benzodiazepines compared to barbiturates has contributed to a high rate of prescription since the seventies. Prevalence of benzodiazepines use remains important worldwide.

A large population survey in 1990 reported that between 10 and 15% of men and women had used benzodiazepines the previous year, including about 2% with chronic use (Kan 1997; Kan 1998; Salzman 1991) but prevalence can be much higher in certain subgroups (alcohol dependent or other substance abusers/ dependents). Although benzodiazepines are highly effective as short-term treatments for disorders such as anxiety and insomnia, in long-term use, the risk of adverse effects impaired cognitive abilities, memory problems, mood swings, overdoses if mixed with other drugs, could outweigh the benefits (Lader 1991). Moreover, benzodiazepines are potentially addictive drugs. They can provide reinforcement in some individuals (Woods 1992) and dependence can develop within a few weeks or months of regular use. The mechanism that causes benzodiazepines dependence appears to be mediated by specific receptors, which enhance GABA transmission (Martin 1982). Although maintenance benzodiazepines therapy has demonstrated efficacy in anxiety disorder (Rickels 1983; Rickels 1988), it places the patient at significant risk for developing benzodiazepines dependence and a withdrawal syndrome upon benzodiazepines discontinuation (Busto 1986; Petursson 1981; Rickels 1983; Winokur 1980). The intensity of withdrawal symptoms (disturbed sleep, anxiety, agoraphobia) could explain dropouts in previous attempts to quit benzodiazepines use (Lennane 1991).

The current management of benzodiazepines withdrawal syndrome consists of: (1) adequate treatment of continuing symptoms of depression or anxiety, (2) utilization of a gradual taper schedule; and (3) switching the patient to an equivalent dose of a long half-life benzodiazepines if difficulty encountered in tapering-off therapy with short half-life benzodiazepines (Schweizer 1991). The most common clinical recommendation for reducing benzodiazepines withdrawal and improving clinical outcome in-

volves the use of a gradual taper schedule (Schweizer 1990). Some studies suggest that initiating adjunctive medication prior to, and continuing it during and after benzodiazepines discontinuation may help facilitate the tapering of benzodiazepines and lead to significantly higher discontinuation success rate (Rickels 1990).

We choose to consider only benzodiazepine mono-dependence because co-dependent patients were less likely to complete medical treatment and as such left treatment at a time where they were highly vulnerable to relapse. Concurrent drugs and benzodiazepine discontinuation may not be the optimal management strategy for co-dependence (Bleich 2002). Patients may suffer not only benzodiazepine-specific withdrawal phenomena, but also experience exacerbated other drugs withdrawal symptoms (de Wet 2004). Results of co-dependent participants should be associated with poorer completion rates and, so, need to be interpreted in a specific context.

The purpose of this systematic review was to point out clinical trials reporting pharmacological interventions for management of benzodiazepines mono-dependence and to evaluate the most effective interventions.

OBJECTIVES

The objective of this study was to evaluate the effectiveness of pharmacological interventions for outpatient management of benzodiazepine mono-dependence.

METHODS

Criteria for considering studies for this review

Types of studies

All relevant randomised controlled studies examining a pharmacological intervention for BZD dependence in comparison with placebo or combinations of pharmacological interventions. Non-randomized trials were excluded from this systematic review.

Types of participants

We considered all benzodiazepines users who met diagnostic criteria of DSM-IV (DSM-IV 1994) or diagnostic given by a clinician for benzodiazepines dependence and seeking detoxification treatment in outpatient settings. All adult patients were included regardless of age (> 18), gender, and nationality. The history of previous treatments was considered, but it was not an eligibility criterion. Exclusion criteria were current dependence on alcohol or any other drug (except nicotine)

Types of interventions

All randomised controlled trials that evaluate at least two treatment programs for benzodiazepine mono-dependence in outpatient settings were considered.
These interventions included:
(1) long half-life benzodiazepine versus short half-life benzodiazepine;
(2) gradual benzodiazepine taper versus placebo;
(3) gradual benzodiazepine taper versus long half-life benzodiazepine;
(4) gradual benzodiazepine taper versus short half-life benzodiazepine;
(5) long-life benzodiazepine versus non-benzodiazepine anxiolytics;
(6) adjunctive medication: antidepressants, serotoninergic anxiolytics, anticonvulsants, beta-blockers, benzodiazepine antagonists;
(7) placebo.

Types of outcome measures

Primary outcomes:
(1) Self-reported use of benzodiazepine with confirmation by urinalysis.
(2) Retention in treatment as measured by total number of dropouts at the end of the trial.
(3) Treatment compliance as measured by number of subjects who adhere to doses and frequency of administration of the treatment.
(4) Severity of benzodiazepine withdrawal: assessed by validated questionnaire.
Secondary outcomes:
(5) Self-reported use of other drugs.

Search methods for identification of studies

We searched:

- Cochrane Drugs and Alcohol Group 'Register of Trials (October 2004);
- Cochrane Central Register of Controlled Trials (*The Cochrane Library* Issue 3, 2004);
- MEDLINE (January 1966 to October 2004);
- EMBASE (January 1988 to October 2004);
- PsycInfo (1985 to October 2004);
- CINAHL (1982 to October 2004);
- Pascal (1991 to October 2004);
- Toxibase (www.toxibase.org) until September 2004

with no language and publication restrictions. To identify studies included in this review, we used detailed search strategies for each database searched. These were based on the search strategy developed for MEDLINE but revised appropriately for each database

to take account of differences in controlled vocabulary and syntax rules, for more details *see* Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6.

We also searched for additional studies using reference lists of review articles and included studies, unpublished and ongoing studies, and pharmaceutical contact.

Data collection and analysis

Study selection

Two review authors independently screened the titles and abstracts of all publications, obtained by the search strategy. We obtained all potentially eligible studies as full articles and two authors independently assessed for inclusion. In doubtful or controversial cases, the authors discussed all identified discrepancies and reached consensus on all items. If consensus was not reached, we referred to the senior author (MA) to solve the problem. Experts familiar to the language translated retrieved studies. When key information relevant to the systematic review was missing, we contacted investigators and requested additional data and clarification. If the majority of trials used the same scale or specific outcome measures, we made an effort to ask primary investigators of the trials that did not report these specific measures to provide relevant data, if available.

We accepted all randomised trials of benzodiazepines dependence management regardless of type of benzodiazepine treatment, daily and total benzodiazepine dose, duration of therapy and type of therapy in outpatient settings. Whenever reports may have pertained to overlapping patients, we retained only the largest study, to avoid duplication of information.

Assessment of the methodological quality

In order to limit bias, gain insight into potential comparisons and guide interpretation of findings, two authors, using the criteria described in the Cochrane Handbook for Systematic Reviews of Interventions, independently assessed the methodological quality of the eligible studies. In the context of a systematic review, the validity of a study was the extent to which its design and conduct were likely to prevent systematic errors, or bias (Moher 1995), *see* Appendix 7.

Data extraction

The reviewers independently extracted the data. ;

Data analysis

Tables were used to display characteristics of eligible trials including trials that were excluded with the reasons for exclusion.

The studies could not be pooled together because of non comparability of interventions and outcomes. Therefore, no graph was included in this review.

Data synthesis

Due to the heterogeneity of the included studies, a meta-analysis could not be performed and the relevant studies were described separately.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

The search strategy resulted in 753 records which were screened by reading both titles and abstracts. Thirty-five studies were considered eligible (Ashton 1990; Ashton 1994; Busto 1989; Busto 1994; Busto 1998; Cantopher 1990; Gerra 1993; Gerra 2002; Goodman 1986; Hallström 1988; Hayward 1996; Lader 1987; Lader 1993; Lemoine 1997; Lilja 2001; McGregor 2003; Mercier-Guyon 2004; Mintzer 1999; Murphy 1991;Nathan 1986; Rickels 1990; Romach 1998; Sanchez-Craig 1987; Saxon 1997; Saxon 1997b; Schweizer 1986; Schweizer 1990; Schweizer 1991; Schweizer 1995; Tyrer 1985; Tyrer 1996; Voderholzer 2001; Vorma 2002; Vorma 2003; Voshaar). Eight of these met the inclusion criteria.

The reasons for exclusion were: design of the study not in the inclusion criteria of this review (Ashton 1994; Busto 1998; Gerra 2002; Goodman 1986; Lilja 2001; McGregor 2003; Nathan 1986; Schweizer 1986; Schweizer 1990); participants' selection criteria not in the scope of this review (Busto 1994; Mercier-Guyon 2004; Mintzer 1999; Romach 1998; Rickels 1990; Voderholzer 2001; Vorma 2002; Vorma 2003); study outcomes (Ashton 1990; Busto 1989; Gerra 1993; Hayward 1996; Lader 1993; Saxon 1997; Saxon 1997b); or study interventions (Sanchez-Craig 1987; Tyrer 1985; Voshaar) differing from inclusion criteria.

Treatment regimen and setting:

Five studies took place in England (Cantopher 1990; Hallström 1988; Lader 1987; Murphy 1991; Tyrer 1996), one took place in France (Lemoine 1997) and two took place in the United States (Schweizer 1991; Schweizer 1995).

All studies had an outpatient design.

All included studies had as main hypotheses that if patients have less withdrawal symptoms, they will be more likely benzodiazepine abstinent at the end of the trial.

In all studies, participants received a stable dose of benzodiazepines before starting discontinuation programs. Benzodiazepine gradual taper was initiated at a rate of 25% per week and completed over four weeks (Hallström 1988; Lader 1987; Schweizer 1991; Schweizer 1995). In one study, the benzodaizepine dosage was reduced in 50% aliquots per week (Lemoine 1997). In one study, the gradual taper was initiated at a rate of 20% per week and completed over eight weeks (Tyrer 1996). In two studies, the benzodiazepine dosage was reduced in 25% aliquots at two-week intervals until complete withdrawal by the end of the tenth week (Cantopher 1990; Murphy 1991). Active adjunctive treatments or placebo were continued for two to four weeks after taper.

Duration of the trials:

The duration of the studies were 28 days (Lemoine 1997), 4 weeks (Hallström 1988), 8 weeks (Schweizer 1995), 10 weeks (Lader 1987), 14 weeks (Murphy 1991; Schweizer 1991; Tyrer 1996),

and 17 weeks (Cantopher 1990). Some studies added a follow-up several weeks after taper: 4 weeks after (Hallström 1988), 5 weeks after (Schweizer 1991), 10 weeks (Cantopher 1990) or 12 weeks after taper (Schweizer 1991; Schweizer 1995).

Participants:

The total number of participants included in the eight selected studies was 458. Their ages were between 18 to 70 years old. In the included studies, their mean ages ranged from 39 to 54. They used benzodiazepines for at least three months (Lemoine 1997), four months (Hallström 1988), six months (Cantopher 1990; Lemoine 1997; Murphy 1991;Tyrer 1996) and one year (Schweizer 1991; Schweizer 1995). They did not need to meet dependence abuse or dependence DSM criteria to be included in the trials, except in one of them (Schweizer 1995). But, all the participants had several times tried unsuccessfully to reduce or stop benzodiazepines use and they had all failed to withdraw. So, all the authors hypothesized that all participants were benzodiazepines dependent. All participants had a past or current history of alcohol or other drugs abuse or alcohol or other drugs dependence.

Types of comparison:

One study compared gradual taper versus abrupt withdrawal (Murphy 1991).

The seven others studies compared gradual taper versus gradual taper withdrawal under adjunctive medications compared with placebo.

Two studies used beta-blockers (propanolol) as adjunctive medication (Cantopher 1990; Hallström 1988).

Two studies used antidepressant: tricyclic antidepressant and serotoninergic 5-HT1a agonist (Lader 1987; Tyrer 1996).

One study used anti-histaminic (hydroxyzine) as adjunctive medication (Lemoine 1997).

One study used anticonvulsant (Schweizer 1991).

One study used steroid hormones with barbiturate-like modulators (progesterone) (Schweizer 1995).

Risk of bias in included studies

Randomization

All the randomised controlled trials studies mentioned the randomisation procedure without further description.

Allocation concealment

Both Cantopher 1990 and Murphy 1991 studies described allocation concealment procedures in sufficient detail to illustrate their adequacy. They stated that patient, pharmacist, investigator all remained blind to treatment by the use of a coded prescribing/dispensing system. No other included studies described allocation concealment but from the article it seems that allocation concealment was kept in all trials.

Performance bias

All included studies reported blinding of those providing and receiving the intervention.

Attrition bias

All included studies reported information about participants either not completing the withdrawal or requiring cessation of study medications. Factors contributing to failure to complete were noted.

Detection bias

All included studies except one (Hallström 1988) were marked A. The control of detection bias in Hallström's study was unclear (marked C).

Intention-to-treat

Intention-to-treat was performed for four studies marked A (Lader 1987; Schweizer 1991; Schweizer 1995; Tyrer 1996). The three others studies were marked B (Hallström 1988; Lemoine 1997; Murphy 1991). No intention-to-treat analysis was performed for one study (Cantopher 1990).

Effects of interventions

Due to heterogeneity of settings, design of studies, source and format of interventions, pooling of data for a meta-analysis was not possible. The main results are presented in tabular form and analyzed in the style of a narrative systematic review.

Primary outcomes

1. Retention in treatment

Murphy 1991 reported 45 participants completed the trial. Twenty-three dropped out (10 allocated to lorazepam, 7 to bromazepam, 6 to diazepam) because of increased symptoms which precluded further reduction at the planned time. The difference was not significantly greater for lorazepam (short half-life benzodiazepines) than for the other two benzodiazepines (mild or long half-life benzodiazepine).

Two studies used β-blockers (propanolol) (Cantopher 1990; Hallström 1988). Hallström 1988 reported 23 out of 31 completed the trial. Of these participants, eight managed to discontinue their benzodiazepine medication and 11 achieved a greater than 50% reduction in their diazepam dose. Five participants were allocated to the propanolol group, 10 were given placebo and 8 were in the "no pill" group. Cantopher 1990 reported taking both groups together, 12 out of the 16 participants dropped out within four weeks of withdrawal. Two participants of the gradual taper group and 10 participants of the abrupt withdrawal using propanolol group dropped out because of withdrawal symptoms.

Tyrer 1996 results during the 14 weeks trial demonstrated that, 45 participants out of 87 randomised participants (21 allocated to dothiepin and 24 to placebo) withdrew from the study. Reasons for drop-out included full recovery (three in dothiepin group, one in placebo group), adverse events (seven dothiepin, five placebo), non-compliance (two dothiepin, seven placebo), lack of efficacy or unknown reasons (9 dothiepin, 11 placebo).

Lader 1987 showed that the attrition rate was faster for participants allocated to buspirone group than for the placebo group. Eight participants of 13 allocated to buspirone group and 5 of 11

allocated to placebo group dropped out because of severe withdrawal symptoms and resumed benzodiazepines use.

In Lemoine 1997 study, 23 participants dropped out in the hydroxyzine group (11 hydroxyzine 25 mg and 12 hydroxyzine 50 mg) and 13 in the placebo group. Twenty-three dropped out after taper was achieved (nine hydroxyzine 25 mg and six hydroxyzine 50 mg and eight in the placebo group) with no significant difference between groups.

In Schweizer 1991 study, 15 participants out of 55 dropped out prior to beginning benzodiazepine therapy taper. Five of eight participants were unable to be benzodiazepine free and only 3 of 13 participants receiving placebo who were receiving diazepam doses of less than 20 mg/d were unable to be so.

2. Treatment compliance

Murphy 1991 reported that 44 out of 45 participants complied with the withdrawal. One participant allocated to bromazepam was found to be taking diazepam.

Cantopher 1990 noted that the plasma diazepam and desmethyldiazepam estimations confirmed that compliance with the treatment regimen was good in both groups.

Nine participants of the Tyrer 1996 trial dropped out because of non-compliance (two dothiepin, seven placebo). Lader 1987 noted that urinalysis revealed no major deviations from the withdrawal regimens. None of benzodiazepines or metabolites were found in participants' urinalysis who claimed to have discontinued benzodiazepines.

3. Benzodiazepine use

Cantopher 1990 reported that all participants who completed the withdrawal remained benzodiazepine-free at six-month follow-up. About half were successfully withdrawn from diazepam, but these were spread between the two groups: 11 out of 16 in the gradual taper group compared with 4 out 15 in the abrupt withdrawal under propanolol group (P = 0.019).

Tyrer 1996 results showed that participants allocated to placebo were more successful in being benzodiazepine-free at the end of the trial than participants allocated to dothiepin group. Of the 41 participants allocated to placebo, 17 were benzodiazepine-free at the date of the final assessment (14-week) compared with 11 of the 36 participants allocated to dothiepin group (OR 1.61, 95% CI 0.63 to 4.1). At 14-week assessment, participants of the dothiepin group took a median benzodiazepine dosage of 3.4 mg (67% reduction from baseline) compared with 2.3 mg for the placebo group (60% reduction from baseline).

At the 88-day follow-up in Lemoine studies (Lemoine 1997), 54% of participants desired to be re given a tranquillizer (without formally requirement), 31% occasionally had a benzodiazepine and 22% formally demanded a prescription of benzodiazepine.

In Schweizer 1991 study significantly more participants treated with carbamazepine were able to stay benzodiazepine-free at five week follow-up. This difference was contributed to primarily by participants receiving placebo who were receiving benzodiazepine doses of 20 mg/d or more of diazepam (or equivalents). Ninety-five per cent of carbamazepine-treated participants were maintained benzodiazepine-free five weeks after taper compared with 62% participants treated with placebo (P < 0.03). These statistically significant differences disappeared at 12-week follow-up (74% for carbamazepine group versus 52% for placebo group).

Schweizer 1995 reported no difference in ability to remain benzodiazepine abstinent at 12-weeks post-taper (57% of progesterone-treated participants versus 58% of placebo-treated).

4. Severity of benzodiazepine withdrawal

Murphy 1991 reported there were no significant differences in withdrawal symptoms intensity (assessed by BWSQ) or anxiety symptoms (assessed by BAS) between the three groups (all *F* values < 1). There were no significant changes in pulse rate, systolic or diastolic blood pressure. Regarding duration of treatment, there were no significant differences between any of the scores although those on higher dosage had higher scores. Longer duration of treatment (> 5 years) was associated with greater total mean scores on the CPRS (P = 0.06) and BWSQ (P < 0.02).

Hallström 1988 reported resting pulse rates for participants under propanolol were significantly lower than participants who did not receive propanolol (P < 0.0005). Anxiety symptoms increased for all treatment groups but this increase was greatest in the non-propanolol treatment groups.

Cantopher 1990 showed eleven of the SW group suffered withdrawal symptoms which were mostly mild, while 14 of the abrupt withdrawal under propanolol group suffered such symptoms, ranging in intensity from mild to severe. Both groups had improved on all scales compared with baseline, although this trend reached significance only in the Hamilton anxiety and Global severity scales of the gradual taper group. Moreover, propanolol did not cause a clinically significant fall in blood pressure in any participant.

Tyrer 1996 noted a greater, but not significant, increase in withdrawal symptoms throughout the 10 weeks trial in those allocated to placebo compared with dothiepin. HAD depression scale showed a significant group x times interaction (P < 0.01) with greater improvement at four weeks in those allocated to placebo. Score of the analogue Satisfaction scale indicating that participants allocated to dothiepin were significantly more satisfied with their study treatment than participants allocated to placebo.

The comparison of overall outcome scores favoured dothiepin but the differences were not significant.

Lader 1987 reported that at the end of the trial both groups were moderately anxious with no difference between the groups. But, buspirone seemed to help to decrease cardiovascular symptoms. Neither the buspirone nor the placebo group experienced any amelioration of symptoms on the Tranquillizer withdrawal scale. In the same way, no group differences appeared on the Bodily symptom scale, the Mood rating scale or the sleep rating scale.

Lemoine 1997 showed that levels of anxiety (HARS and Zung) were significantly improved in hydroxyzine 50 mg group (P < 0.007) and in hydroxyzine 25 mg group (P < 0.012) but not in

placebo group. Withdrawal symptoms (assessed by Tyrer scale) were improved only in hydroxyzine 50 mg group.
No rebound increase was noted by Schweizer et al (Schweizer 1991) in anxiety or depression in the week after abrupt discontinuation of carbamazepine therapy.
Schweizer 1995 reported no difference in the severity of withdrawal between progesterone and placebo. Withdrawal checklist change scores were 17.3 for progesterone and 16.5 for placebo (F 0.63, ns). The Hamilton rating scale for anxiety change scores were 7.8 for progesterone and 6.3 for placebo (F 0.22, ns).

Secondary outcomes
Other drugs use:
Cantopher 1990 noted no significant changes in alcohol or tobacco consumption in either group.
Other outcomes commented by the authors of the included studies:
Tyrer 1996 underlined that 29 of the 41 participants in the dothiepin group had at least one adverse event compared with 26 of the 46 participants allocated to placebo. The average number of events reported was 4.1 with participants allocated in dothiepin group and 3.6 for those in the placebo group and no significant differences were found.
Lemoine 1997 reported that the number of side effects was significantly improved in both hydroxyzine groups (25 and 50 mg) but not in the placebo group.

DISCUSSION

Programs for the treatment of benzodiazepine dependence differ in a number of ways. Outcomes vary; in some of the programs the reduction or elimination of benzodiazepine use was the main objective, in others a reduction in anxiety and depression among patients was regarded as much more important than decreasing benzodiazepine use. These differences in goals made comparative evaluations difficult. Moreover, fewer patients entered and completed the trials and a type II error was possible in the results. Clinical approaches that showed success include, either individually or in combination, gradual tapering of the current benzodiazepine, switching to a long-acting benzodiazepine, treatment of withdrawal symptoms with other medications.

All included studies reported that all participants received a stable dose of benzodiazepine before start of benzodiazepine discontinuation. Murphy 1991 results support the policy of gradual rather than abrupt withdrawal of benzodiazepine. Similar results were found by Lemoine et al (Lemoine 1997): progressive withdrawal appeared preferable if compared to abrupt withdrawal since the number of drop-outs was less important and the procedure judged more favourable by the participants. The findings of Murphy 1991 suggested that a short half-life benzodiazepine was a more difficult benzodiazepine from which to withdraw than a long half-life benzodiazepine. But, despite short half-life benzodiazepine associated with higher drop-out rate, it did not have higher withdrawal symptoms scores. Switching short half-life benzodiazepine to long half-life benzodiazepine before gradual taper withdrawal did not receive much formal support from this study (Murphy 1991) despite its pharmacologic rational. Each study included a rather small number of participants, hence low statistical power might have masked the lack of effect.

Cantopher 1990 concluded slow withdrawal over 10 weeks was successful in the majority of cases and led to relatively mild withdrawal symptoms. Abrupt withdrawal, even under the cover of propanolol, led to more severe symptoms and a lower success rate. But, the role of propanolol in benzodiazepine withdrawal was not clearly shown. In fact, Cantopher 1990 reported slow withdrawal was successful while propanolol alone did not lead to great measure of success in effecting withdrawal. But, Hallström 1988 reported increase in anxiety symptoms was greatest in the non-propanolol treatment group. Adding a tricyclic antidepressant (dothiepin) decreased the intensity of withdrawal symptoms but did not increase the rate of benzodiazepine-free participants at the end of the trial. Moreover, dothiepin seemed to be less effective than placebo in reducing HADS depression scores. In the light of this finding, dothiepin appeared to have no value treating benzodiazepine dependence or benzodiazepine withdrawal symptoms. Lader 1987 underlined the failure of buspirone to suppress any benzodiazepine symptoms.

Lemoine et al results (Lemoine 1997) showed a significant improvement of anxiety in both groups treated by hydroxyzine and a reduction of withdrawal symptomatology in participants treated with hydroxyzine 50 mg. But, the design of the study meant several bias factors (placebo effect control, no benzodiazepine-free control) acted as confounders and may have prevented the potential value of hydroxyzine in the management of benzodiazepine withdrawal symptoms.

Progesterone might also be expected to be of benefit, since it has been shown to have metabolites that act as barbiturate-like modulators of GABAergic transmission. But Schweizer et al trial (Schweizer 1995) did not show any significant effect in controlling benzodiazepine withdrawal and did not improve the rate of benzodiazepine-free patients after gradual taper discontinuation.

As reported by Schweizer et al (Schweizer 1991), carbamazepine showed promise as an adjunctive medication for benzodiazepine withdrawal, particularly in patients receiving benzodiazepines in daily dosages of 20 mg/d or more of diazepam (or equivalent). However, this effects was insufficient to counter the high drop-out rate of the study. High drop-out rates biased the study sample toward a less symptomatically anxious and depressed group. The benefit of carbamazepine in facilitating benzodiazepine taper in a more symptomatic group remains uncertain.

AUTHORS' CONCLUSIONS

Implications for practice

This review considered different pharmacological treatments for the management of benzodiazepine dependence for benzodiazepine mono-dependent patients only, and results cannot be extrapolated to multi-substance users.

It was important to note that all participants received a stable dose of benzodiazepine (long acting for most of participants) before starting benzodiazepine discontinuation programs.

All included studies agreed that gradual taper was preferable to abrupt discontinuation.

Switching short half-life benzodiazepine with long half-life benzodiazepine before gradual taper withdrawal did not receive much formal support from this review. However, only one trial addressed this issue. It is important to note that drop-out rate was higher in the short half-life benzodiazepine group than in the long half-life benzodiazepine group. Sample analysis was small with low statistical power which could explain lack of statistical significance.

The results of this systematic review point to the potential value of carbamazepine (Schweizer 1991) as an effective intervention for benzodiazepine gradual taper discontinuation. Carbamazepine has shown rather modest benefit in reducing withdrawal severity, although it did significantly improve benzodiazepine-free outcome.

Implications for research

Larger controlled studies are needed to confirm that switching short half-life benzodiazepine to long half-life benzodiazepine before gradual taper withdrawal did not have any impact regarding intensity of withdrawal symptoms.

Larger controlled studies are needed to confirm that drop-out rate was higher for short half-life benzodiazepine gradual taper than for long half-life benzodiazepine gradual taper. In fact, in most of the included trials, participants were switched to diazepam and stabilized before entry into the discontinuation programs.

Larger controlled studies are needed to confirm carbamazepine's potential benefit, to assess adverse effects and to identify when its clinical use is indicated.

Other suggested treatment approaches to benzodiazepine discontinuation management should be explored.

1. Flumazenil, a benzodiazepine receptors antagonist may be of benefit as it may up regulate the benzodiazepine receptors. But to our knowledge, no randomised controlled trial have been conducted to assess the potential benefit of flumazenil.

2. Antidepressants, on the basis of their ability to down-regulate monoaminergic receptors and to reduce both depression and anxiety levels might also have benefits. But, to our knowledge, no randomised controlled trials have been conducted or are in progress.

ACKNOWLEDGEMENTS

None

REFERENCES

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Cantopher 1990

Methods	Randomized controlled trial. Participants were randomly assigned between two conditions. Blindness: patient, investigator and pharmacist all remained blind to treatment.
Participants	34 out-patient benzodiazepine dependent users from those attending 58 general practitioners in 26 general practices in Portsmouth and Southampton. n = 34 (analysis sample: n = 31). Age: 18 - 70 years; mean = 45.9 yrs; Sex: male = 9/31, female = 22/31; Mean duration of benzodiazepine use = 9.4 yrs; No. of previous attempts at withdrawal = 1.9; mean starting dose of diazepam = 20.0 mg/day; Past psychiatric history: neurosis = 7/31, depression = 2/31, antisocial behaviour = 2/31.
Interventions	Group SW = slow benzodiazepine withdrawal : diazepam replaced by diazepam placebo in a stepwise manner (week 0 to 10), propanolol placebo throughout. Group PW = abrupt withdrawal under propanolol cover: diazepam replaced by diazepam placebo and active propanolol (40 mg). In both groups, active drugs were stopped at week 10 and placebo stopped at week 12.
Outcomes	Scales: Hamilton Rating Scale for Anxiety; Hospital Anxiety and Depression (HAD); visual analogue scale score; global assessment of severity of illness. Compliance: plasma drug levels, quantitative record of other substances used. Pulse rate and blood pressure. Assessments at weeks 0.4.8.12. Follow-up 6 months after the start of withdrawal.
Notes	Analysis sample: n = 31. Drop-outs: 5/16 for SW group and 11/15 for PW group. Not intention-to-treat analysis.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Hallström 1988

Methods	Randomized controlled trial. Participants were randomly assigned to one of the 3 treatment groups. Blindness: during all the trial.

Hallström 1988 (*Continued*)

Participants	44 out-patients from GPs, psychiatric and hospital departments in London. All participants previously failed to withdraw their benzodiazepines. n = 44 Mean age = 41.4 yrs; Sex: 14 men and 30 women; Mean duration of benzodiazepine use = 10.7 yrs; Benzodiazepine used: diazepam (n = 17; mean = 15.9 mg/d), lorazepam (n = 20, mean = 2.9 mg/d).
Interventions	Group propanolol = reduction in diazepam dose by 25 % per week and propanolol 160 mg/d. Group placebo = reduction in diazepam dose by 25 % per week and placebo. Group "no pill" = reduction in diazepam dose by 25 % per week without any placebo pill.
Outcomes	Scale: Hamilton Anxiety Rating Scale. Resting pulse rates. Compliance: medication pills were counted.
Notes	n = 23 (complied with the full treatment). Drop-outs: 13/44 did not start the trial, 8/44 did not complete the full trial. Analysis sample (outcome): 23/44. Other substance use not controlled.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Lader 1987

Methods	Randomized controlled trial. Participants were randomly allocated to two groups. Blindness: double-blind study, during all the trial
Participants	24 outpatient benzodiazepine-dependent users. Mean age = 39.1 yrs, Sex: 14 female, 10 male; Mean duration of benzodiazepine use = 8.4 yrs; Previous psychiatric diagnosis: anxiety 18/24, depression: 4/24, phobia: 2/24.
Interventions	10-week trial Weeks 1-2: pre-withdrawal, benzodiazepine dose maintained, Weeks 3-4: benzodiazepine dosage halved + buspirone (5mg twice daily) or + placebo. Weeks 5-6: free benzodiazepine + buspirone or placebo Weeks 7-8: full placebo Weeks 9-10: follow-up without placebo

Lader 1987 (*Continued*)

Outcomes	Compliance: drug screenig (urinalysis). Scales: Hamilton Anxiety Scale, Tranquillizer Withdrawal Scale, Bodily Symptoms Scale, Mood Rating Scale.
Notes	Drop-outs: 8/13 buspirone group, 5/11 placebo group.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Lemoine 1997

Methods	Randomized controlled trial. Participants were randomly assigned to 6 groups. Blindness: during all the trial. Double-blind, double-placebo. Multicenter study.
Participants	154 out-patients from 36 GPs. Mean age = 54.1 yrs; Sex: 41 male, 113 female; Mean duration of benzodiazepine use = 86.7 months; Mean duration of lorazepam use = 63.8 months; Mean lorazepam dose = 2.5 mg/d.
Interventions	Withdrawal: 28 days, follow-up: 88 days. 6 groups: Group A: abrupt lorazepam withdrawal + hydroxyzine 50 m/d; Group B: abrupt lorazepam withdrawal + hydroxyzine 25 mg/d; Group C: abrupt lorazepam withdrawal + hydroxyzine placebo; Group D: gradual taper lorazepam withdrawal + lorazepam placebo + hydroxyzine 50 mg/d; Group E: gradual taper lorazepam withdrawal + lorazepam placebo + hydroxyzine 25 mg/d, Group F: gradual taper lorazepam withdrawal + lorazepam placebo + hydroxyzine placebo.
Outcomes	Scales: Hamilton Anxiety Rating Scale, Zung Anxiety self-assessment scale, Benzodiazepine Withdrawal Symptom Questionnaire, Spiegel Sleep scale, Global Clinic Assessment scale.
Notes	Analysis sample: n = 139 (15 protocol violation); Drop-outs: 36/139.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Murphy 1991

Methods	Randomized controlled trial. Participants were randomly assigned to three groups.
Participants	68 out-patients from clinics between Nov 1985 and Jan 1988. Mean age = 44.9 yrs; Sex: 12 female, 46 male; Mean duration of benzodiazepine use = 92.0 months; Patients inluded in the trial changed to one of the three different benzodiazepine: diazepam, lorazepam and bromazepam.
Interventions	Weeks 0-4: switch to either diazepam, bromazepam or lorazepam. Weeks 5-10: gradual taper benzodiazepine withdrawal (25 % less every 2 weeks); Week 10-12: benzodiazepine free and follow-up.
Outcomes	Compliance: serum benzodiazepine estimations; Scales: Comprehensive Psychopathological Rating Scale, Brief Scale for Anxiety, Personality Assessment Schedule, Benzodiazepine Withdrawal Symptom Questionnaire.
Notes	Drop-outs: 23/68 (10 lorazepam group, 7 bromazepam group, 6 diazepam group).

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Schweizer 1991

Methods	Randomized controlled trial. Patients were randomly assigned to two groups. Blindness: double-blind study during all the trial.
Participants	55 benzodiazepine users failed one or more previous attempts to discontinue their benzodiaepine intake. Mean age = 47 yrs; Sex: 21 female, 19 male; Mean duration of benzodiazepine use = 64 months; Benzodiazepine use: alprazolam = 14/40, mean dose 2.2 mg/d; lorazepam = 17/40, mean dose = 2.9 mg/d; diazepam = 9/40, mean dose = 13.2 mg/d.
Interventions	Weeks 1-2: pre-treatment before benzodiazepine taper discontinuation + carbamazepine (200 mg twice a day) or + placebo. Weeks 3-6: benzodiazepine taper, 25 % per week + carbamazepine 200 mg twice a day (Group carbamazepine)or + placebo Carbamazepine or placebo was continued for 4 weeks after benzodiazepine free. Abrupt discontinuation of carbamazepine or placebo after 4 weeks.
Outcomes	Compliance: plasma benzodiazepine determination. Scales: Hamilton Rating Scale for Anxiety, Hamilton Rating Scale for Depression, Physician Withrawal Checklist.

Schweizer 1991 (*Continued*)

Notes	Analysis sample: n = 40 (15 drop-outs during pre-treatment period). Drop-outs: no drop-outs after pre-treatment period.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Schweizer 1995

Methods	Randomized controlled trial. Patients were randomly assigned to two groups. Blindness: double-blind study.
Participants	43 benzodiazepine-dependent patients. Mean diazepam (or equivalent)daily dose = 16.2 mg/d.
Interventions	Weeks 1-3: progesterone (group progesterone)or placebo (group placebo) were co-administered. Benzodiazepine was tapered by 25 % per week. Progesterone or placebo was continued for 4 weeks before being discontinued.
Outcomes	Compliance: plasma benzodiazepine concentration. Benzodiazepine-free at 12-weeks post-taper. Scales: Withdrawal Checklist, Hamilton Rating Scale for Anxiety.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Tyrer 1996

Methods	Randomized controlled trial. Patients were randomly assigned to two groups. Blindness: double-blind study, during all the trial.
Participants	87 out-patients with putative benzodiazepine dependence.
Interventions	Week 0: Random allocation to dothiepin (25 mg) or placebo with increase to 75 mg by week 2 and 150 mg/d dothiepin by week 4 (unless adverse effects were shown). Reduction of benzodiazepine in 20% aliquots between weeks 0 and 8 (intention to be benzodiazepine free at the end of week 8. Reduction of dothiepin to half-dose at week 12 for one week and then stopped at week 13.

Tyrer 1996 (*Continued*)

Outcomes	Benzodiazepine dosage at the end of the trial. Scales: Benzodiazepine Withdrawal Symptom Questionnaire, Comprehensive Pathological Rating Scale, Brief Scale for Anxiety, Hospital Anxiety and Depression Scale.
Notes	No benzodiazepine abuse or dependence criteria. Drop-outs: 21/41 in dothiepin group, 24/46 in placebo group.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Characteristics of excluded studies *[ordered by study ID]*

Ashton 1990	Study design = RCT Participants = 23 chronic benzodiazepine users Intervention = buspirone administered during diazepam withdrawal Outcome = benzodiazepine withdrawal symptoms during diazepam withdrawal Excluded because the outcome considered are not in the scope of the review
Ashton 1994	Study design = review Excluded for not being a study but a review of studies
Busto 1989	Study design = RCT Participants = 23 patients abusing benzodiazepines Outcome = quantification of withdrawal symptoms Excluded because the outcome considered are not in the scope of the review
Busto 1994	Study design = RCT Participants = 28 male volunteers non dependent users Outcome = pharmacologic effects of bretazenil, diazepam and alprazolam different dosages Excluded because the selection of participants are not in the scope of the study
Busto 1998	Study design = RCT Participants = 65 male volunteers who did not meet DSM-III-R criteria for abuse or dependence Setting = out and in-patient treatment Outcome = discontinuation effects of ipsapirone different dosages Excluded because the selection of participants, the setting and the outcome are not in the scope of the review
Gerra 1993	Study design = RCT Participants = 36 flunitrazepam or lormetazepam abusers Intervention = flumazenil Outcome = withdrawal score and flumazenil side effects

(*Continued*)

	Excluded because outcome are not in the scope of the review
Gerra 2002	Study design = RCT Participants = 50 patients who meet DSM-IV criteria for benzodiazepine dependence Setting = in-patient treatment Intervention = intravenous flimazenil versus oxazepam tapering Outcome = withdrawal symptoms and benzodiazepine craving score Excluded because the setting are not in the scope of the review
Goodman 1986	Study design = controlled clinical trial Participants = 3 patients Intervention = clonidine hydrochloride Outcome = efficacy of clonidine in the benzodiazepine withdrawal syndrome Excluded because the study design and the outcome are not in the scope of the review
Hayward 1996	Study design = RCT Participants = 30 benzodiazepine users Intervention = discontinuation of low-dose diazepam Outcome = severity of withdrawal symptoms Excluded because the outcome is not in the scope of the review
Lader 1993	Study design = RCT Participants = 25 benzodiazepine users requesting benzodiazepine withdrawal Intervention = alpidem or placebo Outcome = anxiety and withdrawal symptoms Excluded because the outcomes are not in the scope of the review
Lilja 2001	Study design = review Excluded for not being a study but a review of studies
McGregor 2003	Study design = RCT Setting = in-patient Participants = 44 benzodiazepine dependent users Intervention = fixed or symptom-triggered taper methods Outcome = withdrawal severity, treatment attrition and benzodiazepine use at follow-up Excluded because the setting treatment is not in the scope of the review
Mercier-Guyon 2004	Study design = RCT Participants = 81 subjects treated for at least 6 months with a stable dose of benzodiazepine Intervention = captodiamine or placebo Outcome = extent of withdrawal symptoms Excluded because the selection of the participants and the outcome are not in the scope of the review
Mintzer 1999	Study design = RCT Participants = 13 benzodiazepine users and 13 volunteers without prior exposure to benzodiazepine Intervention = flumazenil and caffeine Outcome = effects of flumazenil in long-term users of therapeutic doses of benzodiazepines Excluded because the selection of the participants and the outcome are not in the scope of the review

(*Continued*)

Nathan 1986	Study design = review Excluded for not being a study but a review of studies
Rickels 1990	Study design = RCT Participants = 57 benzodiazepine users for at least 12 months Intervention = abrupt discontinuation of benzodiazepine Outcome = withdrawal syndrome after abruptly discontinuing short half-life or long half-life benzodiazepines. Excluded because the benzodiazepine dependence or abuse criteria failed and the outcome was not in the scope of the review.
Romach 1998	Study design = RCT Participants = 108 subjects using regularly for at least 3 months alprazolam or lorazepam Intervention = ondansetron (5-HT3 antagonist) Outcome = severity of withdrawal symptoms or level of anxiety Excluded because the selection of the participants and the outcome are not in the scope of the review
Sanchez-Craig 1987	Study deign = RCT Participants = 42 benzodiazepine users seeking treatment Intervention = cognitive-behavioral treatment Excluded because the intervention is not in the scope of the review
Saxon 1997	Study design = single-blind study Participants = 10 benzodiazepine-dependent subjects and 10 controls Intervention = reaction to placebo during benzodiazepine withdrawal with flumazenil Outcome = gender-related differences of benzodiazepine withdrawal symptoms Excluded because the outcome is not in the scope of the review
Saxon 1997b	Study design = RCT Participants = 10 patients treated for benzodiazepine dependency and 10 controls Intervention = flumazenil different dosage Outcome = assessment of withdrawal symptoms Excluded because the outcome is not in the scope of the review
Schweizer 1986	Study design = non randomized controlled trial Participants = 15 patients from a larger study of benzodiazepine withdrawal Intervention = buspirone Outcome = assessment of anxiety Excluded because randomization failed.
Schweizer 1990	Study design = non randomized Participants = 63 benzodiazepine users Intervention = gradual taper Outcome = benzodiazepine withdrawal severity and benzodiazepine plasma concentration Excluded because the study design is not in the scope of the review
Tyrer 1985	Study design = RCT Participants = 3 benzodiazepine-dependent users

(*Continued*)

	Intervention = psychological treatment Excluded because the intervention is not in the scope of the review
Voderholzer 2001	Study design = RCT Participants = male subjects who did not meet any DSM-IV substance dependence criteria Excluded because the selection of participants is not in the scope of the review
Vorma 2002	Study design = RCT Participants = 76 patients meet DSM-III-R criteria for benzodiazepine dependence but could meet other substance abuse or dependence criteria Intervention = gradual benzodiazepine taper combined with cognitive-behavioural therapy or standard withdrawal treatment Outcome = benzodiazepine abstinence or decrease in the dosage during the trial period of up to 12 months' duration Excluded because participants selection and intervention are not in the scope of the review
Vorma 2003	Study design = RCT Participants = benzodiazepine dependent user with concurrent additional substance dependence were not included Exclusion because of inclusion bias
Voshaar	Study design = RCT Participants = 180 subjects attempting to discontinue benzodiazepine use Intervention = tapering-off and cognitive-behavioral therapy Excluded because the interventions are not in the scope of the review

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. CENTRAL search strategy

1.(SUBSTANCE-RELATED DISORDERS):MESH
2.(benzodiazepine*) NEAR (addict* or misuse* or depend* or addict*)
3.#1 or #2
4.BENZODIAZEPINE:MESH
5.benzodiazepine*
6.ANTI-ANXIETY AGENTS:MESH
7.Antidepressive agents:MESH
8.Anticonvulsants:MESH
9.(long near/3 benzodiazepine*)
10.(short near/3 benzodiazepine*)
11.Serotonin Agonists:MESH
12.Adrenergic beta-Antagonists:MESH
13.#4 or#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
14.#3 and #13

Appendix 2. MEDLINE search strategy

1.exp substance-related disorders/
2.exp Substance withdrawal syndrome/
3.(benzodiazepine adj2 dependence).ti,ab
4.1 or 2 or 3
5.exp BENZODIAZEPINE/
6.benzodiazepine.ab,ti
7. exp ANTI-ANXIETY AGENTS/
8. exp Antidepressive agents/
9. exp Anticonvulsants/
10. long half-life benzodiazepine.ti,ab.
11. short half-life benzodiazepine.ti,ab.
12. exp Serotonin Agonists/
13. exp Adrenergic beta-Antagonists/
14. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
Combined with the phases 1 & 2 of the Cochrane Sensitive Search Strategy for the identification of RCTs as published in Appendix 5b2, Cochrane Handbook for Systematic Reviews of Interventions:
15.randomized controlled trial.pt.
16.randomized controlled trials/
17.controlled clinical trial.pt.
18.random allocation/
19. double blind method/
20. single blind method/
21. 15 or 16 or 17 or 18 or 19 or 20
22. clinical trial.pt.

23. exp clinical trials/
24. (clin$ adj trial$).ab,ti.
25. ((singl$ OR doubl$ OR trebl$ OR tripl$) adj (blind$ OR mask$)).ab,ti
26. exp PLACEBOS/
27. placebo$.ab,ti
28. random$.ab,ti
29. exp Research Design/
30. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31. 21 or 30
32.14 and 31
33. limit 32 to human

Appendix 3. EMBASE search strategy

1.exp substance abuse/
2.exp drug dependence/
3.(benzodiazepine$ adj2 (abuse$ OR misuse OR dependen$ OR addict$)).ti,ab.
4.1 or 2 or 3
5.exp Benzodiazepine derivative/
6.benzodiazepine.ti,ab
7. exp antidepressants agent/
8. exp anticonvulsive agent/
9. (long half-life adj2 benzodiazepine$).ti,ab
10. (short half-life adj2 benzodiazepine$).ti,ab
11. 5 or 6 or 7 or 8 or 9 or 10
12. random$.ab,ti
13. placebo.ab,ti
14. (singl$ OR doubl$ OR trebl$ OR tripl$) AND (blind$ OR mask$)).mp
15. (cross-over$ OR crossover$).tw
16. randomized controlled trial/
17.phase-2-clinical-trial/
18.phase-3-clinical-trial/
19. double blind procedure/
20. single blind procedure/
21. crossover procedure/
22. Latin square design/
23. exp PLACEBOS/
24. multicenter study/
25. 12 or 13 or 14 or 15 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. 11 and 25
27. limit 26 to human

Appendix 4. PsycINFO search strategy

1. MM "Benzodiazepines" OR MM "Alprazolam" OR MM "Chlordiazepoxide" OR MM "Clonazepam" OR MM "Diazepam" OR MM "Flunitrazepam" OR MM "Flurazepam" OR MM "Lorazepam" OR MM "Midazolam" OR MM "Nitrazepam" OR MM "Oxazepam"
2. MM "Benzodiazepine Agonists" or MM "Benzodiazepine Antagonists"
3. MM "Drug Withdrawal"
4. MM "Alcohol Withdrawal" OR MM "Nicotine Withdrawal"
5. 1 and 2
6. 5 and 3
7. 6 not 4

Appendix 5. CINAHL search strategy

1.exp "Substance Use Disorders"/
2.exp Substance Withdrawal Syndrome/
3.((benzodiazepine$) adj2 (abuse or dependen$)).ti,ab
4.1 OR 2 OR 3
5.exp Antianxiety Agents, Benzodiazepine/
6.benzodiazepine.ti,ab
7.exp Anticonvulsants/
8.exp Antidepressive agent/
9.5 OR 6 OR 7 OR 8
10. 4 AND 9
11.exp Clinical trials/
12. randomi$.tw.
13. clini$.tw.
14. trial$.tw.
15. (clin$ adj2 trial$).tw.
16. (singl$ OR doubl$ OR tripl$ OR trebl$).mp. AND (mask$ or blind$).tw.
17. crossover.tw.
18. allocate$.tw.
19. assign$.tw.
20. (random$ adj2 (allocate$ or assign$)).tw.
21. exp Random Assignment/
22. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. 10 and 22

Appendix 6. Toxibase search strategy

BENZODIAZEPINE and DRUG DEPENDENCE and PHARMACOTHERAPY and AMBULATORY CARE.

Appendix 7. Assessment of the methodological quality

Allocation concealment:
(A) Adequate allocation concealment, central randomisation (e.g. allocation by a central office unaware of subject characteristics), on-site computer system combined with allocations kept in a locked unreadable; computer file that can be accessed only after the characteristics of an enrolled participant have been entered or other description that contained elements convincing of concealment.
(B) Unclear allocation concealment: when the authors either did not report an allocation concealment approach at all or report an approach that did not fall in the category A or C.
(C) Inadequate allocation concealment: alternation or reference to case numbers, dates of birth, day of the week. Any procedure that is entirely transparent before allocation, such as an open list of random numbers or other description that contained elements convincing of not concealment.
Performance bias: Blinding of those providing and receiving the intervention
(A) Double blind
(B) Single blind (blinding of participants)
(C) Unclear
(D) no blinding
Attrition Bias:
(A) Loss to follow up completely recorded
(B) Loss to follow up incompletely recorded
(C) Unclear or not done
Detection bias:
Blinding of the outcome assessor
A) Blind to treatment allocation at outcome assessment
B) Not blind to treatment allocation at outcome assessment
C) Unclear
Intention to treat analysis
A) Intention to treat analysis performed
B) Intention to treat analysis not performed
C) Unclear

WHAT'S NEW

Last assessed as up-to-date: 10 May 2006.

26 March 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 2, 2005

Review first published: Issue 3, 2006

11 May 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Two authors independently screened the titles and abstracts of all publications, obtained by the search strategy. Two authors independently assessed for inclusion. In doubtful or controversial cases, the authors discussed all identified discrepancies and reached consensus on all items. If consensus was not reached, we referred to the senior author to solve the problem.

DECLARATIONS OF INTEREST

None

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INDEX TERMS

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MeSH check words

Humans