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

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This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in The Cochrane Library 2008, Issue 3

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# Table of Contents

- Header ......................................................... 1
- Abstract ...................................................... 1
- Plain Language Summary ...................................... 2
- Background .................................................... 2
- Objectives .................................................... 3
- Methods ....................................................... 3
- Results ....................................................... 4
- Discussion .................................................... 7
- Authors' Conclusions ......................................... 8
- Acknowledgements ........................................... 8
- References .................................................... 8
- Characteristics of Studies ................................... 10
- Data and Analyses ............................................ 20
- Appendices .................................................... 20
- What's New .................................................... 23
- History ....................................................... 23
- Contributions of Authors .................................... 24
- Declarations of Interest ..................................... 24
- Sources of Support ........................................... 24
- Index Terms ................................................... 24
Pharmacological interventions for benzodiazepine mono-dependence management in outpatient settings

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Editorial group: Cochrane Drugs and Alcohol Group.
Publication status and date: Edited (no change to conclusions), published in Issue 3, 2008.
Review content assessed as up-to-date: 10 May 2006.

Citation: Denis C, Fatseas M, Lavie E, Auriacombe M. Pharmacological interventions for benzodiazepine mono-dependence management in outpatient settings. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD005194. DOI: 10.1002/14651858.CD005194.pub2.

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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 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 benzodiazepine 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, serotonergic 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 searched.
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 2003; 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 benzodiazepine 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 (Hällström 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 (Hällström 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; Hällström 1988).

Two studies used antidepressant: tricyclic antidepressant and serotonergic 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 (Hällström 1988) were marked A. The control of detection bias in Hällströmi'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 (Hällström 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; Hällström 1988). Hällström 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 desmethyl-diazepam 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).

Tyer 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 given a tranquilizer (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 absent 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 patients under propanolol were significantly lower than participants who did not receive propanolol (P < 0.005). 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.

Tyer 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 score 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 to 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 with 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**

**References to studies included in this review**

Cantopher 1990 *(published data only)*


Hallström 1988 *(published data only)*


Lader 1987 *(published data only)*


Lemoine 1997 *(published data only)*


Murphy 1991 *(published data only)*


Schweizer 1991 *(published data only)*


Schweizer 1995 *(published data only)*


Vorma 2002 [published data only]

Vorma 2003 [published data only]

Voshaar [published data only]

References to studies awaiting assessment

Rickels 1999 [published data only]

Saul [published data only]

Additional references

Bleich 2002

Busto 1986

de Wet 2004

DSM-IV 1994

Kan 1997

Kan 1998

Lader 1991

Lennane 1991

Martin 1982

Moher 1995

Petursson 1981

Rickels 1983

Rickels 1988

Salzman 1991

Winokur 1980

Woods 1992

∗ Indicates the major publication for the study
### Characteristics of included studies [ordered by study ID]

**Cantopher 1990**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomized controlled trial. Participants were randomly assigned between two conditions. Blindness: patient, investigator and pharmacist all remained blind to treatment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>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.</td>
</tr>
<tr>
<td>Interventions</td>
<td>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.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>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.</td>
</tr>
</tbody>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

**Hallström 1988**

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

<table>
<thead>
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<th>Item</th>
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<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

**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)

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Notes</td>
<td>Drop-outs: 8/13 buspirone group, 5/11 placebo group.</td>
</tr>
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</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
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<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
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</table>

Lemoine 1997

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomized controlled trial. Participants were randomly assigned to 6 groups. Blindness: during all the trial. Double-blind, double-placebo. Multicenter study.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>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.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Withdrawal: 28 days, follow-up: 88 days. 6 groups: Group A: abrupt lorazepam withdrawal + hydroxyzine 50 mg/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.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Scales: Hamilton Anxiety Rating Scale, Zung Anxiety self-assessment scale, Benzodiazepine Withdrawal Symptom Questionnaire, Spiegel Sleep scale, Global Clinic Assessment scale.</td>
</tr>
<tr>
<td>Notes</td>
<td>Analysis sample: n = 139 (15 protocol violation); Drop-outs: 36/139.</td>
</tr>
</tbody>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
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<tbody>
<tr>
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<td>Yes</td>
<td>A - Adequate</td>
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</table>
### Murphy 1991

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomized controlled trial. Participants were randomly assigned to three groups.</th>
</tr>
</thead>
</table>
| 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 included in the trial changed to one of the three different benzodiazepines: 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

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<th>Item</th>
<th>Authors' judgement</th>
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<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
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</tbody>
</table>

### 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 benzodiazepine 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 Withdrawal Checklist. |
Schweizer 1991  
(Continued)

Notes

Risk of bias

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<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
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<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

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

Notes

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
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<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

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.
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

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<tr>
<th>Item</th>
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<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

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

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<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Design</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Excluded Reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nathan 1986</td>
<td>Review</td>
<td></td>
<td></td>
<td></td>
<td>Not a study but a review of studies</td>
</tr>
<tr>
<td>Rickels 1990</td>
<td>RCT</td>
<td>57 benzodiazepine users for at least 12 months</td>
<td>Abrupt discontinuation of benzodiazepine</td>
<td>Withdrawal syndrome after abruptly discontinuing short half-life or long half-life benzodiazepines.</td>
<td>Benzodiazepine dependence or abuse criteria failed and the outcome was not in the scope of the review</td>
</tr>
<tr>
<td>Romach 1998</td>
<td>RCT</td>
<td>108 subjects using regularly for at least 3 months alprazolam or lorazepam</td>
<td>Ondansetron (5-HT3 antagonist)</td>
<td>Severity of withdrawal symptoms or level of anxiety</td>
<td>Selection of participants and the outcome are not in the scope of the review</td>
</tr>
<tr>
<td>Sanchez-Craig 1987</td>
<td>RCT</td>
<td>42 benzodiazepine users seeking treatment</td>
<td>Cognitive-behavioral treatment</td>
<td></td>
<td>Intervention is not in the scope of the review</td>
</tr>
<tr>
<td>Saxon 1997</td>
<td>Single-blind</td>
<td>10 benzodiazepine-dependent subjects and 10 controls</td>
<td>Reaction to placebo during benzodiazepine withdrawal with flumazenil</td>
<td>Gender-related differences of benzodiazepine withdrawal symptoms</td>
<td>Outcome is not in the scope of the review</td>
</tr>
<tr>
<td>Saxon 1997b</td>
<td>RCT</td>
<td>10 patients treated for benzodiazepine dependency and 10 controls</td>
<td>Flumazenil different dosage</td>
<td>Assessment of withdrawal symptoms</td>
<td>Outcome is not in the scope of the review</td>
</tr>
<tr>
<td>Schweizer 1986</td>
<td>Non-randomized</td>
<td>15 patients from a larger study of benzodiazepine withdrawal</td>
<td>Buspirone</td>
<td>Assessment of anxiety</td>
<td>Randomization failed</td>
</tr>
<tr>
<td>Schweizer 1990</td>
<td>Non-randomized</td>
<td>63 benzodiazepine users</td>
<td>Gradual taper</td>
<td>Benzodiazepine withdrawal severity and benzodiazepine plasma concentration</td>
<td>Study design is not in the scope of the review</td>
</tr>
<tr>
<td>Tyrer 1985</td>
<td>RCT</td>
<td>3 benzodiazepine-dependent users</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Study design</td>
<td>Participants</td>
<td>Intervention</td>
<td>Outcome</td>
<td>Exclusion Remarks</td>
</tr>
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<td>--------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Voderholzer 2001</td>
<td>RCT</td>
<td>Male subjects who did not meet any DSM-IV substance dependence criteria</td>
<td>Psychological treatment</td>
<td>Excluded because the intervention is not in the scope of the review</td>
<td></td>
</tr>
<tr>
<td>Vorma 2002</td>
<td>RCT</td>
<td>76 patients meet DSM-III-R criteria for benzodiazepine dependence but could meet other substance abuse or dependence criteria</td>
<td>Gradual benzodiazepine taper combined with cognitive-behavioural therapy or standard withdrawal treatment</td>
<td>Benzodiazepine abstinence or decrease in the dosage during the trial period of up to 12 months’ duration</td>
<td>Excluded because participants selection and intervention are not in the scope of the review</td>
</tr>
<tr>
<td>Vorma 2003</td>
<td>RCT</td>
<td>Benzodiazepine dependent user with concurrent additional substance dependence were not included</td>
<td>Tapering-off and cognitive-behavioral therapy</td>
<td></td>
<td>Exclusion because of inclusion bias</td>
</tr>
<tr>
<td>Voshaar</td>
<td>RCT</td>
<td>180 subjects attempting to discontinue benzodiazepine use</td>
<td>Tapering-off and cognitive-behavioral therapy</td>
<td></td>
<td>Excluded because the interventions are not in the scope of the review</td>
</tr>
</tbody>
</table>
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. OR 6 OR 7 OR 8
10. 4 AND 9
11. exp Clinical trials/
12. randomi$.tw.
13. clin$.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

SOURCES OF SUPPORT

Internal sources

• No sources of support supplied

External sources

• EDAP Project (Evidence for Drugs and Alcohol Policy) sponsored by the European Community- Directorate Public Health (Grant Agreement SPC.2002454), Not specified.

INDEX TERMS

Medical Subject Headings (MeSH)

*Ambulatory Care; *Benzodiazepines; Analgesics, Non-Narcotic [*therapeutic use]; Carbamazepine [*therapeutic use]; Randomized Controlled Trials as Topic; Substance-Related Disorders [*drug therapy]

MeSH check words

Humans