Strategies for discontinuing long-term benzodiazepine use: meta-analysis

CRD summary
This review assessed different strategies for discontinuing long-term benzodiazepine use. The authors concluded that stepped care (minimal intervention followed by systematic discontinuation alone) is effective in discontinuing long-term use. This conclusion was not derived directly from the data presented in the paper, and it excludes some information on effective strategies that include medication. It should therefore be viewed with caution.

Authors’ objectives
To determine the efficacy of different benzodiazepine discontinuation strategies.

Searching
PubMed and PsycINFO (both from inception to September 2004) and the Cochrane Library (December 2004) were searched; the search terms were reported. The references of all relevant articles were also checked.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with at least 5 participants were eligible for inclusion.

Specific interventions included in the review
Benzodiazepine discontinuation or discontinuation augmentation studies were included. Studies evaluating the efficacy of benzodiazepine treatment for a fixed period were excluded. The interventions were categorised as minimal intervention (simple interventions applicable to large groups such as an advisory letter or group meeting) or systematic discontinuation (treatment programmes guided by a physician or psychologist), and were sub-categorised into systematic discontinuation alone or discontinuation with either medication or psychotherapy. The majority of benzodiazepine discontinuation studies were of systematic discontinuation alone, whereas the majority of the discontinuation augmentation studies were of systematic discontinuation with medication. Both fixed and abrupt steps to taper benzodiazepine use were used. Full details of treatment arms (including medication) and other study characteristics, as well as the results of the individual included studies, were provided in a supplemental table.

Participants included in the review
Studies of individuals with long-term benzodiazepine use were included (long-term benzodiazepine use was defined as daily use for at least 3 months). Where reported, the mean duration of use ranged from 3.5 to 19.1 years. The studies were conducted in a variety of settings: primary care, psychiatric clinics, addiction clinics and homes for the elderly. The majority of the included participants did not come from an in-patient setting.

Outcomes assessed in the review
Studies in which the outcomes of discontinuation were presented separately for each treatment arm were eligible for inclusion. The primary outcome presented in the included studies was the success rate.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected papers for inclusion in the review. Any discrepancies were resolved by discussion.

Assessment of study quality
Two reviewers independently assessed the quality of the included studies using the Amsterdam-Maastricht consensus list, which evaluates studies against a number of validity, descriptive and statistical criteria. A maximum score of 19 could be obtained (17 for psychotherapeutic augmentation studies).
Data extraction

Two reviewers independently extracted the data from the included studies. Interventions were categorised by each reviewer, and any disagreements were resolved by discussion. Dosages in diazepine equivalents were calculated where possible. Where insufficient information was presented, dosages were categorised as low (within therapeutic range or less than 15 mg), high (above therapeutic range or more than 30 mg), or medium (within and above therapeutic range or 15 to 30 mg). Odds ratios (ORs) and corresponding confidence intervals (CIs) were calculated for each study.

Methods of synthesis

How were the studies combined?
The studies were combined in a meta-analysis using fixed-effect methods; a random-effects method was used where statistical heterogeneity was found. Summary estimates for success rates were presented as ORs with 95% CIs, grouped by intervention type and comparator, and further sub-grouped by drug for studies which included medication in the intervention.

How were differences between studies investigated?
The authors indicated that statistical heterogeneity was assessed but did not report how it was evaluated.

Results of the review

Twenty-nine RCTs, providing 34 data sets, were included in the review (n=2,398 in total): 3 minimal intervention (n=526), 1 systematic discontinuation alone (n=84), 5 systematic discontinuation with psychotherapy (n=342) and 25 systematic discontinuation with medication (n=1,261).

The quality of the included studies was deemed to be moderate to excellent: the total scores ranged from 8 to 17.

Benzodiazepine discontinuation strategies.

A significantly higher discontinuation success rate was found in those receiving minimal intervention compared with usual care (OR 2.8, 95% CI: 1.6, 5.1), based on 3 studies (n=526). No statistical heterogeneity was found.

One study, which compared systematic discontinuation alone with usual care (n=84), found a significantly higher discontinuation success rate in those receiving systematic discontinuation (OR 6.1, 95% CI: 2.0, 18.6).

Benzodiazepine discontinuation augmentation strategies.

A higher success rate was found for systematic discontinuation with psychotherapy compared with systematic discontinuation alone (OR 1.8, 95% CI: 1.1, 2.9), based on 5 studies (n=342). Statistically significant between-study heterogeneity was present.

Systematic discontinuation with medication (21 studies, 25 data sets, n=1,261).

Significantly higher discontinuation success rates were found in patients receiving systematic discontinuation plus imipramine (OR 3.1, 95% CI: 1.1, 9.4, p=0.03), while higher success rates of borderline significance were found in patients receiving systematic discontinuation plus carbamazepine (OR 3.5, 95% CI: 0.9, 16.7, p=0.06), compared with those receiving systematic discontinuation alone; based on 3 studies (n=94) and 2 studies (n=75), respectively. No statistical heterogeneity was found. No significant difference in the discontinuation rates was found between groups for systematic discontinuation augmented with trazodone, propranolol or buspirone compared with systematic discontinuation alone. Statistical heterogeneity was found in the studies evaluating augmentation with propranolol and buspirone. The authors reported that this heterogeneity was explained by differences in the tapering procedure (propranolol only), transfer to long-acting agent, baseline benzodiazepine dosage, type of benzodiazepine, and the diagnosis of included patients (propranolol and buspirone).

Eleven studies evaluated systematic discontinuation with a different single pharmacological agent (aldipidem, progesterone, dothiepin, hydroxyzine, melatonin, Asp Mg, valproate, homeogene 46, sedative PC, paroxetine and
Melatonin, valproate and flumazenil were all found to demonstrate higher benzodiazepine discontinuation success rates in comparison with the control groups.

**Authors' conclusions**
Evidence for the efficacy of stepped care (minimal intervention followed by systematic discontinuation alone) in the discontinuation of long-term benzodiazepine use was shown.

**CRD commentary**
The review question was supported by clear inclusion and exclusion criteria. A number of electronic databases were searched, although the authors did not say whether the search strategy was restricted by language. There was no apparent attempt to locate unpublished material and no assessment of publication bias was reported. The procedures undertaken for the selection of studies, data extraction and quality assessment were likely to have minimised reviewer error or bias. The studies were quantitatively combined using generally appropriate methods, and statistical heterogeneity was assessed. Where found, some attempts were made to investigate the source of this heterogeneity. The authors acknowledged that generalisability of the findings may be limited due to heterogeneity of the included studies in some comparison groups. This raises questions about the usefulness of generating pooled estimates for these comparison groups. Details of the participant were limited, making it difficult to fully interpret the generalisability of the results.

While the results from the review suggest that minimal intervention might be promising, the interventions evaluated do not appear to include a direct evaluation of a stepped care approach (minimal intervention followed by systematic discontinuation alone), but rather a comparison of minimal intervention alone with usual care in a set of 3 studies and a comparison of systematic discontinuation with usual care in a separate fourth study. The authors' conclusion should, therefore, be interpreted with caution since it does not appear to derive directly from the data presented. In addition, the conclusion makes no mention of the effectiveness of strategies which include medication, some of which achieved comparable significance.

**Implications of the review for practice and research**
Practice: The authors stated that the minimal intervention strategy followed by systematic discontinuation alone is effective for cases resistant to treatment in primary care.

Research: The authors stated the need for a direct comparison of different taper schedules in RCTs. In addition, future research should rigorously evaluate stepped care programmes and promising augmentation strategies.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.