TITLE: Discontinuation Strategies for Patients with Long-Term Benzodiazepine Use: Clinical Evidence and Guidelines

DATE: 23 January 2015

RESEARCH QUESTIONS

1. What is the clinical evidence regarding strategies to safely and effectively discontinue adult patients from long-term benzodiazepine use?

2. What are the evidence-based guidelines regarding discontinuation of long-term benzodiazepine use?

KEY FINDINGS

Three systematic reviews and meta-analyses, two randomized controlled trials, and five non-randomized studies were identified regarding strategies to safely and effectively discontinue adult patients from long-term benzodiazepine use.

METHODS

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2015, Issue 1), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses and guidelines. The results of a focused search (with main concepts appearing in title or major subject heading) were also included. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and January 19, 2015. Internet links were provided, where available.

SELECTION CRITERIA

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.
### Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Adults in a community (outpatient) setting with long-term (&gt; 3 months) benzodiazepine use (frequent and infrequent users)</th>
</tr>
</thead>
</table>
| Intervention                              | • Interventions to promote the discontinuation of benzodiazepine use  
• Interventions to manage withdrawal symptoms when discontinuing benzodiazepines |
| Comparator                                | • Abrupt benzodiazepine withdrawal alone  
• Gradual benzodiazepine withdrawal alone  
• No comparator                             |
| Outcomes                                  | • Clinical effectiveness  
• Evidence-based guidelines |
| Study Designs                              | Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, evidence-based guidelines |

### RESULTS

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, and evidence-based guidelines.

Three systematic reviews and meta-analyses, two randomized controlled trials, and five non-randomized studies were identified regarding strategies to safely and effectively discontinue adult patients from long-term benzodiazepine use. No relevant health technology assessments or evidence-based guidelines were identified.

Additional references of potential interest are provided in the appendix.

#### Health Technology Assessments
No literature identified.

#### Systematic Reviews and Meta-analyses


   BACKGROUND: The use of benzodiazepines has been advised against in older people, but prevalence rates remain high. AIMS: To review the evidence for interventions aimed at reducing benzodiazepine use in older people. METHOD: We conducted a systematic review, assessment of risk of bias and meta-analyses of randomised controlled trials of benzodiazepine withdrawal and prescribing interventions. RESULTS: Ten withdrawal and eight prescribing studies met the inclusion criteria. At post-intervention, significantly higher odds of not using benzodiazepines were found with supervised withdrawal with psychotherapy (odds ratio (OR) = 5.06, 95% CI 2.68-9.57, P<0.00001) and withdrawal with prescribing interventions (OR = 1.43, 95% CI 1.02-2.02,
P = 0.04) in comparison with the control interventions treatment as usual (TAU), education placebo, withdrawal with or without drug placebo, or psychotherapy alone. Significantly higher odds of not using benzodiazepines were also found for multifaceted prescribing interventions (OR = 1.37, 95% CI 1.10-1.72, P = 0.006) in comparison with control interventions (TAU and prescribing placebo). CONCLUSIONS: Supervised benzodiazepine withdrawal augmented with psychotherapy should be considered in older people, although pragmatic reasons may necessitate consideration of other strategies such as medication review.


INTRODUCTION: Benzodiazepines (BZDs) are potentially inappropriate for older adults, yet their use persists. Patients and providers may hesitate to discontinue BZDs due to concerns for withdrawal or relapse. We reviewed the literature for BZD reduction protocols to examine common elements, safety and efficacy. A framework is proposed for clinicians to address BZD reduction challenges. AREAS COVERED: Following a systematic literature review, this analysis included 28 studies of older out-patients tapering chronic BZDs. Populations included insomnia, depression and anxiety. Protocols included taper alone (32%), taper plus cognitive behavioral therapy (32%) and taper plus medication substitution (36%). Success rates were favorable for all modalities (mean 60%, median 67%, range 25-85%) and independent of dose or duration of use. Common schedules included a 25% dose reduction over 1-2 weeks until drug-free. Withdrawal symptoms included mainly mild psychological and somatic concerns. No serious safety events were reported. EXPERT OPINION: BZD reduction protocols among older adults are feasible and successful. Given unique cognitive and functional abilities and comorbidities of older adults, a patient-centered approach to reduction is needed. Our framework guides clinicians in planning and persisting with BZD reduction, while our checklist addresses tailored tapers. Monitoring and support is emphasized, and taper modifications are proposed for struggling patients.


BACKGROUND: Long-term use of benzodiazepines (BZDs) is common. Not only is such use ineffective, but it also has several risks in addition to dependence, and remains a significant problem among the older population. AIM: To systematically review randomised controlled trials that evaluate the effectiveness of minimal interventions to reduce the long-term use of BZDs in primary care. DESIGN AND SETTING: Systematic review and meta-analysis of randomised controlled trials in UK general practices. METHOD: Cochrane Central, MEDLINE, and Embase (1967-2010) were searched for trials of minimal interventions (such as a single letter or one consultation from a GP) for patients in primary care with long-term (>3 months) BZD use. Pooled risk differences were calculated with 95% confidence intervals. RESULTS: From 646 potentially relevant abstracts, three studies (615 patients) met all the inclusion
criteria. The pooled risk ratio showed a significant reduction/cessation in BZD consumption in the minimal intervention groups compared to usual care (risk ratio [RR] = 2.04, 95% confidence interval [CI] = 1.5 to 2.8, [corrected] P<0.001; RR = 2.4, 95% CI = 1.3 to 4.3, P = 0.008) respectively. Two studies also reported a significant proportional reduction in consumption of BZD from baseline to 6 months in intervention groups compared to the control group. The secondary outcome of general health status was measured in two studies; both showed a significant improvement in the intervention group. CONCLUSION: A brief intervention in the form of either a letter or a single consultation by GPs, for long-term users of BZD, is an effective and efficient strategy to decrease or stop their medication, without causing adverse consequences.

Randomized Controlled Trials


BACKGROUND: Benzodiazepines are extensively used in primary care, but their long-term use is associated with adverse health outcomes and dependence. AIMS: To analyse the efficacy of two structured interventions in primary care to enable patients to discontinue long-term benzodiazepine use. METHOD: A multicentre three-arm cluster randomised controlled trial was conducted, with randomisation at general practitioner level (trial registration ISRCTN13024375). A total of 532 patients taking benzodiazepines for at least 6 months participated. After all patients were included, general practitioners were randomly allocated (1:1:1) to usual care, a structured intervention with follow-up visits (SIF) or a structured intervention with written instructions (SIW). The primary end-point was the last month self-declared benzodiazepine discontinuation confirmed by prescription claims at 12 months. RESULTS: At 12 months, 76 of 168 (45%) patients in the SIW group and 86 of 191 (45%) in the SIF group had discontinued benzodiazepine use compared with 26 of 173 (15%) in the control group. After adjusting by cluster, the relative risks for benzodiazepine discontinuation were 3.01 (95% CI 2.03-4.46, P<0.0001) in the SIW and 3.00 (95% CI 2.04-4.40, P<0.0001) in the SIF group. The most frequently reported withdrawal symptoms were insomnia, anxiety and irritability. CONCLUSIONS: Both interventions led to significant reductions in long-term benzodiazepine use in patients without severe comorbidity. A structured intervention with a written individualised stepped-dose reduction is less time-consuming and as effective in primary care as a more complex intervention involving follow-up visits.


Despite its acute efficacy for the treatment of panic disorder, benzodiazepines (BZs) are associated with a withdrawal syndrome that closely mimics anxiety sensations, leading to difficulty with treatment discontinuation and often disorder relapse. An exposure-based cognitive-behavioral treatment for BZ discontinuation, Panic Control Treatment for BZ
Discontinuation (CBT) targets the fear of these sensations and has demonstrated efficacy in preventing disorder relapse and facilitating successful BZ discontinuation among patients with panic disorder. In this randomized controlled trial, CBT was compared to taper alone and a taper plus a relaxation condition to control for the effect of therapist contact and support among 47 patients with panic disorder seeking taper from BZs. Based on the primary outcome of successful discontinuation of BZ use, results indicate that adjunctive CBT provided additive benefits above both taper alone and taper plus relaxation, with consistently medium and large effect sizes over time that reached significance at the six month follow-up evaluation. The efficacy of CBT relative to either of the other taper conditions reflected very large and significant effect sizes at that time. These findings suggest that CBT provides specific efficacy for the successful discontinuation from BZs, even when controlling for therapist contact and relaxation training.

Non-Randomized Studies


PURPOSE: To evaluate the effectiveness and tolerability of pregabalin in the management of the discontinuation of benzodiazepines in long-term users. SUBJECTS AND METHODS: We performed a 12-week, prospective, uncontrolled, non-interventional, and observational study in patients aged 18 years old or above, who met DSM-IV-TR criteria for benzodiazepine dependence without other major psychiatry disorder. Evaluations included the Benzodiazepine Withdrawal Symptom Questionnaire, the Hamilton Anxiety Rating Scale, the Clinical Global Impression Scale, and the Sheehan Disability Scale. A urine drug screen for benzodiazepines was performed at baseline and every 4 weeks thereafter. The primary effectiveness variable was success rate, defined as achievement of benzodiazepine-free status at week 12 according to the urine drug screen. RESULTS AND DISCUSSION: The mean dose at week 12 was 315 (+/-166) mg/day. The success rate of the benzodiazepine taper in the primary efficacy population (n=282) was 52% (95% confidence interval [CI], 46-58). Success rates for women and men were 58% (95% CI, 49-67) and 46% (95% CI, 38-55), respectively. The success rates did not differ according to either the benzodiazepine of abuse or the presence of other substance use disorders. Significant and clinically relevant improvements were observed in withdrawal and anxiety symptoms, as well as in patients' functioning. At week 12, tolerability was rated as good or excellent by 90% and 83% of the clinicians and patients, respectively. CONCLUSION: Our results suggest that pregabalin is an efficacious and well-tolerated adjunctive treatment for benzodiazepine withdrawal.


Benzodiazepine dependence is a common problem. However, there is limited data on safe and effective detoxification protocols for benzodiazepine-dependent patients. We...
reviewed the medical records of 310 patients treated with a 3-day fixed-dose phenobarbital taper for benzodiazepine dependence over a 5-year period between 2004 and 2009. We recorded the incidence of seizures, falls, delirium, and emergency department (ED) visits or readmission to our institution within 30 days as markers for safety; we also recorded how many patients had doses held because of sedation. The taper was well tolerated, although one quarter of the patients had at least one dose held because of sedation. There were no seizures, falls, or injuries reported. Six percent had a readmission, and 7% had an ED visit at our institution within 30 days of discharge, but only 3 patients required readmission for withdrawal symptoms. Overall, this protocol appears to be safe and effective.


BACKGROUND: Several interventions aiming at discontinuation of long-term benzodiazepine use have been proven effective in the short term. However, data on the persistence of discontinuation are lacking. OBJECTIVES: To assess 10-year follow-up status in patients who succeeded in stopping benzodiazepine use after a discontinuation letter from the patient’s own GP. To identify determinants of successful discontinuation on the long term. METHODS: Follow-up data of patients who participated in a large prospective, controlled stepped care intervention programme among long-term benzodiazepine users in primary care. RESULTS: At 10-year follow-up, the percentage of benzodiazepine abstinence was 58.8%. Non-abstinent patients used lower doses of benzodiazepine. Being abstinent at 21 months after the intervention predicted abstinence at 10-year follow-up. CONCLUSIONS: Ten years after a minimal intervention to decrease long-term benzodiazepine use, the majority of patients who were able to discontinue benzodiazepine use initially, does not use benzodiazepines at 10-year follow-up. Patients who did not succeed in maintaining abstinence from benzodiazepines appear to use lower or average dosages.


AIM: To evaluate the effectiveness of pregabalin as a tapering therapy on the subjective sleep quality of patients who underwent a benzodiazepine withdrawal program in routine medical practice. METHODS: Secondary analysis of a 12-week prospective, open noncontrolled study carried out in patients who met DSM-IV-TR criteria for benzodiazepine dependence. Sleep was evaluated with the Medical Outcomes Study Sleep Scale (MOS Sleep Scale). RESULTS: 282 patients were included in the analysis. Mean (+/-SD) pregabalin dose was 315 +/- 166 mg/day at the end of the trial. We observed a significant and clinically relevant improvement in sleep outcomes at the endpoint, with a total score reduction from 55.8 +/- 18.9 to 25.1 +/- 18.0 at week 12 (i.e. a 55% reduction). Similar findings were apparent using the six dimensions of the MOS Sleep Scale. Moderate correlations were observed between the MOS Sleep summary index and sleep domains, and there were improvements in anxiety symptoms.
and disease severity. CONCLUSIONS: These findings suggest that pregabalin may improve subjective sleep quality in patients who underwent a benzodiazepine withdrawal program. This effect appears to be partly independent of improvements in symptoms of anxiety or withdrawal. However, controlled studies are needed to establish the magnitude of the effect of pregabalin.


Benzodiazepine withdrawal has been associated with hostile and aggressive behavior. The benzodiazepine antagonist flumazenil has reduced, increased or not affected hostility and aggression in animal and human studies. In the present study we analyzed data collected in a placebo-controlled study of the effects of the benzodiazepine antagonist flumazenil in patients previously treated for benzodiazepine dependency, and healthy controls. The aim was to analyze the effects of flumazenil on hostility and aggression. Ten patients and 10 controls received, on two separate occasions, cumulative doses of flumazenil (0.05, 0.1, 0.25, 0.5 and 1mg at 15min intervals) or placebo. Withdrawal symptoms were rated after each injection. Patients had been free from benzodiazepines for 47 (4-266) weeks on the first injection. A three-way interaction (groupxtreatmentxdose) was found, and was explained by: 1) patients rating aggression and hostility higher than controls at all times during placebo, while 2) during the flumazenil provocation i) the initial significant difference between patients and controls was no longer significant above the 0.5mg dose, and ii) patients rated aggression and hostility significantly lower above the 0.5mg dose compared to base-line. The results suggest that self-rated aggression and hostility in patients treated for benzodiazepine dependency was reduced by the partial benzodiazepine agonist flumazenil.

Guidelines and Recommendations
No literature identified.
APPENDIX – FURTHER INFORMATION:

Clinical Practice Guidelines – Uncertain Methodology

   See: Withdrawal, page 3

Review Articles

   See: Effectiveness of withdrawal interventions, page 7


   INTRODUCTION: Both alcohol and benzodiazepine dependence (AD, BD) are severe and chronic conditions with devastating physical and mental health effects. The relative scarcity and controversial evidential status of available pharmacological interventions for the treatment of patients’ acute withdrawal syndrome and/or relapse prevention call for the clinical investigation of novel safe and efficacious agents. AREAS COVERED: We review published studies of pregabalin as monotherapy in the treatment of AD and BD in more than 450 patients. Available evidence includes four RCTs, two in AD with active comparator drugs (naltrexone, tiapride, and lorazepam) and one placebo-controlled, and one placebo-controlled in BD. We also review other available studies on pregabalin’s potential to reduce benzodiazepine consumption, its side effects, especially cognitive, as well as extant reports on its liability for abuse. EXPERT OPINION: Available evidence suggests that monotherapy with pregabalin, within the dosage range of 150 - 600 mg/d, is a promising "novel" option for the safe and efficacious relapse prevention of both AD and BD. However, its efficacy as monotherapy in the acute treatment of AD withdrawal syndrome is still controversial. Clinicians should be cautious in prescribing pregabalin to patients with a history of multiple substance recreational use, and monitor its effects on cognition at dosages above 450 mg/d. Further, well-designed clinical research is still needed for the eventual consolidation of pregabalin’s place in the treatment of AD and BD.