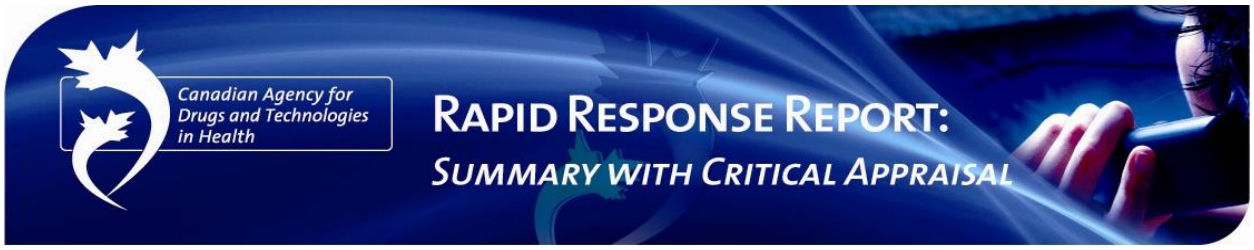

TITLE: Discontinuation Strategies for Patients with Long-term Benzodiazepine Use: A Review of Clinical Evidence and Guidelines

DATE: 29 July 2015

CONTEXT AND POLICY ISSUES

Benzodiazepines (BZD) are a widely used class of drugs prescribed extensively to treat anxiety and sleep disorders, and used as adjuvant therapy in depression, pain management, and as muscle relaxants.[1-3] They are popular for their rapid onset of action and clinical efficacy, as well as low toxicity and decreased risk of suicide.[1] In Canada, approximately 3% to 9% of adults use a BZD, although the proportion is higher among elderly, as approximately 25% of non-institutionalized seniors in Quebec used a BZD in 2010.[3,4] Although it is recommended that treatment with BZD be limited to only a few weeks, the prevalence of long-term use for months, years, or even decades remains widespread in Canada.[5]

Benzodiazepine use has both short and long-term drawbacks. Short-term, untoward effects include sleepiness that may interfere with daily function, increased risk of motor vehicle accidents, falls that may be accompanied by fractures especially in the elderly, and potential for abuse or misuse.[1] Long-term drawbacks include tolerance and physical dependence, cognitive and memory impairment leading to withdrawal or rebound symptoms following treatment discontinuation.[1,2] Withdrawal symptoms may include anxiety, depression, hypersensitivity to sensory stimuli, perceptual distortions and depersonalizations. Rebound psychiatric symptoms may be greater in severity than pre-treatment levels and may persist for extended periods.[1,2] Therefore, a carefully planned and supervised discontinuation protocol is warranted to minimize adverse events of withdrawal.

This review aims to summarize current evidence-based discontinuation strategies and clinical guidelines for long-term adult BZD users to validate policy changes and promote best practices amongst clinicians.

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

Simple strategies such as letters from clinicians, self-help information, or a single consultation with a GP aimed at advising patients about the risk of long-term BZD use and the benefits of discontinuation can be effective interventions to promote discontinuation. Gradual dose-tapering is an effective discontinuation intervention, more so when supported with psychotherapy, follow-up visits, or written instructions to manage withdrawal symptoms. Melatonin used as adjuvant therapy to dose-tapering protocols did not produce additional benefit in terms of discontinuation rates.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including Medline, PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and June 24, 2015.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults in a community (out-patient) setting with long term (>3 months) benzodiazepine use (frequent and infrequent users)
Intervention	• Interventions to promote the discontinuation of benzodiazepine use • Interventions to manage withdrawal symptoms when discontinuing benzodiazepines
Comparator	Standard approaches (e.g. abrupt or gradual withdrawal alone)
Outcomes	• Effectiveness of interventions to discontinue benzodiazepines; effectiveness of withdrawal symptom management • Guidelines on BZD discontinuation
Study Designs	HTA/ systematic review/meta-analysis, randomized controlled trials, non-randomized studies, clinical guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2010. Guidelines from countries other than Canada, USA, UK and Australia were excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using the AMSTAR measurement tool[6] to assess the methodological quality of systematic reviews, and randomized and non-randomized studies were critically appraised using the Black and Down checklist[7] for measuring study quality. Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study are summarized and presented in Appendix 3.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 503 citations were identified in the literature search. Following screening of titles and abstracts, 465 citations were excluded and 38 potentially relevant reports from the electronic search were retrieved for full-text review. Three potentially relevant publications were retrieved from the grey literature search. Of the 41 potentially relevant articles, 30 publications were excluded for various reasons, while 11 publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Appendix 2 provides further details of individual study characteristics

Study Design

Three systematic reviews,[8-10] five randomized controlled trials (RCTs),[2,11-14] and three non-randomized trials.[15-17] were identified. Two of the RCTs had cluster designs.[2,12]

Country of Origin

The systematic reviews were published by authors originating from the United Kingdom (UK),[9] USA,[8] and Australia.[10] The systematic review from the UK included 16 RCTs from Argentina, Australia, Canada, the UK and seven other European countries. The systematic review from Australia was based on 3 RCTs all from the UK. The systematic review from the USA involved 28 studies of heterogeneous designs (information on primary study designs was not provided) and the countries of origin were not stated. The RCTs included in this review were published by authors originating from Canada,[12] Denmark,[14] Finland,[11] Spain,[2] and the USA.[13] The non-randomized studies included in this review were published by authors originating from The Netherlands,[17] and Spain.[15,16]

Patient Population

Participants in all the included studies[2,8-17] were adults with mean ages ranging from 41 to 79 years who received BZD for the treatment of insomnia, anxiety, panic disorders, or psychiatric disorders.

Interventions and Comparators

A combination of BZD dose-tapering with other psychotherapy measures (including cognitive behavioral therapy [CBT]) patient education, written self-help instructions, and pharmacotherapy was the most common intervention in the included studies.

One systematic review[9] included a combination of gradual BZD withdrawal (dose-tapering) with either a psychotherapy or prescribing intervention (e.g. medication review, consultation or education), compared with each component alone, or with either treatment as usual, education with/without placebo, or tapering with drug support. Another systematic review[8] compared a tapering intervention alone with a combination of tapering plus either CBT or medication substitution. A third systematic review[10] compared minimal intervention (e.g. letter from a clinician, self-help information, or short consultation with a general practitioner [GP]) with continuation of usual doses.

One RCT[14] compared melatonin with placebo, each in combination with slow tapering of BZD doses. Another RCT[11] compared melatonin with placebo, each in combination with psychosocial support. The two cluster RCTs[2,12] compared the combination of patient education and BZD dose-tapering with usual care. In one of the cluster RCTs,[2] the intervention also included a fortnightly follow-up visit or written instructions. In another RCT,[13] CBT was compared with either BZD tapering alone or the combination of tapering plus relaxation.

One non-randomized study[16] compared pregabalin alone with pregabalin plus other drugs (details of the other drugs was not provided). Another non-randomized observational study[17] evaluated the effect of GP letters for the discontinuation of BZD. In a third non-randomized study,[15] patients undergoing a gradual reduction of BZD dose had the option of pharmacological support with either hydroxyzine or valerian when needed.

Outcomes

The most common reported primary outcomes were complete discontinuation or reduction of BZD use at the end of the study. One of the systematic reviews[9] assessed the odds of not using BZD over short (0.5 to 3 months) and long-term (12 months) periods. Adverse events (mainly withdrawal symptoms) were also commonly reported.

Summary of Critical Appraisal

Appendix 3 provides further details of the critical appraisal of individual studies.

All the included studies had well-defined objectives and generally well-described inclusion and exclusion criteria. Two systematic reviews[9,10] were based on comprehensive literature searches However, a more limited literature search was performed in the other systematic review as only one electronic database was searched.[8]. In each systematic review, multiple reviewers independently screened and selected studies for inclusion, and extracted data. In two

systematic reviews,[9,10] multiple reviewers independently evaluated the quality of included studies.

Baseline characteristics were generally similar for the study arms of all included RCTs and analysis of outcomes were based on intention-to-treat populations. Four RCTs[2,11,12,14] were adequately powered to detect relevant differences in outcomes between treatment groups. However, one RCT[13] did not conduct a sample size calculation. Therefore, with a relatively small number (n=47) of participants split among three treatment groups, it was uncertain whether the study was sufficiently powered to detect significant differences in outcomes. One RCT[14] involved participants with diagnoses of schizophrenia or bipolar disorders, and another RCT[12] restricted participation to patients 65 years of age or older. A third RCT[13] involved only patients who were seeking treatment for BZD discontinuation and were therefore likely to be more motivated than the general BZD user population. A fourth RCT[2] included only patients who were free from severe medical condition and excluded patients with major depressive or anxiety disorder, or currently receiving psychiatric treatment. Thus, the generalizability of findings from these studies is unknown. One of the RCTs did not use a standardized BZD tapering strategy and the details of the individualized schedules were not provided. Therefore, the comparative effectiveness of the individual withdrawal strategies is indeterminate.

The non-randomized studies[15-17] have higher potential for bias due to the absence of randomization to limit differences at baseline to chance, and to permit differences in outcome to the effects of the intervention alone. One of the non-randomized studies[16] had a high proportion (47%) of patients with multiple substance abuse disorders which could confound the reported outcomes. Another study[17] analyzed long-term (10 years) follow-up data of a discontinuation intervention with limited patient information for the period in-between. Therefore, the possibility of the reported outcomes resulting from influences other than the intervention cannot be ruled out. Although adjunctive pharmacotherapy with hydroxyzine or valerian was permitted on an as needed basis in another non-randomized study[15], there were no data or analyses to assess the contribution of adjuvant intervention to the reported outcomes. Thus, it is unknown whether the reported findings were due to dose-tapering, which was the intervention being assessed, or whether the support of the pharmacotherapy had an impact on successful outcomes.

Summary of Findings

A total of 11 studies (three systematic reviews, five RCTs, and three non-randomized studies) met the inclusion criteria of this report and were included.[2,8-17] All the studies assessed interventions for BZD discontinuation among adult long-term users. No evidence-based clinical guidelines on BZD discontinuation were identified. Most of the studies (9 of 11) involved BZD dose-tapering as standalone or as background to other interventions. Two RCTs[11,14] compared the effect of melatonin to placebo when used as adjunct therapy, while one observational study[16] evaluated pregabalin as adjunct to BZD dose-tapering. The remaining studies had non-pharmacologic interventions. Further details of findings of individual studies have been provided in Appendix 4.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

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

One systematic review[10] and one observational study[17] reported that simple interventions such as discontinuation letters from clinicians, self-help information and a single consultation with a GP to discuss risk of long-term BZD use and the benefit of discontinuation are effective intervention strategies to discontinues BZD use in adult long-term users. The systematic review[10] found that patients who received such interventions were twice as likely to completely withdraw from BZD use (relative risk [RR] = 2.3; 95% CI: 1.3 to 4.2, *P* = 0.008) or reduce BZD use (RR = 2.04; 95% CI: 1.5 to 2.8, *P*<0.001). The observational study[17] found that abstinence was sustained among 58.8% patient who discontinued BZD use following discontinuation letters from their GP.

Two systematic reviews[8,9] and one RCT[13] assessed the effect of CBT for long-term BZD use. One systematic review[9] found that the odds of discontinuing BZD use was highest among patients treated with supervised withdrawal and psychotherapy compared with usual care, or other prescribing interventions (e.g. medication review, consultation or education) (odd ratios [OR] = 5.06; 95% CI: 2.68, 9.57; *P* <0.00001, number need to treat [NNT] = 3). The other systematic review[8] also found that a combination of CBT and BZD dose-tapering resulted in higher BZD discontinuation rates (65% to 85%) compared with dose-tapering alone (25% to 54%). The RCT[13] reported that at 6-month follow-up, CBT had a higher BZD discontinuation rate (62.5%) than individualized relaxation therapy (12.5%) and BZD dose-tapering (26.7%) interventions.

Two cluster RCTs[2,12] assessed adjunctive educational interventions. One RCT [12] reporting that the likelihood of achieving discontinuation of long-term BZD was significantly increased using patient empowerment education in combination with dose-tapering compared with usual care (OR 8.3 [95% CI: 3.3, 20.9]). In the other RCT,[2] a higher discontinuation rate was reported for either structured individualized education with dose-tapering and follow-up visits (45%), or structured individualized education with dose-tapering and written instructions every two weeks (45%),when compared with usual care (15%) among long-term BZD users.

Three included RCTs[11,14,16] assessed the effectiveness of pharmacotherapy for discontinuation of long-term BZD use. One RCT[14] found no significant difference in BZD discontinuation rates between prolonged-release melatonin and placebo among long-term BZD users undergoing slow dose-tapering after 24 weeks of treatment (38.1% versus 47.7%, respectively; OR = 0.64; 95% CI: 0.26, 1.56). Another RCT[11] reported that controlled-release melatonin (CRM) with dose tapering, resulted in a higher discontinuation rate than placebo with dose tapering (85% versus 67%) among long-term BZD users after one month. After 6 months, 30.4% of participants in the CRM group and 43.5% in the placebo group remained non-users of BZD. The difference was not statistically significant in either analysis. A prospective, uncontrolled, observational study[16] reported that 52% (95% CI: 46%, 58%) of patients who used pregabalin as adjunctive treatment to BZD dose-tapering achieved a BZD-free status after 12weeks.

One before-after pseudo-experimental study[15] assessing gradual reduction of BZD dose with the option of pharmacological support with hydroxyzine (25 mg/day) or valerian when needed, reported that 80.4% of the patients had discontinued BZD by the end of the 6-month intervention, and 64% maintained abstinence at one year.

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

The literature search for this review did not find any literature on evidence-based guidelines regarding discontinuation of long-term BZD use.

Limitations

Benzodiazepine dose-tapering was the most common intervention in the included studies. However, in many cases the details about the number of dose reductions and time schedules were not provided. Further details of the limitations of the individual included studies have been provided in Appendix 3.

A major limitation of two of the systematic reviews[9,10] is the small number of included primary studies. A total of 16 RCTs were included in one systematic review,[9] however a variety of interventions were considered resulting in a relatively small number of studies per intervention (ranging from 1 to 4 studies). Another systematic review[8] had 28 primary studies of heterogeneous designs, and the methodological quality of each were not assessed.

In one included RCT,[14] participants were patients diagnosed with schizophrenia or bipolar disorder, which make the generalizability of its findings in other patient populations uncertain. Another RCT[11] limited participation to patients who used one particular BZD (temazepam) or two other drugs (zolpidem or zopiclone) which are technically not BZDs but have similar short-term effects. Therefore, it is uncertain whether the reported results from this RCT[11] will be reproducible using other BZDs. In one RCT,[13] there was no indication that a sample size calculation was performed, and included a relatively small sample size (n=47) across three treatment arms. Thus, it is uncertain if it was sufficiently powered to detect statistically significant differences in clinical outcomes. One cluster RCT[12] had only 30 (18%) eligible community pharmacies and 303 (11%) patients agreeing to participate. Reasons for declining participation included lack of interest, competing priorities, inability to obtain consent from owners, and inadequate staff. Although there does not seem to be selection bias, the low level of participation raises concern about how adequately representative the findings are of the communities under study. In the other cluster RCT,[2] only 34% of eligible patients participated. Therefore, it is unknown whether the study participants and, by extension, the reported outcomes in these studies[2,12] were sufficiently representative populations.

For the non-randomized studies,[15-17] the absence of randomization increased the potential for bias due to differences in potential confounders in study participants; and the possibility of variable influences besides the studied interventions to contribute significantly to the reported outcomes cannot be ruled out. One study[16] included an intervention consisting of a combination of pregabalin and other drugs, but failed to provide further details regarding the dose or type of drugs that were included. Thus, the interpretation of comparative effectiveness from this study is limited.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Evidence from studies included in this review indicate that gradual tapering of doses is the most common BZD discontinuation strategy for adult patients with long-term BZD use. Minimal interventions such as a discontinuation letter from a clinician or consultation with a GP explaining both the risk of long-term BZD use and the advantages of discontinuation were effective in initiating the intervention process and achieving better BZD discontinuation outcomes when compared with usual care. A combination of psychotherapy interventions (including CBT) with tapering protocols resulted in superior discontinuation outcomes when compared to either individual strategy alone, and compared with alternative prescribing interventions such as medication review, consultation or education, and relaxation therapy. Coupling a dose-tapering intervention with patient education also improved the odds of BZD discontinuation significantly when compared with dose-tapering alone. Furthermore, dose-tapering with structured education and follow-up visits, or written self-help instructions, achieved higher BZD discontinuation rates than usual care. In terms of pharmacologic interventions, adding melatonin to a tapering protocol did not achieve higher BZD discontinuation than adding placebo. Also, pregabalin used adjunctively to a BZD dose-tapering intervention resulted in a significant proportion of BZD-free patients. However, it is difficult to make a firm conclusion from this outcome since it was reported by a non-comparative observational study.

In general, evidence from the included studies indicates that a combination of dose-tapering and non-pharmacological interventions such as CBT, self-help instructions, and patient education produced better BZD discontinuation outcomes compared with stand-alone strategies. However, melatonin as an adjunct to tapering did not have added value, and evidence from adding pregabalin to a tapering protocol was inconclusive.

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REFERENCES

1. Vikander B, Koechling UM, Borg S, Tonne U, Hiltunen AJ. Benzodiazepine tapering: a prospective study. Nord J Psychiatry. 2010 Aug;64(4):273-82.

2. Vicens C, Bejarano F, Sempere E, Mateu C, Fiol F, Socias I, et al. Comparative efficacy of two interventions to discontinue long-term benzodiazepine use: cluster randomised controlled trial in primary care. Br J Psychiatry [Internet]. 2014 Jun [cited 2015 Jul 10];204(6):471-9. Available from: http://bjp.rcpsych.org/content/bjprcpsych/204/6/471.full.pdf

3. Effective interventions to manage symptoms of benzodiazepine withdrawal in seniors [Internet].Canadian Centre on Substance Abuse; 2014 Nov. [cited 2015 Jul 22]. (Rapid review). Available from: http://www.ccsa.ca/Resource%20Library/CCSA-Benzodiazepine-Withdrawal-Seniors-Rapid-Review-2014-en.pdf

4. Voyer P, Preville M, Cohen D, Berbiche D, Beland SG. The prevalence of benzodiazepine dependence among community-dwelling older adult users in Quebec according to typical and atypical criteria. Can J Aging. 2010 Jun;29(2):205-13.

5. Neutel CI. The epidemiology of long-term benzodiazepine use. Int Rev Psychiatry. 2005 Jun;17(3):189-97.

6. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol [Internet]. 2007;7:10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf

7. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health [Internet]. 1998 Jun;52(6):377-84. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf

8. Paquin AM, Zimmerman K, Rudolph JL. Risk versus risk: a review of benzodiazepine reduction in older adults. Expert Opin Drug Saf. 2014 Jul;13(7):919-34.

9. Gould RL, Coulson MC, Patel N, Highton-Williamson E, Howard RJ. Interventions for reducing benzodiazepine use in older people: meta-analysis of randomised controlled trials. Br J Psychiatry [Internet]. 2014 Feb [cited 2015 Jul 10];204(2):98-107. Available from: http://bjp.rcpsych.org/content/bjprcpsych/204/2/98.full.pdf

10. Mugunthan K, McGuire T, Glasziou P. Minimal interventions to decrease long-term use of benzodiazepines in primary care: a systematic review and meta-analysis. Br J Gen Pract [Internet]. 2011 Sep [cited 2015 Jul 3];61(590):e573-e578. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3162180

11. Lahteenmaki R, Puustinen J, Vahlberg T, Lyles A, Neuvonen PJ, Partinen M, et al. Melatonin for sedative withdrawal in older patients with primary insomnia: a randomized double-blind placebo-controlled trial. Br J Clin Pharmacol. 2014 Jun;77(6):975-85.

12. Tannenbaum C, Martin P, Tamblyn R, Benedetti A, Ahmed S. Reduction of inappropriate benzodiazepine prescriptions among older adults through direct patient education: the EMPOWER cluster randomized trial. JAMA Intern Med. 2014 Jun;174(6):890-8.

13. Otto MW, McHugh RK, Simon NM, Farach FJ, Worthington JJ, Pollack MH. Efficacy of CBT for benzodiazepine discontinuation in patients with panic disorder: further evaluation. Behav Res Ther [Internet]. 2010 Aug [cited 2015 Jul 15];48(8):720-7. Available from: http://www.thblack.com/links/RSD/BehavResTher2010_48_720_UseOfPsychotherapy.pdf

14. Baandrup L, Lindschou J, Winkel P, Gluud C, Glenthoj BY. Prolonged-release melatonin versus placebo for benzodiazepine discontinuation in patients with schizophrenia or bipolar disorder: A randomised, placebo-controlled, blinded trial. World J Biol Psychiatry. 2015 Jun 18;1-11.

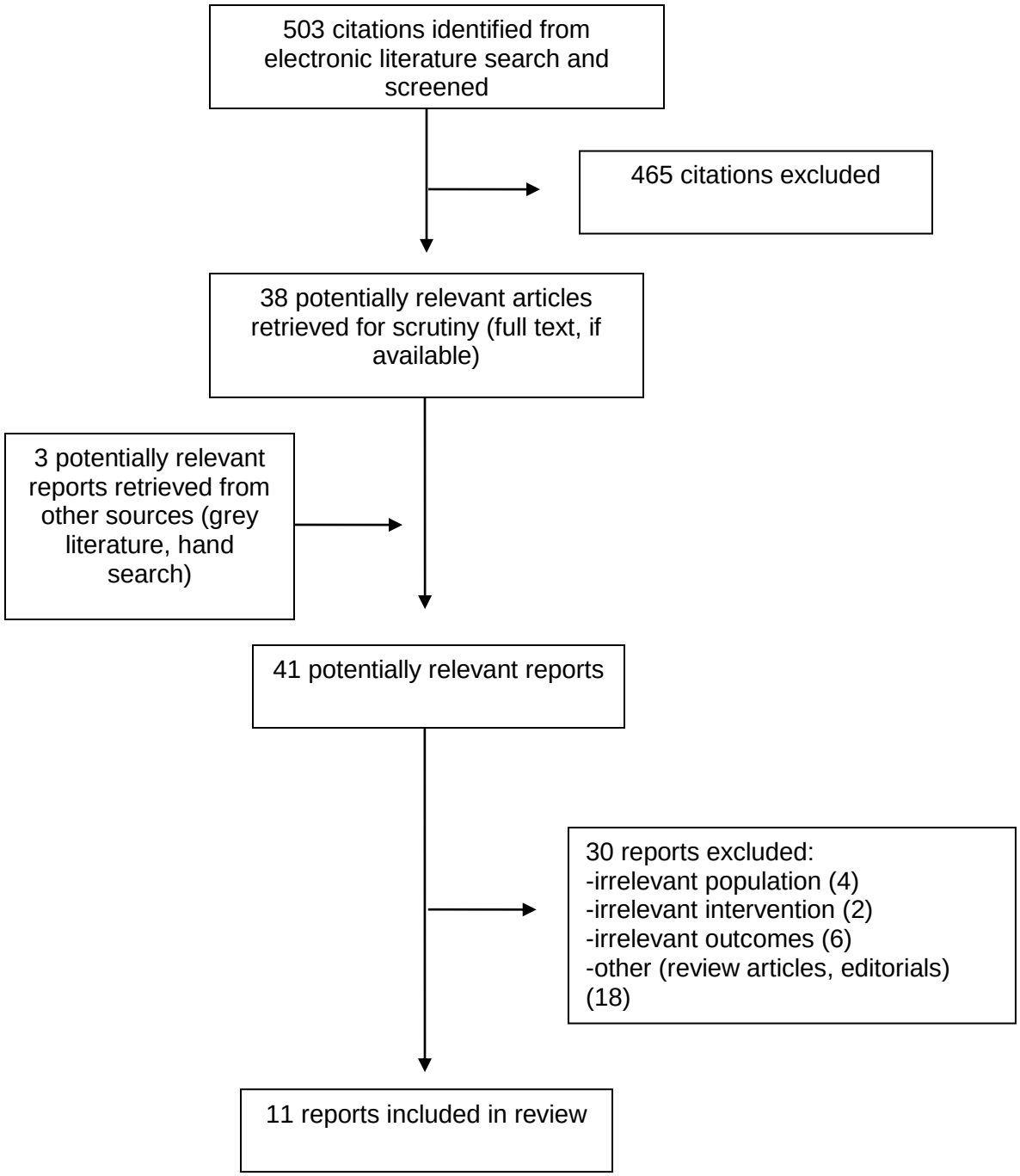
15. Lopez-Peig C, Mundet X, Casabella B, del Val JL, Lacasta D, Diogene E. Analysis of benzodiazepine withdrawal program managed by primary care nurses in Spain. BMC Res Notes [Internet]. 2012 [cited 2015 Jul 3];5:684. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3598901

16. Bobes J, Rubio G, Teran A, Cervera G, Lopez-Gomez V, Vilardaga I, et al. Pregabalin for the discontinuation of long-term benzodiazepines use: an assessment of its effectiveness in daily clinical practice. Eur Psychiatry. 2012 May;27(4):301-7.

17. de Gier NA, Gorgels WJ, Lucassen PL, Oude VR, Mulder J, Zitman F. Discontinuation of long-term benzodiazepine use: 10-year follow-up. Fam Pract. 2011 Jun;28(3):253-9.

18. Iyer S, Naganathan V, McLachlan AJ, Le Couteur DG. Medication withdrawal trials in people aged 65 years and older: a systematic review. Drugs Aging. 2008;25(12):1021-31.

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Gouls, 2014,[9] UK	16 RCTs	Older patients (mean age in years 74.1 for withdrawal and 79.4 for prescribing interventions)	Withdrawal with psychotherapy or prescribing [a]	TAU, education placebo, withdrawal with/without drug placebo, psychotherapy alone	Odds of not using BZD at patients or prescription level post-intervention, short-term (0.5 to 3 months), and long-term (12 months).
Paquin, 2014,[8] USA	Variety (n = 28; details not specified)	Outpatients with mean age ranging from 40 to 77 years, who had insomnia, depression, anxiety/panic disorder, and general population	Taper alone, taper plus CBT, or medication substitution.	Comparison of outcomes among studies	Proportion of BZD-free patients relative to number of patients undergoing protocol. Adverse events following withdrawal (length of follow up not provided)
Mugunthan, 2011,[10] Australia	RCTs (n = 3)	Adult patients (mean age was 60 years) in primary care with long-term (>3months) BZD use.	Minimal interventions (e.g. letter, self-help information, or short consultation with a GP)	Continuation of usual dose, active intervention	Reduction or cessation of BZD use. Changes in general health status at 6 months follow-up

BZD = benzodiazepine; CBT = cognitive behavioral therapy; GP = general practitioner; NR = not reported; RCT = randomized controlled trial; UK = United Kingdom = United States of America

[a] Prescribing interventions included medication review, consultation or education.

Table A2: Characteristics of Included Clinical Studies					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
Baandrup, 2015,[14] Denmark	DB placebo-controlled RCT	Adult patients (n = 86, mean [SD] age 47.9 [8.7] in PRM and 49.4 [12.3] in placebo) diagnosed with schizophrenia or bipolar disorder who are chronic users of BZD (mean duration of BZD treatment at enrolment was 10 years)	PRM plus slow tapering of BZD doses	Placebo plus slow tapering of BZD doses	Reduction of BZD use at 24 weeks as measured by mean daily dosage. Pattern of BZD reduction over time. BZD cessation proportion at 24 weeks BZD withdrawal symptoms
Lahteenmaki 2014,[11] Finland	DB placebo-controlled RCT	Adults (n = 92; age ≥ 55 years) with primary insomnia who are long term users of BZDs as hypnotics.	CRM combined with psychosocial Support.	Placebo combined with psychosocial Support.	Total BZD withdrawal at 1 month verified by BZD plasma concentration. Reduction in BZD use at 1 month, and persistence of abstinence at 6 months.
Tannenbaum, 2014,[12] Canada	Cluster RCT (randomized 15 community pharmacies each to intervention or control)	Community-dwelling adults (n=303, mean (SD) age 75 (6.3) years, range 65 to 95 years) who are long-term users of BZD.	Patient empowerment educational material on deprescribing describing risk of BZD use and a stepwise tapering protocol	Usual care	BZD therapy discontinuation at 6 months after randomization, ascertained by pharmacy medication renewal profiles
Vicens, 2014,[2] Spain	Cluster RCT (involving GPs in 21 primary care centers in three regions)	Adult patients (n=532; median age 64 years, IQR 55 to 72) taking BZDs for ≥ 6 months	A structured educational intervention with gradual dose-tapering backed up by fortnightly follow-up visits or supported by written instruction.	Usual care	Self-declared BZD discontinuation or consumption of fewer than four doses in the previous month confirmed by prescription claims at 12 months. Secondary: BZD discontinuation at

Table A2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
					6 months and safety at 6- and 12 months.
Otto 2010,[13] USA	RCT	Panic disorder patients (n =47) treated with alprazolam or clonazepam for a minimum of 6 months and who were seeking taper from BZD	CBT	BZD dose taper alone, and taper + IRT	Successful discontinuation of BZD use and maintenance of BZB-free functioning during the six months follow-up period
Bobes, 2012,[16] Spain	Prospective observational study	Adult patients (n = 282, mean age 41 years) who met DSM-IV-TR criteria for BZD dependence without other major psychiatry disorder. Mean duration of BZD Dependence was 2 years	Pregabalin at mean doses ranging from 127 (±79) mg/ day at initiation to 315 (±116) mg/day at week 12	Pregabalin in combination with other drugs	Achievement of BZD-free status at week 12 according to the urine drug screen. Severity of withdrawal symptoms, anxiety, symptoms, and functional impairment
de Dier, 2011,[17] The Netherlands	Prospective observational study [a] (a 10-year follow-up)	Adult patients (mean age 60.1 years old) who discontinued long-term (>3 months) use of BZDs. Mean duration of BZD use before intervention was 116.7 months	Discontinuation letter from patients' GP	None	BZD abstinence, determinants of BZD abstinence.
Lopez-Peig, 2012[15] Spain	Before-after pseudo-experimental study	Patients (n=51, mean age 7-.4 years) who had used BZD daily for more than 6 months	Gradual reduction of BZD dose (25% every 2 to 4 weeks) with the option of pharmacological support with hydroxyzine 25 mg per day or valerian when needed.	None	Cessation of BZD use after 6 and 12 months as verbally reported by the patients and confirmed by prescription data

BZD = benzodiazepine; CBT = cognitive behavioral therapy; CRM = controlled-release melatonin; DB = double-blind; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, 4th edition with text revision; GP = general practitioner; IRT = individual relaxation treatment; PRM = prolonged-release melatonin; RCT = randomized controlled trial; RSB = randomized single-blind; TAU = treatment as usual; USA = United States of America

a The study assessed the 10-year follow-up status in patients who succeeded in stopping BZD use after a discontinuation letter from their GP.

APPENDIX 3: Critical Appraisal of Included Publications

Table A3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using the AMSTAR checklist[6]

Strengths	Limitations
Gouls, 2014,[9]	
• A comprehensive literature search of multiple electronic databases was conducted, and studies were also identified from citations in studies, reviews and meta-analyses of interventions that aimed to reduce BZD use in adults of any age. • Inclusion and exclusion criteria were clearly described. • Three authors independently screened and selected studies for inclusion, evaluated study quality, and extracted data. Disagreements were resolved by consensus. • Studies were examined for publication, and adjustments were made where it was detected • Appropriate statistical tools were used to combine data and calculate effect estimates, and sensitivity analyses were conducted to examine the robustness of findings. • The study compared the efficacy of different types of interventions for reducing BZDs use in older people in a variety of setting. • The authors had no conflict of interest that could bias the conduct and reportage of the study.	• None of the included studies achieved adequate ratings in all areas (n=5) assessed for risk of bias, although no study was rated as inadequate or unclear in all five areas. • Generalizability of the study findings in a younger (< 60 years of age) population is uncertain.
Paquin, 2014,[8]	
• The study design and objectives were clearly described, and inclusion and exclusion criteria were defined. • Abstracts or titles were screened by two independent reviewers for relevance, although it was not specified how disagreements were resolved. • Characteristics of primary studies, including population size, intervention type and duration, as well as outcome measure were provided. • The authors had no interest in conflict with the subject matter or materials discussed with potential for bias.	• Literature search was conducted in only one electronic database (PubMed), and date limits for the search was not provided. Studies involving use of BZD for < 90 days were excluded, suggesting that potentially relevant studies meeting the definition of long-term as used in the protocol for this review (i.e. > 30 days), could be excluded. • Since a mean population age of >40 years old was required for a study to be eligible in the systematic review, generalizability of its finding in younger populations is unknown. • Designs of included studies were not specified and the scientific quality of the individual studies was not assessed.

Table A3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using the AMSTAR checklist[6]

Strengths	Limitations
Mugunthan, 2011,[10]	
• A comprehensive literature search was conducted, with two reviewers independently selecting and assessing the trials, rating quality of the included studies, and extracting relevant data. Disagreements were resolved through discussion with a third author. • The authors declared no competing interests	• Only a few studies (n = 3) were included in the systematic review, and although the scientific quality were reported to be assessed, the ratings were not reported. The secondary outcomes (patients' general health status) were reported on the primary study basis without pooling and without an appropriate link to the scientific quality of the studies.

BZD = benzodiazepine; CBT = cognitive behavioral therapy; RCT = randomized controlled trial; UK = United Kingdom

Table A4: Strengths and Limitations of Randomized Controlled Trials using the Downs and Black Checklist of Study Quality[7]

Strengths	Limitations
Baandrup, 2015,14	
• The objectives and main outcomes in the study were clearly defined • Inclusion and exclusion criteria were well-defined, and the characteristics of included patients as well as the nature of the interventions and control being examined were described. • Sample size calculation was done to ensure the study was adequately powered to detect statistically significant differences in outcome between the study arms. • Patients were randomly allocated to treatment groups, with participants, staff, and outcome assessors blinded to the allocated treatment. • Baseline demographic and clinical characteristics were generally similar across study groups. • Analysis was based on ITT population to retain randomization effect at baseline. For patients who left the trial early and those with missing data, the actual BZD dose at 24 weeks was collected from patient files. • The authors declared they had no interests that may be relevant to the work.	• Eligibility criterial was changed 4 to 6 months after recruitment begun, and the number of participants was increased to replace patients who left the trial early. However, baseline characteristics seemed fairly balanced across treatment groups suggesting that this change might not have introduced any significant bias. • Participants were patients diagnosed with schizophrenia or bipolar disorder. It is unknown whether or not the psychiatric co-morbidities of the patients influenced the reported outcomes. With the steady decline in the daily dosage of BZD throughout the study, it is uncertain whether a longer follow-up period than 24 weeks could have resulted in a difference between the two treatments. Furthermore, it remains unclear whether 12 weeks is a sufficient duration to evaluate relapse which is reported to occur later among patients who successfully discontinue long-term BZD use.
Lahteenmaki 2014,[11]	
• The objectives and main outcomes to be measured in the study were clearly defined, and the outcomes were reported with estimated of random variability.	• Exclusion criteria included use of a BZD other than temazepam, zopiclone or zolpidem. Given that zopiclone and zolpidem are BZD-like but not BZDs, it is

Table A4: Strengths and Limitations of Randomized Controlled Trials using the Downs and Black Checklist of Study Quality[7]

Strengths	Limitations
• Inclusion and exclusion criteria were well-defined, and the characteristics of included patients as well as the nature of the interventions and control being examined were described. • Sample size calculation was performed to ensure the study was adequately powered to detect statistically significant differences in outcomes between the study arms. • Patients were randomly allocated to treatment groups, with participants, staff, and outcome assessors blinded to the allocated treatment. • Baseline demographic and clinical characteristics were generally similar across study groups. • Primary endpoint analysis was based on ITT population to maintain the randomization effect at baseline, although per protocol analysis were also done. • High study completion rates with low dropout rates and balance across treatment arms suggest that reported outcomes were unlikely to be significantly impacted by missing data • The authors declared they have no interests that may be relevant to the work.	unknown whether the outcomes are reflective of populations that use other BZDs • Withdrawal schedules were individualized following agreement between study physicians and participant. While this may be ideal for actual practice, it implies that details of the strategy varied from patient to patient making it difficult to assess the effectiveness of a particular schedule.
Tannenbaum, 2014,[12]	
• Baseline characteristics of participants were generally balanced across study groups. • Participants were screened and enrolled prior to randomization. This ensures that eligible participants are representative of the cluster to foster unbiased estimates of the effect of intervention from analysis. • Analysis was based on the ITT population ensuring that the randomization effect at baseline was maintained to reduce bias. • Participants, physicians, pharmacist, and evaluators were blinded to outcome assessment.	• Of 165 community pharmacies requested to participate in the study, only 30 (18%) participated and only 303 (11%) of the 2716 potentially eligible patients participated in the study. • The study was restricted to seniors (≥ 65 years). Therefore, generalizability to a younger population is unknown. • The BZD tapering protocol was not described. Therefore, it is impossible to assess or replicate.
Vicens, 2014,[2]	
• The objectives and main outcomes to be measured in the study were clearly defined, and the outcomes were reported with estimated of random variability.	• Patients and GPs could not be masked to their random allocation because of the study procedures. However, this was not likely to result in bias since the main

Table A4: Strengths and Limitations of Randomized Controlled Trials using the Downs and Black Checklist of Study Quality[7]

Strengths	Limitations
• Inclusion and exclusion criteria were well-defined, and the characteristics of included patients as well as the nature of the interventions and control being examined were described. • Sample size calculation was performed to ensure the study was adequately powered to detect statistically significant differences in outcome between the study arms. • Patients were randomly chosen and systematically assed for eligibility by GPs, who were randomized following patient enrolment to avoid cluster heterogeneity and post-randomization selection bias. • Patients' characteristics at baseline were generally similar across study groups. • The main findings of the study including AEs were clearly reported, based on ITT population to maintain the randomization effect at baseline. • There were no GP dropouts over the course of the study, and data were not available for only 1.7% of patients based on the ITT analysis. • The authors declared they had no conflicts of interest.	outcome was externally evaluated through personal interviews by psychologists who were not involved in the study and masked to patient allocation, and the statistician and data-entry staff were also unaware of patient allocation. • The characteristics of the GPs differed in the three study groups, with those in the control group being slightly older and with less experience in BZP withdrawal than those in the intervention groups. Although all physicians received training about the interventions and controls prior to the commencement of the study, it is unknown whether these differences impacted the outcomes. • Of the eligible patients (n=1564) only 532 (34%) met the inclusion criteria and agreed to participate in the study. Most were excluded because of severe psychiatric disorders or medical illness such as dementia and epilepsy, and alcohol or drug misuse. Thus the results may not be applicable to such patients.
Otto, 2010,[13]	
• At baseline, the characteristic of participants were generally similar in terms of demographics, medication history, psychiatric comorbidity, and severity of anxiety symptoms. • To reduce potential for bias, study assessments were conducted by monitoring physicians who were blind to the treatment conditions of the patients. • Detailed description of the intervention and comparators could facilitate replication. • The authors declared they had no conflicts of interest.	• The sample size calculation was not performed. Therefore, the relatively small number of participants (n=47) in this 3-arm study raises a question about its power to detect significant differences. • Participants were recruited from patients who were seeking treatment for BZD discontinuation and were therefore likely to be very motivated and inclined towards strong adherence. It is unknown whether the findings will be generalizable in a BZD-user population without a similar level of motivation. • Exclusion criteria were broad, eliminating many patients with medication and medical history who are likely to use BZD therapy. Thus the generalizability of the study in the broad population of long-term BZD users is uncertain.

Table A4: Strengths and Limitations of Randomized Controlled Trials using the Downs and Black Checklist of Study Quality[7]	
Strengths	**Limitations**
	• CBT and relaxation interventions were administered by highly trained post-doctoral clinical therapists in a specialty clinic of a large teaching hospital with experience in the administration of PCT and relaxation interventions. The extent to which these strategies can be successfully implemented in other settings and without such specialized staff is unknown. • Results of BZD discontinuation have uncertain reliability because they were self-reported without biological verification of BZD levels.

AE = adverse event; BZD = benzodiazepine; CBT = cognitive behavioral therapy; GP = general practitioner; ITT = intention to treat; RCT = randomized controlled trial;

Table A5: Strengths and Limitations of Non-Randomized Trials using the Downs and Black Checklist of Study Quality[7]	
Strengths	**Limitations**
Bobes, 2012,[16]	
• Overall, the study was reported in detail, with clearly described objectives, inclusion and exclusion criteria, interventions to be used, and the main outcomes to be measured. • The main findings of the study were clearly described with estimates of variability for outcomes, where applicable. • Efficacy and tolerability analyses were based on all patients who were prescribed pregabalin and met the inclusion criteria, with missing data imputed using LOCF. Thus potential for bias in reported outcomes due to variability in study population from baseline was minimized. • Outcomes were measured with well-known validated tools and methods that are reliable, and appropriate statistical analysis were applied.	• Study population was not randomized to the interventions, and there was no indication that the study interventions were blinded to patients or those who measured the main outcomes of the interventions. The study included high proportion of patients with multiple substance use disorder, and it was not stated if they were undergoing simultaneous detoxification for different disorders. Thus, it is unclear if the reported result were influence by concomitant medication use other than the interventions under study. • There was no information about compliance with the interventions. Thus one is unable to determine whether the reported outcomes were influenced by differences in compliance with the interventions. • Unclear whether twelve weeks is sufficient to conclusively evaluate the success of a detoxification program, given the high incidence of replace among patience with drug dependency. • The study was funded by a pharmaceutical company of which two of the investigators are fulltime employees; and a third

Table A5: Strengths and Limitations of Non-Randomized Trials using the Downs and Black Checklist of Study Quality[7]

Strengths	Limitations
	investigator works for the organization contracted by the pharmaceutical company to conduct the study.
de Dier, 2011,[17]	
• Study was based on electronic medical files of GPs instead of patient reported information which is very subjective to patients' memory, • Rigorous sensitivity analyses to identify determinants of abstinence were performed • The authors declared no conflict of interests	• It is difficult conclude whether the GP discontinuation letters solely accounted for the BZD abstinence among patient 10 years after the intervention. • Of the 446 patients who discontinued BZD use after discontinuation letters, data were found for only 194 patients, of whom 163 had complete follow-up data. Those with incomplete data had either died or moved. The effect of the large proportion of missing data on the reported findings is uncertain.
Lopez-Peig, 2012[15]	
• Objectives of the study and the details of the intervention were clearly defined • Inclusion and exclusion criteria were defined. • A sample size determination was performed and the number of participants was large enough to detect clinically relevant minimum BZD cessation rates, and statistically significant results.	• Pharmacotherapy (with hydroxyzine or valerian) was an important part of the discontinuation intervention recommended as adjuvant for patients who needed it. However there was no report of how many participants used it; neither were there any analysis to evaluate its contribution to the outcomes.

BZD = benzodiazepine; CBT = cognitive behavioral therapy; GP = general practitioner; LOCF = last observation carried forward; PRM = prolonged-release melatonin

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A6: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
Gould, 2014,[9]	
• Compared with control interventions, the odds of not using BZDs after intervention were highest with supervised withdrawal with psychotherapy (OR = 5.06; 95% CI: 2.68, 9.57; *P* <0.00001, NNT = 3); followed by withdrawal with prescribing interventions (OR = 1.43; 95% CI; 1.02, 2.02; *P* =0.04, NNT = 13) and supervised withdrawal with pharmacotherapy (OR = 1.31; 95% CI; 0.68, 2.53; *P* =0.42 [not statistically significant], NNT = 20). • At 0.5 to 3 months follow-up (short-term), the odds of not using BZDs were higher with supervised withdrawal plus psychotherapy than control interventions (OR = 3.9; 95% CI; 1.94, 7.82; *P* = 0.0001, NNT = 4). • One primary study reported that the odds of not using BZD were 4.00 times higher than for the control intervention (95% CI: 0.68, 23.41, NNT= 5) at short-term follow-up. No study examined withdrawal with a prescribing intervention. • At 12 months follow-up (long-term), the odds of not using BZDs were 3 times higher for supervised withdrawal plus psychotherapy compared with control interventions (95% CI: 1.43, 6.28, *P* = 0.004, NNT= 5). No study assessed withdrawal with a prescribing intervention or supervised withdrawal with pharmacotherapy • Multifaceted [a] prescribing interventions had significantly higher odds of not using BZDs than control interventions such as TAU and prescribing placebo (OR = 1.37; 95% CI: 1.10, 1.72, *P* = 0.006), whereas single-faceted prescribing interventions were not superior than control interventions (OR = 0.87; 95% CI: 0.68 , 1.11 *P* = 0.27)	• "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."[9] page 98 • "Finally, the results of the meta-analysis imply that a multi-strategy approach incorporating both supervised withdrawal with psychotherapy and multifaceted prescribing interventions, with 'buy-in' from both prescribers and patients, … could be most beneficial for reducing benzodiazepine use in older people."[9] page 105 • Evidence reviewed here, albeit limited, suggests that a number of strategies might be beneficial in assisting older people to withdraw from benzodiazepines: first, medication review and consultation, together with provision of a withdrawal schedule and education about benzodiazepine use (for both those taking and those prescribing benzodiazepines); and second, provision of a supervised withdrawal schedule augmented with psychotherapy (mainly aimed at addressing underlying pathology). Although higher odds of not using benzodiazepines were found with the latter strategy, pragmatic reasons (such as access to psychotherapy) may mean that the former strategy is initially preferred within a stepped care approach.
Paquin, 2014,[8]	
• The overall mean success rate of BZD discontinuation was 60% (range 25 to 85%, median 67%).	• "In this systematic literature review, we found that safely stopping BZDs among older, chronic users is feasible and

Table A6: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
• For taper alone, the mean success rate was 54% (range 25% to 80%, median 54%). • For taper + CBT, success rate ranged from 67% to 85%. • For drug substitutions, success rate ranged from 45% to 79%. • Sub-analyses did not find any differences in median success rates, defined as becoming drug-free, among patients who used lower dose [b] BZD (48%) compared with those who used higher doses DEs (55%), or among patient used BZD for longer duration [c] (57%) compared with those with a shorter duration of use (61%).	frequently successful. Importantly, we did not find evidence suggestive of severe withdrawal symptoms or safety concerns, even with high BZD dose and long duration of use."[8] page 922
Mugunthan, 2011,[10]	

• The pooled results indicated
  ○ twice the reduction in BZD consumption in the intervention groups compared with the control group (RR = 2.04; 95% CI: 1.5 to 2.8, *P*<0.001).
  ○ twice the rate of cessation in the intervention groups compared with the usual care group (RR = 2.3; 95% CI: 1.3 to 4.2, *P* = 0.008).
• There was one cessation of BZD use for every 12 letters sent (i.e. NNT = 12); and additional intervention (self-help information or a short consultation with a GP) did not appear to have additional advantages over letters alone.
• Two of the three primary studies observed a 20% to 35% reduction from baseline in BZD use at 6 months in the intervention group compared with a 10% to 15% reduction in the control group.
• There was a trend towards greater mental well-being among the intervention groups, with 11% lower psychiatric morbidity (on GHQ scale) in the intervention group compared to 3% the control group in one primary study, while another primary study reported a mean increase of 5.4 in the mental sub-score of the SF-36 scale among those who reduced BZD use compared to a decline of 2.2 in those who did not.
	• "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."[10] page e573
	• "Given the problems of cognitive impairment and falls induced by BZDs and other hyposedatives, the routine and widespread use of this simple letter intervention appears warranted. While only a modest percentage of patients will reduce or cease their BZD, the minimal effort required suggests it would have a high benefit-to-effort ratio."[10] page e576

Table A6: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
Baandrup, 2015,[14]	
• An MMRM analyses found a significant decline in BZD daily dosage throughout the trial period in both intervention groups (-3.14; 95% CI: 3.89, 2.40; *P* < 0.0001) • There was no significant difference between the PRM and placebo groups with respect to BZD withdrawal symptoms over time (-0.018; 95% CI: -0.66 to 0.63; *P* = 0.96). • The mean BZD daily dosage (in DE) at 24 weeks was 8.01 mg (95% CI: 5.51, 10.5) and 5.72 mg (95% CI: 3.25, 8.19) for the PRM and placebo groups, respectively. There was no significant difference between the two groups (MD = -2.29; 95% CI: -5.72, 1.21; *P* = 0.20) • The proportion of patients who discontinued BZD use at 24 weeks was 38.1% and 47.7% in the PRM and placebo groups, respectively, with no significant difference in the odds of discontinuation between the two groups (OR = 0.64; 95% CI: 0.26, 1.56; *P* = 0.32).	• "Benzodiazepine dosage was comparably low between the groups after 24 weeks of guided gradual dose reduction. In this context, prolonged-release melatonin did not seem to further facilitate benzodiazepine discontinuation."[14] page 1
Lahteenmaki 2014,[11]	
• After a 1 month, BZD discontinuation rates were 67% (95% CI: 54, 81) and 85% (95% CI: 74, 95) in the CRM and placebo groups, respectively (*P* = 0.051), and plasma BZD concentrations decreased to at least half of the baseline level among most of those who had not discontinued use. • After 6 months, 14 (30.4%) participants in the CRM group and 20 (43.5%) in the placebo group remained non-users of BZD (*P* = 0.220, per protocol analysis). • Reduction in BZD use was similar or even more rare in the CRM than in the placebo group (*P* = 0.052 per protocol). • Although the DDD of BZD decreased significantly from baseline across both study groups, there was more BZD usage by DDD in the CRM group compared with the placebo group (COR = 2.5, 95% CI: 1.1, 5.5, *P* = 0.025). • Withdrawal symptoms did not differ between the CRM and placebo groups	"In conclusion, CRM or placebo combined with a gradual BZD withdrawal program, sleep hygiene counselling and psychosocial support can produce high short term BZD withdrawal and reduction rates and moderate long term abstinence rates in older patients. CRM 2mg does not offer an advantage over placebo for patient withdrawal from long term BZD use for treatment of primary insomnia."[11] page 983

Table A6: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
(median [IQR]: 3.6 [3, 0] vs. 3.1 [2, 8], respectively, *P* = 0.198)	
Tannenbaum, 2014,[12]	
• At 6 months, 40 (27%) participants in the intervention group discontinued BZD use compared with 7 (5%) in the control group (RD 0.23 [96% CI: 0.14, 0.32]). A total of 56 (37.8%) discontinued or reduce BZD dose in the intervention group compared with 17 (11.0%) in the control group (RD 0.27 [96% CI: 0.18, 0.37]). • The likelihood of achieving discontinuation was 8-fold higher with intervention than with control (OR 8.3 [95% CI: 3.3, 20.9) • No major adverse events requiring hospitalization occurred. However, 42% of participants who attempted tapering reported withdrawal symptoms such as rebound insomnia, or anxiety. • Multivariate analyses showed age >80 years, sex, duration of use, indication for use, dose, previous attempt to taper, and concomitant drug use did not have significant interaction effect with BZD therapy discontinuation. • Majority (72%) of participants who wanted to discontinue BZD use chose to use the tapering protocol provided by the study. • Majority (98%) of participants who completed the trial (n = 123) were satisfied with receiving medication risk information.	• "Our findings suggest that direct-to-consumer education successfully leads to discussion with physicians and/or pharmacist to stop unnecessary or harmful medication. Discontinuation or dose reduction of benzodiazepines occurred in more than one-third of the participants who received the empowerment intervention."[12] page 895 • Supplying older adults with evidence-based information that allows them to question medication overtreatment appears safe and effective and is consistent with the ABIM Choosing Wisely campaign. Without a direct-to-patient education component, promotional effort for deprescription physicians may fail or have a smaller impact. In an era of multi-morbidity, polypharmacy, and costly therapeutic competition, direct-to-consumer education is emerging as a promising strategy to stem potential overtreatment and to reduce the risk of drug harms. The value of the patient as a catalyst for driving decision to optimize health care utilization should not be underestimated.""[12] page 897
Vicens, 2014,[2]	
• At 12 months, 76 (45%) of patients in the SIW group and 86 (45%) in the SIF group had discontinued BZD use compared with 26 (15%) in the usual care group (RR [95% CI]: were 3.01 [2.03, 4.46], in the SIW and 3.00 [2.04, 4.40, in the SIF group; *P*<0.0001 in both cases) • There was no statistically significant difference in efficacy between the SIF and SIW groups (RR = 1.00, 95% CI: 0.78, 1.28, *P*= 0.984), and both groups had NNT of 4 (95% CI: 3, 5) • The discontinuation rate at 12 months was significantly greater for patients taking less than 10 mg than those taking more than 10	• "Both interventions led to significant reductions in long-term benzodiazepine use in patients without severe comorbidity. A structured intervention with a written individualized stepped-dose reduction is less time-consuming and as effective in primary care as a more complex intervention involving follow-up visits."[2] page 471 • Indeed, we found that more intensive patient follow-up was more effective in patients taking higher doses of benzodiazepines and those with higher anxiety."[2] page 478

Table A6: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
mg DE in each of the study groups (50% vs. 32% for SIF; 53.3% vs. 23.9% for SIW; and 21.2% vs. 1.8% for control). • The discontinuation rate at 12 months was greater for less anxious patients, as assessed by the HADS anxiety scale (46.7% vs. 46.9% for SIF; 54.2% vs. 26.8% for SIW; and 18.2% vs. 3.0% for control group). • The most frequently reported withdrawal symptoms were insomnia, anxiety and irritability.	
Otto, 2010,[13]	
• At the post-discontinuation visit, 56.3% of patients in the CBT group had achieved BZD-free status compared to 31.3% in the IRT group, and 40% in the dose taper alone group. • At 3-month follow-up, 43.7% of patients in CBT group maintained BDZ-free status compared to 12.5% in the IRT and 26.7% in the dose-tapering alone groups. • At 6-month follow-up, 62.5% of patients in CBT group were BDZ-free while the rates remain unchanged from 3-month follow-up for the IRT and dose-tapering alone groups (12.5% and 26.7%, respectively). • Post treatment and follow-up withdrawal distress was lower in among patients in the taper alone group who successfully discontinued compared to relative to the other groups (PWC score- mean [SD], 7.1 [8.0] vs. 17.8 [13.3] for IRT, and 14.5 [17.7] for CBT). • Logistic regression analysis found that years of BDZ use was a significant predictor ($p < 0.02$) for remaining BDZ-free, with those who had been using BZs longer having a more difficult time remaining BDZ-free at the 3- and 6-month evaluation time points.	• "In summary, the results from this randomized controlled trial support findings from previous studies suggesting that adjunctive CBT facilitates discontinuation from BZs among those with panic disorder and prevents the return of panic symptoms often seen with discontinuation." "Results suggest that CBT has a specific effect on BZ discontinuation beyond that accounted for by therapist contact alone. Given the reported high rates of unsuccessful BZ discontinuation and return of panic symptoms upon medication discontinuation, adjunctive CBT provides a particularly promising strategy for aiding with the discontinuation of BZ treatment in panic patients."[13] pages 725-6
Bobes, 2012,[16]	
• The success rate of achieving a BZD-free status determined by urine drug screening in the ITT population (n = 282) was 52% (95% CI: 46%, 58%). • Among patients who completed the 12-	"Our results suggest that pregabalin is an efficacious and well-tolerated adjunctive treatment for benzodiazepine withdrawal that improves anxiety and withdrawal symptoms and reduces the degree of disability to a

Table A6: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
week follow-up (n = 211) the success rate was 70% (95% CI: 63, 76). Success rates for women and men were 58% (95% CI: 49, 67) and 46% (95% CI: 38%, 55%), respectively. The difference was not statistically significant (*P* = 0.052). • The success rate in the pregabalin monotherapy group was 49% (95% CI: 41.0%, 56%) compared to 58% (95% CI: 48.0%, 67%) in the pregabalin plus other drugs group, but the difference was not statistically significant (*P* = 0.13). • The proportion of patients who were BZD-free at the end of the study did not differ according to the BZD of abuse, or other substance use disorders. • Withdrawal symptoms as measure by mean (SD) BWSQ score, decreased progressively and significantly from 11 (7.5) at week 1 to 4.4 (5.5) week 12 • The mean change from baseline in anxiety symptoms, as measured by HARS total score was 17, with 50% (95% CI: 44%, 56%) of patient showing remission of anxiety symptoms at the endpoint. • At week 12, the somatic and psychic factors showed significant improvements on the HARS scale with a decrease from baseline of 70% (an effect size of 1.29) and 66% (an effect size of 1.83), respectively. • The mean (SD) decrease in disease severity from baseline to week 12 was 4.5 (1.0) to 2.3 (1.3) by clinician evaluation, and 4.6 (1.3) to 2.5 (1.4) by to patient assessment (P < 0.0001 in all cases) • At week 1, tolerability was evaluated as good or excellent in 80% and 64% of the clinicians and patients, respectively, while at week 12 the corresponding rates were 90% and 83%.	relevant extent. However, these preliminary and promising results should be confirmed in placebo-controlled trials. Long-term maintenance of the pregabalin efficacy, risk of withdrawal symptoms with pregabalin in this population, and what is the most appropriate dosage schedule for these patients are points that should be also evaluated."[16] page 306
de Dier, 2011,[17]	
• BZD abstinence dropped from 100% at 3 months to 59.8% at 21 months. • 58.8% of patients who discontinued BZD use 3 months after intervention were BZD abstinent at 10-year follow-up. • Multivariate analyses showed that	"We conclude that 10 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

Table A6: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
abstinence at 21 months was the strongest predictor of abstinence at 10-years follow-up, with ORs (95% CI) of 3.5 (1.9, 6.5) overall, and 5.1 (2.4, 10.5) among patients with complete follow-up data *P* = 0.000 in all cases). • Attendance of evaluation consults were a marginal predictor of abstinence (ORs [95% CI]: 1.9 [1.0, 3.6], *P* = 0.047 overall; and 2.1 [1.0, 4.3], *P* = 0.044 with complete follow-up data.)	succeed in maintaining abstinence from benzodiazepines appear to use lower or average dosages. In our opinion, the results support the application of minimal intervention strategies in primary care."[18] page 258
Lopez-Peig, 2012[15]	
• 80.4% of the patients had discontinued BZD by the end of the six-month intervention, and 64% maintained abstinence at one year. • Among patients who discontinued BZD use, a significant improvement was observed in the mental component of SF-12 (3.3 points; *P* = 0.024), • Patients who discontinued BZD use showed improvement in anxiety and depression as indicated in all parameters of the Goldberg scale (p <0.05), and had better sleep. • No significant differences in these scales were observed among patient who had not discontinued BZD use.	• "Our withdrawal program, conducted by nurses, was successful in that a period of one year 2/3 of the patients in our sample ceased taking BZD. These results are similar to studies conducted by other professionals such as physicians or psychologists. Our work confirms the fact that nurses in a Primary Care setting can successfully implement a BZD withdrawal program."[15] page 7

ABIM = American Board of Internal Medicine; BWSQ = benzodiazepine withdrawal symptom questionnaire; BZD = benzodiazepine; CBT = cognitive behavioral therapy; CI = confidence interval; COR = cumulative odds ratio; DDD = defined daily dose; DE = diazepam equivalent; GHQ = General Health Questionnaire; HARS = Hamilton Anxiety Rating Scale; MD = mean difference; NNT = number needed to treat; OR = odds ratio; PRM = prolonged-release melatonin; PWC = Physician's Withdrawal Checklist; RCT = randomized controlled trial; RR = relative risk; SD= standard deviation; UK = United Kingdom;

[a] Multifaceted interventions included two or more prescribing interventions (e.g. education plus medication review) as opposed to single-faceted intervention which used only one (e.g. education alone).

[b] Diazepam equivalents (DE) were calculated by the authors based for the various benzodiazepines, and lower dose was defined as a mean < 10 mg/day DE while a higher dose was ≥ 10 mg/day DE of BZDs.

[c] The median duration in the sub-analysis was 7 years.

APPENDIX 5: Additional References of Potential Interest

Hogan D. B. (2014). Strategies for discontinuing psychotropic medications. Canadian Geriatrics Society Journal of CME. 4(2). 14-18 http://www.canadiangeriatrics.ca/default/index.cfm/linkservid/0844EB81-E025-AE0C-595582DFCE2E49DA/showMeta/0/

Jorgensen VR. Benzodiazepine reduction in general practice. Are the elderly neglected? J Affect Disord. 2012 Feb;136(3):1216-21.

Kawasaki SS, Jacapraro JS, Rastegar DA. Safety and effectiveness of a fixed-dose phenobarbital protocol for inpatient benzodiazepine detoxification. J Subst Abuse Treat. 2012 Oct;43(3):331-4.

Saxon L, Borg S, Hiltunen AJ. Reduction of aggression during benzodiazepine withdrawal: effects of flumazenil. Pharmacol Biochem Behav. 2010 Aug;96(2):148-51.