A systematic review of interventions to deprescribe benzodiazepines and other hypnotics among older people

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Abstract

Purpose: Benzodiazepines are effective medicines for insomnia and anxiety but are commonly used beyond recommended treatment time frames, which may lead to adverse drug events. The aim of this systematic review was to critically evaluate the success of interventions used to reduce benzodiazepines and 'Z-drugs' use, and the impact of these interventions on clinical outcomes in older adults. **Methods:** A search was conducted in PubMed, Embase, Informit, International Pharmaceutical Abstracts, Scopus, PsychINFO, Cochrane Central Register of Controlled Trials (CENTRAL), and CINAHL. Studies conducted in older adults (≥65 years), and published between January 1995–July 2015 were included. Two authors independently reviewed all articles for eligibility and extracted the data. **Results:** Seven studies of benzodiazepines and Z-drugs withdrawal were identified. Benzodiazepine discontinuation rates were 64.3% in one study that employed pharmacological substitution with melatonin, and 65.0% in a study that employed General Practitioner targeted intervention. Mixed interventions including patient education and tapering (n=2), pharmacological substitution with psychological support (n=1) and tapering with psychological support (n=1) yielded discontinuation rates between 27.0-80.0%. Five studies measured clinical outcomes following benzodiazepine discontinuation. Most (n=4) observed no difference in prevalence of withdrawal symptoms or sleep quality, while one study reported decline in quality of life in those who continued taking benzodiazepine versus those who discontinued over 8-months. **Conclusions:** Current evidence shows that benzodiazepine withdrawal is feasible in the older population, but withdrawal rates vary according to the type of intervention. As the benefits and sustainability of these interventions are unclear, further studies should be conducted to assess this.

Key words: benzodiazepines, Z-drugs, deprescribing, older adults.

Introduction

For several decades, benzodiazepines (BZDs) have been used in clinical practice for the management of sleeping disorders and anxiety [1]. BZDs and Z-drugs are effective pharmacological treatments; however, there is concern about long-term use, which, despite heterogeneity in the quality of the existing evidence, has been associated with harms such as drug dependence, falls and fractures ([2-4]. Moreover, it has been hypothesized, with some supporting observational data that long-term use might have a detrimental effect on cognition and an increased risk of Alzheimer's disease [3, 5, 6]. Prolonged use of BZDs is of particular concern in the older population as older adults are at higher risk of medication related harms due to age-related pharmacokinetic and pharmacodynamic changes, multi-morbidity (≥2 chronic medical conditions) and polypharmacy (≥5 medications) [7]. Additionally, older people have a higher use of hypnotic medications than younger individuals with insomnia and anxiety [8-11]. Prescribing of Z-drugs has been observed to increase as prescribing of BZDs has fallen in some countries [10, 12, 13]. General Practitioners (GPs) report that these medications are more effective for insomnia and safer in older adults, despite no evidence to support this belief [12, 14].

Treatment guidelines recommend that BZDs should be used intermittently for less than two weeks in the treatment of insomnia and should not be used for more than six weeks (including tapering before withdrawal) in the treatment of anxiety [15]. However, most observational studies have shown that a significant proportion of older adults use BZDs chronically [16-19]. In Australia, 15% to 42% of all older adults use BZDs long-term [8, 9, 13, 20, 21]. Recent studies found that 16.6% of the community-dwelling participants aged 75 years and over were using BZDs for at least 4.5 years [20]. Therefore, to minimise drug-related harm and mitigate the impact of medication burden on quality of life, long-term use of BZDs should be regularly reviewed, tapered and/or ceased when appropriate. [22].

Deprescribing can be defined as the "withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes" [23]. Dose reduction and switching to a more appropriate agent or intervention can also be positive outcomes of deprescribing. There are many reasons for deprescribing, including the lack of evidence to support efficacy for medication therapies, increased risk of drug-drug interactions, the development of serious side effects, resolution of existing condition and change in the patient's care goals [24, 25]. There are potential benefits to deprescribing of inappropriate medications in general, including improved adherence, quality of life and reduced risk of adverse drug reactions and mortality; however, there is limited robust data from clinical trials on these benefits [26, 27]. It can be difficult to determine if a medication is inappropriate and whether deprescribing will be beneficial or not in an individual. As such it is important to monitor after withdrawal for adverse withdrawal reactions and return of condition [26, 27].

Recent reviews have examined the success of different types of BZD withdrawal interventions in the older population and aimed to characterise the literature on deprescribing BZDs and Z-drugs in the community dwelling population [28, 29]. The aim of this review is to evaluate the evidence on which interventions are most effective (prevalence of discontinuation, reduction and/or substitution) and sustainable to deprescribe BZDs and

Z-drugs in older people, across different settings. Additionally, we sought to identify the impact of these interventions on both positive and negative (e.g. return of condition/loss of benefit, adverse drug withdrawal reactions) clinical outcomes.

Methods

Search Strategy

Studies were identified by searching electronic databases PubMed, Embase, Informit, International Pharmaceutical Abstracts, Scopus, PsychINFO, Cochrane Central Register of Controlled Trials (CENTRAL), and CINAHL using following keywords and strategy: ('deprescrib*' OR 'de-prescrib*' OR 'stop*' OR 'cease*' OR 'cessation' OR 'withdraw*' OR 'discontinu*') AND ('benzodiazepine*' OR 'alprazolam' OR 'bromazepam' OR 'clobazam' OR 'clonazepam' OR 'chlordiazepoxide' OR 'chlorazepate' OR 'diazepam' OR 'estazolam' OR 'flunitrazepam' OR 'flurazepam' OR 'medazepam' OR 'lorazepam' OR 'nitrazepam' OR 'oxazepam' OR 'prazepam' OR 'quazepam' OR 'temazepam' Or 'triazolam' OR 'sedative*' OR 'hypnotic*' OR 'Z drug*' OR 'Zolpidem' OR 'Zopiclone' OR 'eszopiclone' OR 'zaleplon') AND ('elderly' OR 'aged' OR 'older' OR 'geriatric*) NOT ('alcohol' in the title) for original research articles published between January 1995 and July 2015. Relevant drug names were identified through searching Australian and international product information for orally available BZD and Z-drugs.

Titles and abstracts generated by the search strategy were screened independently by two authors (AW and MO) to identify eligible articles. After screening, full texts of potential articles were retrieved and reviewed independently by AW and MO. A manual search for additional relevant and eligible articles was done using the citations of retrieved articles. Where the eligibility and relevance of articles was unclear, it was discussed with the senior authors (DG and ER).

Inclusion and exclusion criteria

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed [30]. Studies were included if they were original research articles including randomised controlled trials (i.e. controlled clinical trials) and non-randomised studies evaluating interventions used to deprescribe long term use (more than four weeks) of BZDs and/or Z-drugs, which targeted/included an older population (all participants ≥ 65 years of age) in community, hospital or aged care settings. Duplicate articles, conference abstracts, opinion pieces and previous systematic reviews were excluded (although reference lists were hand searched for potential inclusion). In addition, articles looking at 'as-needed'/ pro re nata (PRN) use of BZDs/Z-drugs and articles focusing only on prevalence of BZD/Z-drug use or prescribing patterns of BZD/Z-drugs were excluded.

Data extraction and quality assessment

The following information was extracted by AW and MO independently and reviewed: (1) author, country and year in which the study was conducted; (2) study design and study setting; (3) intervention or control groups; (4) number of participants and mean age; (5) time points of follow up; (6) duration of hypnotic use prior to withdrawal; (7) impact of intervention on number of participants continuing versus stopping BZD or Z-drug use;

and (8) impact of intervention on both positive and negative (e.g. adverse drug withdrawal reactions) clinical outcomes. The Cochrane Risk of Bias Assessment Tool was used to assess the quality of randomised clinical trials (RCTs) [31], and the NIH Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group was used for the non-RCTs [32].

Results

A total of 5063 unique articles were retrieved from the electronic databases. After excluding articles that did not fulfil the inclusion criteria, seven studies were included for evaluation (Figure 1). Of the seven studies, one involved a General Practitioner (GP) targeted intervention, one trialled pharmacological substitution and the remaining four were mixed interventions which included temporary pharmacological substitution with psychological support (n=2), tapering with psychological support (n=1) and tapering with patient education (n=2). These studies were conducted in Belgium (n=3), Canada (n=1), Finland (n=1), Ireland (n=1) and Spain (n=1). Five of the studies were RCTs and two were pre/post intervention studies. Among included studies, five studies assessed the clinical outcomes of BZD/Z-drug withdrawal while the others focussed on the success of the intervention in reducing use of BZDs. Z-drugs were included in two of the studies. Due to the variability in study types and outcomes collected, the results of this systematic review are reported in a narrative way with studies grouped according to intervention type.

GP targeted intervention

In the study by Bourgeois *et al* (Table 1), GPs of eligible nursing home patients who were using BZD and Z-drugs chronically were sent a letter asking if they were willing to initiate discontinuation of BZD/Z-drug [33]. If the GP agreed, the patient was then asked for their willingness. The letter suggested a discontinuation plan but GPs were allowed to discontinue BZDs for their consenting patients at their own professional judgement. Of 135 residents identified to be prescribed a BZD or Z-drug long-term, GPs indicated that discontinuation was feasible in 51 residents. Thirty-eight of these residents consented to trial withdrawal (74.5%). The intervention led to 25/38 (65.8%) participants discontinuing their BZDs/Z-drugs, and 7/38 (18.4%) participants reduced their dose at two months. At eight months, one additional participant had successfully discontinued and one had restarted BZD/Z-drug use [33]. The study also measured clinical outcomes following BZD/Z-drug withdrawal using Pittsburgh Sleep Quality Index (PSQI), Benzodiazepine Withdrawal Sleep Questionnaire (BWSQ), EQ-5D-3L for quality of life and Activities of Daily Living (ADL) for functional status [33]. There was no significant difference in withdrawal symptoms experienced by the participants, and no change in function over the eight months [33]. Although there was no change in sleep quality, participants who relapsed were found to have poorer quality of life from baseline to eight months (0.676 vs. 0.556, p=0.012) [33].

Pharmacological substitution

Garzon *et al* conducted an 18-week, randomised controlled crossover trial of melatonin versus placebo. Of the 14 previous BZD users, nine (64.3%) were able to discontinue drug therapy while on melatonin but not on placebo, one was able to discontinue in both phases and four were not able to discontinue in either phase [34]. The study also assessed the impact of the replacement therapy (substitution) on clinical outcomes. It was found that the use of melatonin significantly improved sleep quality measured by the Northside Hospital Sleep Medicine Institute test (NHSMI) when compared to baseline and placebo groups (1.78±0.40 vs. 3.72±0.45,

p=0.001 vs. 3.44±0.56, p=0.025) [34]. Participants also reported improvement in depression (F=3.44, p=0.043) and anxiety (F=5.36, p= 0.009) after melatonin administration [34].

Mixed Interventions

Temporary pharmacological substitution and psychological support

Petrovic *et al* conducted a feasibility study to measure the effect of one-week replacement therapy prior to withdrawal on BZD abstinence at 1-week. In addition, psychological support was also offered. The investigators replaced regular BZD regimen with 1mg lormetazepam (n=24) or 50mg trazodone (n=25) for a week before complete withdrawal [35]. The discontinuation rate was higher in the trazodone group (80.0%) than lormetazepam group (75.0%) although this was not significant [35]. The study found no difference in sleep quality measured using Groningen Sleep Quality Scale (GSQ) between the two groups [35].

In 2002, Petrovic *et al* conducted a RCT to measure the effect of one-week replacement therapy before complete BZD cessation. Participants were randomly assigned to 1mg lormetazepam (n=20) or placebo (n=20) groups, and were provided psychological support during the study period [36]. The rate of successful discontinuation was significantly higher in the lormetazepam group than the placebo group (80.0% vs. 50.0%, p<0.05) [36]. Secondary measures including sleep quality and withdrawal symptoms were assessed using the validated tools Pittsburgh Sleep Quality Index (PSQI) and BWSQ and compared between the groups. The PSQI and BWSQ scores reflected an initial poorer sleep quality and worsening withdrawal symptoms, with the placebo group having worst scores during the withdrawal phase [36]. However, the scores improved over time as measured at 15 and 30 days after withdrawal. At 1-year follow-up, 46% (12/26) of the participants who had discontinued at 1-month, remained off the BZD [36].

Patient education with tapering recommendation

Studies involving patient education, which involved providing information on harms associated with long-term use of hypnotic medications and tapering to reduce use of these medications, have yielded 27.0% to 36.0% reduction in BZD use. Salonoja *et al* measured the effect of a medication review by a geriatrician where they were provided with oral and written instructions to withdraw, reduce or change psychotropic drugs (including BZDs and Z-drugs). Participants also attended a 1-hour lecture on the adverse effects of fall-risk increasing drugs (FRIDs) [37]. Interestingly, the study reported a 35.0% decrease in number of regular users of BZD/Z-drugs who received the intervention in comparison to 4.0% increase in regular BZD/Z-drug users who received usual care at one year follow up (p=0.012) (the study population included both BZD and Z-drug users and non-users prior to the intervention) [37].

The study by Tannenbaum *et al* measured the effect of patient education booklet to facilitate discontinuation of BZDs over 6-months [38]. The study found that 27% of those who received the patient education booklet stopped taking BZDs, significantly more than the 5% in the control group at 6-months follow-up (risk difference 0.23, 95%CI 0.14-0.32) [38]. The investigators also found that 61.7% (76/123) of the intervention group, had

initiated a discussion with a doctor and/or pharmacist to discontinue their drug therapy and 41.4% (51/123) attempted discontinuation following the 21-week tapering protocol provided in the booklet [38].

Tapering with psychological support intervention

Curran *et al* measured the effect of tapering intervention (slowly reducing the dose prior to discontinuation) to reduce use of BZD among older people at 24 weeks and 52 weeks [39]. Overall the discontinuation rate at 6-months was 80.0% [39]. Participants who had discontinued BZDs were found to have better quality of life over 24-weeks as compared to those who continued using BZD ($p<0.005$) [39]. Participants who discontinued BZDs also had better social functioning skills at 24 weeks ($p<0.05$) and at 52 weeks ($p<0.015$) [39]. Sleep quality did not differ between those who discontinued and those who did not discontinue BZD. Among participants who discontinued BZDs there was no difference in cognitive and psychomotor function, mood and health-related quality of life and somatic symptoms [39].

Risk of bias assessment

Five of the studies (Curran, Garzon, Petrovic 2002, Salonoja and Tannenbaum) were RCTs and were assessed according to the Cochrane Risk of Bias Assessment criteria (Electronic Supplementary Material, Table 1A). Tannenbaum, Salonoja and Curran had one out of six items of the assessment tool rated as high risk of bias, with the remaining items rated as low or unclear risk of bias. Allocation concealment and selective reporting were unclear in the majority of studies. The remaining two studies were pilot interventional studies which looked at a before versus after outcomes and as such they were assessed using the NIH Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group (Electronic Supplementary Material, Table 2A). Due to the varied nature of the interventions and study types it is not possible to compare the quality of the studies, as such the results of one could not be rated as a higher quality over another.

Discussion

Overall, a range of interventions were employed to deprescribe BZDs/Z-drugs in older people, including a GP directed strategy, pharmacological substitution with melatonin and mixed interventions. The mixed interventions included combinations of tapering by doctors and pharmacists, patient education, psychological support and short term pharmacological substitution. BZD/Z-drug discontinuation rates varied substantially across studies and interventions tested. Patient education and tapering tended to result in lower discontinuation rates compared to pharmacological substitution with psychological support. In most studies the main outcome measure was the change in BZD/Z-drug use. Studies also assessed the impact of deprescribing BZDs/Z-drugs on clinical outcomes. Most studies found no difference in sleep quality and no significant adverse drug withdrawal reactions when tapering or substitution were used. Two studies indicated deprescribing was beneficial.

The findings of this review suggest that pharmacological interventions that focused on substitution to withdraw BZD with or without psychological support had the highest success rates [34-36]. These studies not only demonstrated the feasibility of using replacement therapy to deprescribe BZDs but also found that the intervention was beneficial with reported improvements in mood, withdrawal symptoms and sleep quality after BZD withdrawal [34-36]. The GP targeted intervention and tapering with psychological support also showed

promising results in reducing use of BZDs with 65% to 80% withdrawal rates [33, 39]. Both these studies reported no change in sleep quality following BZD/Z-drug cessation. In addition, in both studies patients who restarted taking BZDs had a poorer quality of life compared to those who stopped taking BZDs [33, 39]. Interestingly, while most of these studies had a short follow up period, two studies reported that 30% to 48% of participants had successfully abstained from BZDs over a 1-year follow-up period [36, 39].

Patient-directed educational strategies offer a potentially beneficial intervention to optimise medication use through deprescribing of inappropriate medications. While the patient education interventions identified in this review had a lower success rate (27% and 35% across two studies) [37, 38] compared to other interventions, they potentially reflect real-life practice better than the controlled pharmacological substitution studies. Patient-directed interventions have the added benefit of being low-cost, easily integrated into regular care and ensure that patients are involved in decisions about changes in medication use. Due to their limited effectiveness, combination of this type of intervention with other strategies may prove beneficial. For example, Tannenbaum *et al* are conducting a study where they have paired their patient empowerment brochure described in this review with a pharmacist led intervention which will also involve targeted information to the GP [40].

Other studies not included in this review (as they did not fulfil inclusion criteria) have employed multi-disciplinary interventions to reduce the use of sedative drugs including BZDs. The reducing use of sedatives (RedUse) project, conducted in nursing homes in Australia involved a multi-faceted, interdisciplinary intervention led by pharmacists to reduce use of sedatives, through audit, feedback educational sessions and review [41]. The intervention led to a significant reduction in regular BZD use from 31.8% at week 0 to 26.9% at week 26 [41]. The study did not explicitly state the age of participants and reported prevalence, hence it was excluded from our evaluation. Another study by Lopez-Peig *et al* which was not specific to older adults showed that a nurse-led intervention to withdraw BZD use in combination with tapering in primary care setting is feasible [42]. The study reported 80.4% BZD discontinuation rates at 6-months, and 60.4% of patients maintained abstinence at 1-year follow-up [42]. Moreover, there were significant improvements in mood ($p<0.05$) and mental health ($p=0.024$) [42]. Interestingly, we did not identify any nurse-led interventions to reduce BZD use in older people specifically. Further studies should assess the feasibility of nurse-led interventions especially among older people residing in residential aged care where the use of sedative drugs including BZDs is of particular concern.

Strengths and Limitations

This review involved a rigorous systematic review approach with two reviewers independently determining eligibility and extracting the data.

However, this review has several limitations. Limiting the search strategy to people over 65 years of age meant that a number of studies conducted in a wider population that had included a sub-analysis of older people may have been missed. Most of the studies were conducted in community-dwelling and hospitalised older adults living in the European region; therefore, the findings of this review may not be generalizable to other older

adults in other settings or other parts of the world. Future reviews should include adults of all ages, and studies published in other languages should be included for a more comprehensive review.

The results of the quality assessment are reported and limitations of the individual studies need to be considered when viewing the results of our review. Most of the studies were not powered for many of the outcomes investigated in the individual studies. Moreover, most studies had rather short-term follow up with only three studies following patients for a year. Hence, long-term sustainability and impact of interventions are still unclear. It was difficult to compare the quality across studies as the type of intervention and outcomes measured varied. For example, a number of studies measured sleep quality as an outcome while others focussed on the reduction of BZD use. Those which used blinded withdrawal of the medication using placebo cannot be compared to blinding in studies where the intervention includes patient involvement (i.e. Tannenbaum and Salonoja).

Implications for clinical practice and future research

Long term use of BZDs and Z-drugs in older adults is generally not recommended due to potential harms, lack of evidence of long-term benefits and potential for tolerance [3]. The prevalence of use of these drugs is higher than desirable, however, there is some evidence to support that use is decreasing, and that many older adults are using them appropriately for a short period of time [10, 13, 43]. The decision to deprescribe a BZD/Z-drug must be made through shared-decision making between the health care professional and the patient, taking into account the individual's preferences. It is essential that appropriate monitoring is conducted throughout tapering and after discontinuation to determine if deprescribing has been safe and if there have been any benefits. Substitution and tapering appear to be effective at minimising adverse drug withdrawal reactions and return of sleep problems. If substitution (replacement therapy) is planned, the risks of this medication, including its contribution to polypharmacy, needs to be considered. It was outside the scope of this review to consider which (if any) replacement therapy is the most appropriate in older adults. Future studies should focus on the benefits of withdrawal and how to minimise the harms, as well as cost benefit analyses (e.g. considering the cost of resources and support such as psychological interventions). Additionally, more research is needed into how health care professionals should discuss deprescribing of BZDs and Z-drugs to optimise patient-centred care.

Conclusion

Despite the frequent use of BZDs in the older age group, withdrawal in older people and the clinical outcomes of withdrawal has not been the subject of extensive investigation. Current evidence shows that BZD withdrawal is feasible and safe in the older population, but withdrawal success may vary according to the type of intervention employed and evidence on clinical outcomes is limited. Overall, BZD discontinuation rates ranged from 27% to 80%. However, the benefits and sustainability of these interventions are unclear.

Conflicts of Interest

None.

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None.

Contributions of Authors

ER was involved in the conception and design of the work, supervised screening and data extraction, conducted quality assessment, was involved in drafting and revising the manuscript for important intellectual content and approved the final version.
MO was involved in the conception and design of the work, conducted screening of abstracts and data extraction, drafted the manuscript and approved the final version.
AW was involved in the conception and design of the work, conducted screening of abstracts and data extraction, reviewed the manuscript and approved the final version.
JJ was involved in the conception and design of the work, reviewed the manuscript critically for important intellectual content and approved the final version.
MP was involved in the conception and design of the work, reviewed the manuscript critically for important intellectual content and approved the final version.
DG was involved in the conception and design of the work, supervised screening and data extraction, was involved in drafting and revising the manuscript for important intellectual content and approved the final version.

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Figures and Tables

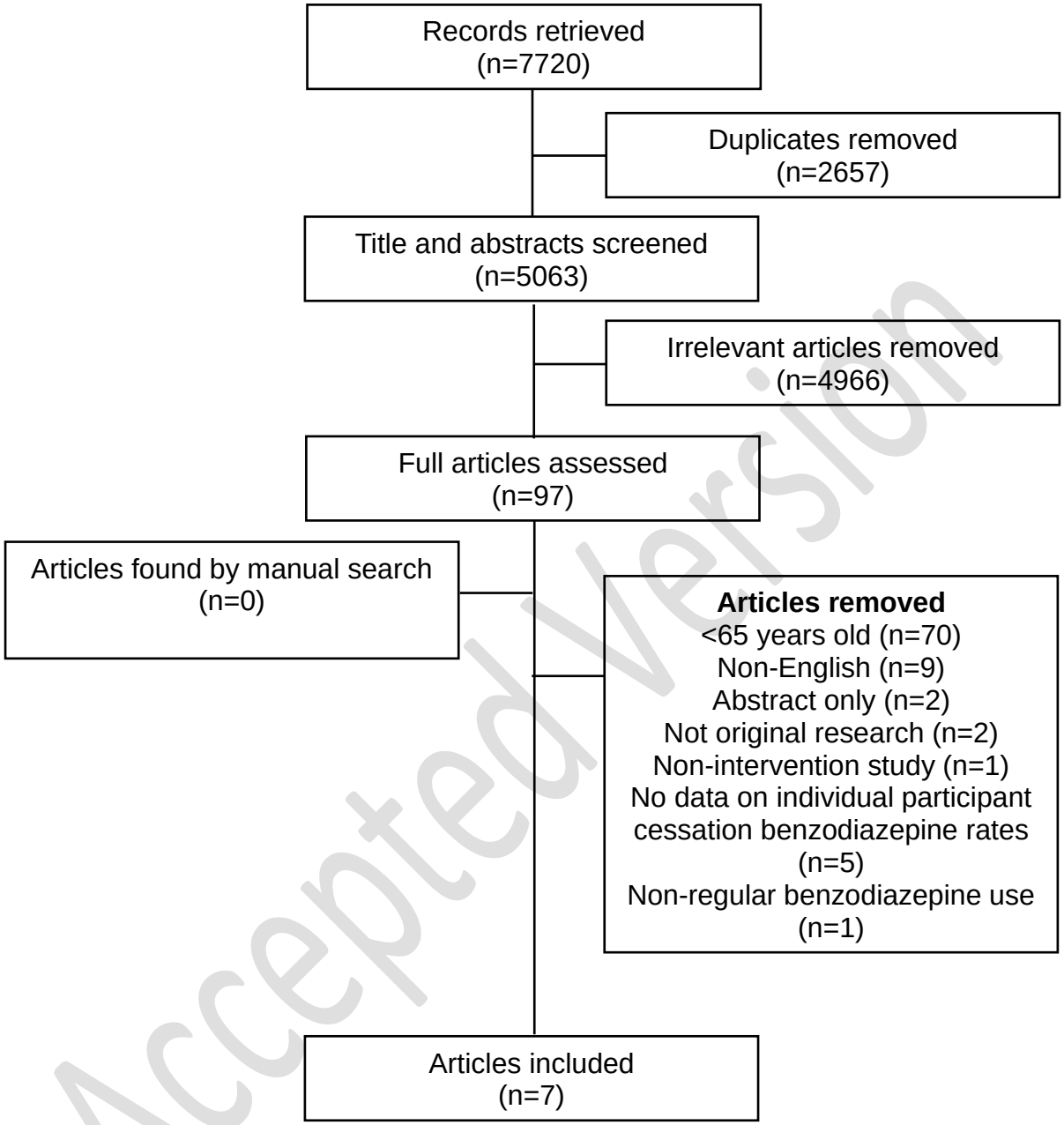

Figure 1: Search strategy and flow of articles

Table 1. Impact of interventions on withdrawal of benzodiazepine or Z-drugs and clinical outcomes

Author, Year, Country, Study design, Setting	Intervention / control	Number of participants Mean (SD) age	Follow-up duration	Study results	
				Effect of intervention on withdrawal	Clinical Outcomes
Petrovic *et al*, 1999, Belgium, feasibility withdrawal study, Hospital	Temporary substitution with 1 week of 1 mg lormetazepam vs. 1 week of 50 mg trazodone Psychological support was provided as well	56 (7 refused; 24 lormatezapem/25 trazodone) 80.9 years	6 weeks	Discontinuation rate: lormetazepam: 18/24 (75.0%) vs. trazodone: 20/25 (80.0%) ($p>0.05$)	No significant difference in the Groningen Sleep Quality score between groups
Petrovic *et al*, 2002, Belgium, double-blinded, placebo controlled RCT, Hospital	Temporary substitution with 1 week of 1 mg lormetazepam vs. 1 week of placebo, followed by complete withdrawal Psychological support was provided if participants faced any problems	40 (20 lormetazepam/20placebo) 81.5 years	12 months	Discontinuation rate at 1-month: lormetazepam 16/20 (80%) vs. placebo 10/20 (50%) ($p<0.05$) At 1 year follow-up: lormetazepam 8/20 (40%) vs. placebo 4/20 (20%)	Higher proportion of placebo group (40%) to lormetazepam group (25%) reported worsening sleep on the Pittsburgh Sleep Quality Index (PSQI) ($p<0.001$). Benzodiazepine Withdrawal Symptom

					Questionnaire (BWSQ): no difference between groups at 1-month ($p>0.05$)
Curran *et al*, 2003, Ireland, RCT, Community[a]	Patients allocated to Group A (BZD dose tapering from week 1); Group B (given usual BZD dose for 12 weeks and then taper); Group C (continued using BZD). All groups received psychological support	138; 104 agreed to participate in the withdrawal study and 34 chose to participate but not withdraw, these were allocated to Group C Age range 65-93 (mean:77±6.9)	6 months	Overall discontinuation rate: 83/104 (80.0%) No difference between groups A and B	No difference in sleep between groups Withdrawal group had higher Medical outcomes study Short Form-36 scores and higher social functioning at 24 weeks ($p<0.05$)
Garzon *et al*, 2009, Spain, placebo controlled, double-blind, crossover RCT, Community	5mg melatonin substitution for 2 months, followed by 2 months of placebo, vice versa	14 regular users of BZD 74.7 years	2 months	9/14 (64.3%) were able to discontinue BZD during melatonin substitution, 1/14 (7.1%) discontinued during both phases, and 4/14 (28.5%) were not able to discontinue	Northside Hospital Sleep Medicine Institute test, Geriatric Depression Scale and Goldberg Anxiety Scale scores improved with melatonin

					vs. baseline and vs. placebo (p<0.025 for all)
Salonoja *et al*, 2010, Finland, RCT, Community	Medication review by a geriatrician plus patient education with gradual tapering vs. usual care	528 (259 intervention vs. 269 control) [b] 34 participants in the intervention group and 46 in the control group were taking BZD/Z-drugs at baseline Mean (SD) age intervention group:72.8 (5.6) years [b] Mean (SD) age control group:72.9 (5.9) years [b]	12 months	BZD use decreased by 12/34 (35%) in intervention group vs. increased by 2/46 (4%) in usual care group (p=0.012)	Not measured
Bourgeois *et al*, 2014, Belgium,	GP's willingness to initiate BZD discontinuation with	Of 135 residents, GPs indicated that	8 months	At 2-months: 25/38 (65.8%) discontinued BZD/Z-drug,	No significant change in Benzodiazepine

feasibility study, Nursing homes	tapering recommendation	discontinuation was feasible in 51 residents Of 51 residents that GPs agreed, 13 residents refused leaving 38 residents 84.3 years		7/38 (18.4%) reduced dose, 6/38 (15.8%) relapsed At 8-months: 66% completely discontinued BZD/Z-drugs	Withdrawal Symptom Questionnaire No change in Activities of Daily Living scores over 8 months. Those who relapsed did not have reduced sleep, but did have reduced quality of life.
Tannenbaum *et al*, 2014, Canada, cluster RCT (i.e. community pharmacies randomised to intervention/control group) Community	Patient empowerment education booklet and 21 week, gradual tapering protocol vs. usual care	148 intervention group vs. 155 control group Mean (SD) age 75.0 (6.3) years	6 months	40/148 (27%) of intervention group discontinued vs. 7/155 (4.5%) in control group Additional 16/148 (11%) in intervention group achieved dose reduction (95%CI 6%-16%)	Not measured

Table sorted according to year and authors. BZD=benzodiazepine; RCT=Randomized Controlled Trial.

[a]Subjects were allocated randomly to two study groups (Group A and B). Group C was allocated non-randomly and consisted of patients that were not willing to stop taking benzodiazepines.

[b] Total study population involved users and non-users of BZD/Z-drugs. Mean ages are of the total study population.

NB: None of the studies apart from Tannenbaum *et al* 2014 reported a power calculation.