Discontinuation of benzodiazepines by non-pharmacological interventions in primary care: a systematic review

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Discontinuation of benzodiazepines by non-pharmacological interventions in primary care: a systematic review

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Abstract

Background: Benzodiazepine receptor agonists (BZRA) are frequently prescribed drugs to treat insomnia. However, they come with important side effects such as substance dependence, cognitive impairment and risk of falling. Furthermore, their helpful effect on insomnia only lasts for a short period. Chronic use is frequently observed and quitting is challenging for the patient. Consequently, in the setting of primary care, a discontinuation strategy is often required.

Aim: This systematic review aims to evaluate which non-pharmacological interventions are effective for discontinuing benzodiazepines in a primary care setting.

Methods: To identify relevant studies, we searched different databases: Pubmed, Web of Science, PsycARTICLES, CINAHL, Embase and the Cochrane Library. We selected studies with a controlled, interventional design, carried out in primary care and focussing on discontinuation of benzodiazepines prescribed for primary insomnia by use of non-pharmacological interventions. The Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines were respected while creating this review.

Results: We identified 6868 articles through an electronic search of which 13 studies met the inclusion criteria. 4 studies investigated the effects of a tapering scheme and/or cognitive behavioural therapy. 3 out of 4 studies showed a good effect on benzodiazepine discontinuation. 7 studies focused on minimal interventions. Especially a stop letter and patient educational information seem to be relatively easy and promising strategies. Lastly, 3 studies looked at the effect of the combination of a tapering scheme with minimal interventions. Mainly the combination of a GP (general practitioner) consult, a tapering scheme and educational information shows significant results, even on the long-term.

Conclusions: Different non-pharmacological interventions seem to have a positive effect on benzodiazepine discontinuation. More research is needed to clarify which one is the most effective and the easiest to carry out.

Introduction

Benzodiazepine receptor agonists (BZRAs), including classical benzodiazepines and the related 'Z-drugs' (i.e. zopiclone and zolpidem), are frequently prescribed drugs to treat insomnia. These drugs can be an effective treatment for insomnia in short term but they are frequently associated with side effects such as falling (with risk of hip fractures), traffic accidents, cognitive impairment/decline and especially the development of tolerance and substance dependence /addiction.(1–6)

Given these numerous side effects, it is stunning that the incidence of long-term benzodiazepine use in North-America and Europe has been estimated to be as high as 0.4 to 6%, with even a higher incidence in patients older than 65 years. (7)

In Belgium, use of BZRAs is estimated to be even more frequent: a national survey performed in 2018 reported that 14% of responders used drugs to treat anxiety or insomnia. Use in elderly patients was even higher: in the group of responders who were 75 years or older, 37% of women and 28% of men reported to use drugs to treat anxiety or insomnia. It should be noted that in this survey BZRA-use was not included as a separate group. However, one can assume that BZRAs are the most frequent used drugs to treat anxiety or insomnia.(8)

It is no surprise that the Flemish guidelines for general practitioners emphasize the importance of a non-pharmacological treatment for insomnia and that pharmacological treatments such as BZRAs should only be used with caution and if possible for a short term. (9) This is also in line with recommendations from the task force of the European Sleep Research Society who promote a restricted use of these drugs and recommend a treatment duration of less than 4 weeks.(10)

Nonetheless, chronic use is frequent and discontinuing use in patients who have developed a dependence of BZRAs can be challenging. Different strategies to discontinue the use of these drugs have been developed including pharmacological measures (such as alternative medication) and non-pharmacological methods (such as the use of patient education materials, a stop letter and cognitive behavioural therapy). There are, however no clear evidence-based guidelines to help health care providers (HCP) choose the right strategy for discontinuation.(11)

Therefore, we decided to do a review of the current literature on the effectiveness of non-pharmacological approaches to discontinue BZRAs, hoping to shed a light on the most efficient way to help people quit their chronic use.

Methods

We set up a systematic review following the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines.(12) (Figure 1)

Search strategy

Studies were identified searching following databases: Pubmed, Web of Science, PsycARTICLES, CINAHL, Embase and the Cochrane Library. The concepts that were used were: benzodiazepines and Z-drugs, discontinuation, non-pharmacological intervention, and a fourth concept connecting the beforementioned concepts with sleep disorder, adult, primary care or long-term/chronic use. A sample syntax for Pubmed can be found in appendix A.

Only studies published in Dutch or English were included. The search was carried out on 11th of November in 2019. References of the articles identified in this search were incorporated in Mendeley.(13)

Eligibility criteria

Studies were included in the review if they met following criteria:

- Controlled, interventional design
- Focussing on non-pharmacological interventions for the reduction of BZRA-use
- The indication for BZRA-use was insomnia
- Patients were 18 years or older
- Study is carried out in primary health care

We excluded trials, case series, reviews, guidelines, animal research and double publications. If there was a clear indication for BRZA-use other than insomnia, the study was also excluded. Studies in which the objectivity of investigators could be questioned (e.g. investigators with a financial incentive to stop BZRA) were excluded as well. Furthermore, we excluded studies in hospital or residential care setting. When the interventions were carried out at the level of the prescribing physician, pharmacist or other HCP, the study was also not included. The selected studies focussed on interventions aimed directly at the patients. This review focuses on non-pharmacological interventions, so studies that tested pharmacological interventions were neglected.

Outcome measures

We evaluated the effectiveness of non-pharmacological interventions in primary health care to discontinue the use of BZRAs for primary insomnia. Consequently, the most important

outcome for our review is the discontinuation of benzodiazepines. Other outcomes that were of value for our review were dose reductions and the number of nights per week of benzodiazepine use.

Study selection

After removal of duplicates in Mendeley, all unique references were uploaded to RAYYAN QCRI. This is an online application that facilitates the screening of articles.(14) Screening of title and abstracts was carried out by two independent researchers (RP and SP). A third reviewer (KC) verified all included titles. Thereafter, the screening process was continued by RP and SP. Any discrepancies were discussed with a third reviewer (KC). Figure 1 displays detailed information about the amount of articles that were identified, screened and finally included in the review.

Data collection process and synthesis of results

To obtain more insight in the included studies, a data extraction form was created in Microsoft Excel. Using this form, RP and SP extracted the following data:

- Reference of the study, using Vancouver reference style and including title, authors, journal and year of publication
- Characteristics of the study: setting, design, duration of intervention, year of intervention
- Characteristics of the population: baseline characteristics (e.g. age and gender), sample size, number of included patients and number of patients who completed the study, average use of BZRA prior to start of the study
- Inclusion and exclusion criteria of the study
- Description of the intervention and of the control method
- All reported primary and secondary outcomes

Description of included studies

Through electronic search in the selected databases as stated above, we identified 6868 articles. After the removal of duplicates and after the screening process, 13 studies remained relevant and met the inclusion criteria.

The 2 studies by Vicens et al (dated 2014 and 2016) were counted as one included study, because they analyze the same data but at a different time of follow-up. All studies were published in English between 1989 and 2018. They took place in different countries: 5 studies were conducted in Canada, 3 in the Netherlands, 2 in the United Kingdom, 2 in the United States and 1 in Spain. All of the studies have a controlled design. 8 of them have a

completely randomized setup, while 3 are cluster randomized. One of the studies chose a quasi-experimental design, because randomization at general practice level did not seem to be achievable.(15) Finally, one study has a controlled design without randomization (16). The setup of this study is as follows: all patients of 30 general practices were screened using defined in-and exclusion criteria. The selected patients were used as the intervention group. After the follow-up period of this intervention group a population of 19 other family practices served as the control group after screening using the same criteria.

Most studies recruited their population through primary care. More specifically, the population was recruited from general practices (6 studies), pharmacies (2 studies) or through a health care delivery system (2 studies). A health care delivery system is an organization of people, institutions and resources which deliver health care services to meet the health needs of a targeted population. 2 studies recruited patients using a media campaign in combination with referral by a general practitioner. Finally, one study relied solely on a media campaign to include subjects.

The follow-up period of the studies varied between 6 weeks and 36 months. An overview of these study characteristics is displayed in table 1.

Figure 1: Prisma Flow Diagram



PRISMA 2009 Flow Diagram (12)

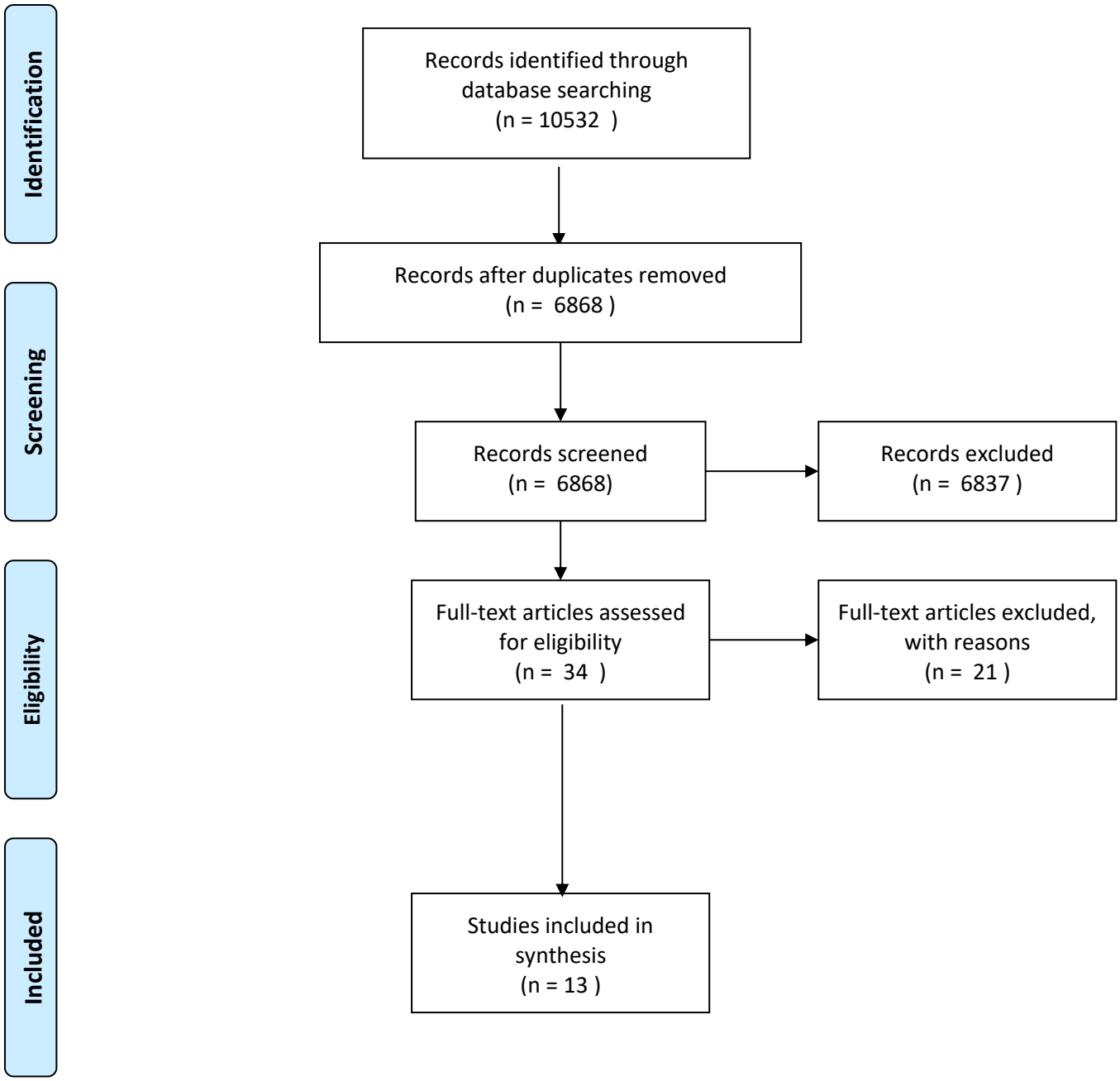


Table 1: Description of included studies
Legend: I = Intervention group; C = Control group, RCT = randomized controlled trial

Study	Duration	Design	Recruitment	Control	Intervention	Sample Size	Primary outcome
Baillargeon_2003 (17)	No data	RCT	Media advertisements + referral by GP in Quebec	Tapering scheme (8w)	Tapering scheme + CBT (weekly group session for 8w)	65 (30I; 35C)	Discontinuation of BZRA: I >C
Cormack_1994 (18)	1989-1990	RCT	3 group practices in UK	Standard care	**Intervention 1:** Stop letter **Intervention 2:** Stop letter + Monthly information sheets	209 (65I1; 75I2; 69C)	Total Daily Dose BZRA 6m after study: I>C; No difference between I's
Navy_2018 (19)	2016-2017	RCT	Integrated Health Care delivery System in Colorado	Standard care	Stop letter	346 (173I;173C)	Discontinuation of BZRA: I=C
Niessen_2005 (15)	1998-2000	Prospective, quasi experimental	147 General practices in the NL	Standard care	Stop letter	8837 (1343I; 7545C)	Discontinuation of BZRA for 6m: I>C
Tannenbaum_2014 (20)	2010-2012	Cluster RCT	30 Pharmacies in Quebec	Standard care	Educational information + Tapering scheme	261 (123I; 138C)	Discontinuation of BZRA for 6m: I>C
Martin_2018 (21)	2014-2018	Cluster, RCT	69 Pharmacies in Quebec	Standard care	Educational information from pharmacist to patient and to GP	219 (105I;114C)	Discontinuation of BZRA: I>C
OudeVoshaar_2003 (22)	1998-2001	RCT	30 General practices in the NL	Standard care	**Intervention 1:** Tapering scheme (4w) **Intervention 2:** Tapering scheme+ CBT (1x/w for 5w)	180 (73I1;73I2; 34C)	Discontinuation of BZRA: I's>C; No difference between I's
Kuntz_2018 (23)	2017	RCT	Integrated Health Care Delivery System in America	Standard care	**Intervention 1:** Educational information **Intervention 2:** Educational information + Phone call pharmacist	150 (50I1;50I2;50C)	Discontinuation of BZRA for 6m after study: I's>C; No influence of phone call by pharmacist

Table 1 continued: Description of included studies

Vicens_2014 (24)	2010-2012	Cluster RCT	75 GP's in Spain selected 8 patients	Standard care	**Intervention 1:** GP consult + Tapering scheme + educational information **Intervention 2:** GP consult + Tapering scheme + follow-up visits	532 (191I1; 168I2; 173C)	Discontinuation of BZRA after 12m: I's >C; No difference between I's
Vicens_2016 (25)	2010-2014	Cluster RCT	75 GP's in Spain selected 8 patients	Standard care	**Intervention 1:** GP consult + Tapering scheme + educational information **Intervention 2:** GP consult + Tapering scheme + follow-up visits	532 (191I1; 168I2; 173C)	Discontinuation of BZRA 36m after study: Patients stopped at 12m, are still stopped at 36m
Morin_2004 (26)	2001-2002	RCT	Media advertisements + referral by GP in Canada	Supervised tapering	**Intervention 1:** CBT **Intervention 2:** Tapering scheme + CBT	76 (24I1;27I2;25C)	Discontinuation of BZRA: I2> I1 and C -Dose reduction: C=I's -Nights per week of BZRA use: I2>I1 and C
Belleville_2007 (27)	2003-2005	RCT	Media advertisements in Quebec	Tapering scheme	Tapering scheme + self-help CBT	53 (23I;25C)	Discontinuation of BZRA -Nightly dose of BZRA -Nights per week of BZRA use: I=C for all
Heather_2004 (28)	1997-1999	RCT	7 General practices in UK	Standard care	**Intervention 1:** GP consult **Intervention 2:** Stop Letter	284 (98I1; 93I2; 93C)	Dose reduction + Discontinuation of BZRA: I2>C; I1>C, but no significance
Gorgels_2005 (16)	1998-2001	Prospective controlled intervention	30 General practices in the NL	Standard care	Stop letter (+ Evaluation consultation)	4416 (2595I; 1821C)	Discontinuation of BZRA after 3m, 4-6 and 21m: I>C -Patient daily dose (PDD) of BZRA: I>C

Results

Studies were grouped based on the interventions they researched: tapering scheme and/or cognitive behavioral therapy, minimal interventions, and tapering scheme combined with minimal interventions. The primary outcome of most studies was the discontinuation of benzodiazepines, dose reduction of benzodiazepines and/or nights per week use of benzodiazepines. A representation of these findings can be found in table 2.

Interventions: tapering scheme and/or cognitive behavioral therapy

Oude Voshaar et al. studied the effect of a tapering scheme in comparison to standard care and found a significant higher rate of discontinuation and dose reduction in the group with the tapering scheme. This study also evaluated the combination of a tapering scheme and cognitive behavioral therapy (CBT), which also had a significant higher rate of discontinuation and dose reduction in comparison to the control group. Furthermore, they stated that there was no difference between these two interventions, because the rate of discontinuation and dose reduction in both groups was approximately the same and therefore not significant.(22)

Morin et al. analyzed the outcomes of CBT compared to a supervised tapering scheme. Both groups achieved a significant dose reduction and a significant reduction in nights per week of benzodiazepine use. The rate of benzodiazepine discontinuation in both groups was about 50%. So, there was no difference between the effect of both treatments. Furthermore, the authors evaluated the consequences of a tapering scheme combined with CBT. This combination showed a significant higher rate of discontinuation in comparison to medication taper or CBT alone. In the combination group there was also a significant decrease in dose reduction and a significant reduction in nights per week of benzodiazepine use, but there was no significant difference compared to the other two groups.(26)

In contrast to Oude Voshaar et al., Morin et al. did conclude that a combination of a tapering scheme and CBT has a better effect on the discontinuation of benzodiazepines in comparison to a tapering scheme or CBT alone.(22,26)

Other studies that investigated the results of a combination of a tapering scheme and CBT in comparison to a tapering scheme were the trials of Belleville et al. and Baillargeon et al.(17,27) Baillargeon et al. also showed a significant better effect on discontinuation and dose reduction in the combination group compared to the taper group alone. These effects were still significant after 12 months follow-up.(17)

On the other hand, Belleville et al. could not confirm this. Their study showed a significant effect in dose reduction and a reduction in nights per week of benzodiazepine use in both groups. Also, the rate of BZRA discontinuation in both groups was high. 72,7% discontinued

their use in the group that combined CBT and tapering, 64% in the group that only used tapering. This was not found to be statistically significant. Therefore, the authors suggest that a tapering scheme could be sufficient for benzodiazepine discontinuation.(27)

Finally, we can conclude that Oude Voshaar et al. showed that a tapering scheme had better results on benzodiazepine discontinuation in comparison to standard care.(22) Morin et al. demonstrate that CBT alone also has a good effect on benzodiazepine discontinuation, dose reduction and nights per week of benzodiazepine use. However, they could not prove that it is more effective than a tapering scheme alone.(26) Nonetheless, two studies (Morin et al. and Baillargeon et al.) demonstrated that a combination of a tapering scheme and CBT is an effective strategy for benzodiazepine discontinuation.(17,26). The results of Belleville et al. contradict this, because they found no difference in benzodiazepine discontinuation with a tapering scheme alone or a tapering scheme combined with CBT. This suggests that a tapering scheme alone could be sufficient if the goal is discontinuation.(27)

Minimal interventions

"A minimal intervention is the minimal or lowest level of intervention intensity, expertise, and resources needed to achieve a clinically significant improvement in a specified outcome for a particular target population under a particular set of conditions, when delivered by a specified type of staff or interactive modality", as stated by Glasgow et al.(29).

The minimal interventions that have been studied in our review are: a stop letter, a consultation with the general practitioner (GP) during which the discontinuation of BZRA is discussed, and educational information sent to the patient. These educational leaflets typically contain the most important reasons for BZRA discontinuation and some general advice to facilitate this discontinuation.

A stop letter is a letter, mostly send by the GP, in which the discontinuation of BZRA is advised. Five studies evaluated the effect of the stop letter. Heather et al. and Niessen et al. found a significant effect on benzodiazepine discontinuation and dose reduction in comparison to standard care.(15,28) Also, Cormack et al. and Gorgels et al. showed a significant effect of the stop letter on dose reduction. In both studies, there were also more people who discontinued BZRAs in the group that received the stop letter, but this effect was not significant.(16,18) These positive results are contradicted by the study of Navy et al. who did not find a significant effect on discontinuation or dose reduction compared to standard care.(19)

Heather et al. investigated the effect of a consult with the GP on discontinuation of BZRAs. They found that more patients reduced and stopped BZRAs in the consultation group (37%) compared with standard care (24%), but this finding was not statistically significant

Furthermore, they could not show a difference in discontinuation and dose reduction between the GP consultation and the stop letter.(28)

Gorgels et al. compared the combination of a stop letter and an evaluation consultation with the GP to a stop letter alone. They could not find a significant effect for the evaluation consultation.(16)

In the study of Martin et al. the intervention was carried out by the pharmacist. The pharmacist sent educational information consisting of a visual tapering protocol and a brochure about why BZRA may be inappropriate and potential alternative treatment options to the patient. Also, he delivered a deprescribing brochure to the GP. The result was a greater amount of discontinuation in the intervention group (48,6%) compared to standard care (10,5%). There were no data about significance available.(21) Kuntz et al. also conducted a study about the effect of educational information. Their information sheet contained the same topics as the one of Martin et al mentioned above. They also added a self-assessment quiz about the risks of benzodiazepine use. The educational intervention was sent to the patient by the prescribing physician. After 6 months follow-up they also found that significantly more patients discontinued BZRA in the educational group (56%) compared to standard care (26%). Furthermore, Kuntz et al. examined if a follow-up phone call by the pharmacist 2 to 4 weeks later resulted in a greater rate of discontinuation. There was no difference.(23)

Tapering scheme combined with minimal interventions

Vicens et al. checked if a GP consult combined with a tapering scheme and educational information led to better rates of discontinuation after 12 months follow-up compared to standard care. The intervention started with a structured, educational interview with the prescribing physician. The physician also provided the patient with a gradual tapering scheme and with educational information which reinforced the information discussed during the interview. The discontinuation rates after 12 months (45%) were significantly higher compared to the control group (15%)(24) In a follow-up study Vicens et al. re-evaluated the results after 36 months of follow up and showed that patients who successfully discontinued benzodiazepines at 12 months (45%), remained abstinent at 36 months (39,2%).(25) In addition, in the first study the effectiveness of the combination of a GP consult with a tapering scheme and follow-up visits with the GP every 2-3 weeks was tested. This intervention led approximately to the same results. At 12 months, 45% of patients in the intervention group had discontinued their benzodiazepines. At 36 months 41,3% remained abstinent. Thus, no difference could be demonstrated between the two intervention groups. Vicens et al. conclude that a GP consult combined with a tapering scheme and educational information

led to significant reductions in long-term benzodiazepine use and is less time-consuming and as effective in primary care as a more complex intervention involving follow-up visits.(24,25)

At last, Tannenbaum et al. conducted a study about the effects of a tapering scheme combined with educational information. The educational information contained a self-assessment component about the risks of benzodiazepine use, presentation of the evidence for benzodiazepine-induced harms, knowledge statements designed to create cognitive dissonance about the safety of benzodiazepine use, education about drug interactions, peer champion stories intended to augment self-efficacy and suggestions for equally or more effective therapeutic substitutes for insomnia and/or anxiety. At 6 months follow-up, more patients in the intervention group (27%) discontinued BZRAs compared to the control group (5%), which was a significant difference. An additional 11% of individuals who received the intervention achieved dose reductions.(21)

Table 2: Results: intervention groups with primary outcome
Legend: I=intervention group; C= control group; Studies that found a statistical significance in the discontinuation of benzodiazepines are in italic

		Primary outcome						
		Discontinuation of BZRA		Dose reduction		Nights per week of BZRA use		
Interventions:	**#studies**	**I>C**	**I=C**	**I>C**	**I=C**	**I>C**	**I=C**	**Study**
Tapering scheme	1	1	0	1	0	No data		*Oude Voshaar_2003* (22)
Cognitive behavioural therapy (CBT)	1	0	1	0	1	0	1	Morin_2004(26)
Tapering scheme + CBT	4	3	1	2	2	1	1	Belleville_2007(27) *Morin_2004* (26) *Oude Voshaar_2003*(22) *Baillargeon_2003* (17)
Minimal interventions:								
Stop letter	5	2	2	4	1	No data		*Heather_2004* (28) *Niessen_2005* (15) Navy_2018(19) Cormack_1994(18) Gorgels_2005(16)
GP consult	1	0	1	1	0	No data		Heather_2004(28)
Educational information	2	2	0	No data		No data		Martin_2018(21) *Kuntz_2018* (23)
Tapering scheme + Minimal intervention:								
GP consult + Tapering scheme + educational information	1	1	0	No data		No data		Vicens_2014 (24)Vicens_2016 (25)
GP consult + Tapering scheme + follow-up visits	1	1	0	No data		No data		*Vicens_2014* (24) *Vicens_2016* (25)
Tapering scheme + educational information	1	1	0	1	0	No data		*Tannenbaum_2014* (20)

Discussion

The negative consequences of chronic BZRA are generally known to most HCPs, yet discontinuing BZRA use remains a challenge. There are many non-pharmacological strategies for BZRA discontinuation and there are no clear guidelines available to help select a strategy. Non-pharmacological strategies found to be effective in our review are tapering schemes, CBT, minimal interventions (such as a stop letter, educational information sent to the patient or a consultation with their GP discussing the stopping of BZRA) and combinations of these strategies.

The results can be quite confusing with studies obtaining contradicting results, e.g. some studies have demonstrated superiority of the combination tapering and CBT versus tapering alone where other studies cannot confirm this finding.(17,26,27) Tapering of BZRA is an important part of the solution as it reduces acute withdrawal symptoms compared to abruptly stopping BZRA.(22,30,31) Whether or not the addition of CBT was useful was recently further examined in a systematic review which included a meta-analysis of 8 RCT's.(32) The conclusion was that the combination of tapering and CBT was significantly more effective than tapering alone for stopping BZRA at 3 months follow up (risk ratio 1.68 with 95 confidence interval 1.19 – 2.39 and p value 0.0009). Yet, this result was not significant at long term follow-up (12 months in this meta-analysis).(32)

Results of minimal interventions are also not equivocal for stop letters, with most studies showing benefit, but Navy et al could not show the same effect.(15,16,18,19,28) There are many possible causes for this finding. The most interesting explanation proposed by Navy et al. is that the integrated health care system where the study was performed already provided other means to alert patients (and caregivers) to the possible detrimental effects of BZRA use. So, it might be that the letter sent to the patient did not provide new insights to the patient. More specifically, the letter sent to the patient asked them to call the clinical pharmacologist to discuss stopping BZRA. However clinical pharmacologists are a permanent member of the team taking care of patients included in the above-mentioned integrated health care system and part of their usual standard of care is to discuss and, if possible, to reduce or stop potentially inappropriate medication such as BZRA.(19) So, it is quite possible that patients in this study already had received extensive educational information before they received the 'stop letter'.

This is especially interesting as educational information provided to the patient seems to have favorable results compared to standard care in two studies, albeit that only one study had results about significance.(21,23) Martin et al. did not mention the indication for BZRA use, so for this paper the specific numbers of BZRA use for insomnia were obtained from the

author. As this is data from a subgroup no analysis for statistical significance was available.(21)
Not surprisingly the combination of educational information and tapering was proven to be effective as was the combination of tapering, educational information and a GP consultation.(20,25)

Some authors also published data not only about how efficient their interventions were but also about the cost-effectiveness. Given the increasing concern about health care budgets this is also an important aspect of the different strategies to discontinue BZRA. Data about this subject is limited, but Oude Voshaar et al demonstrated that tapering alone was more cost-effective versus tapering plus CBT. In other words, addition of CBT to tapering was proven to have no benefit from an economical point of view.(33) As minimal interventions are more likely to have minimal cost, the favorable results of the different minimal intervention strategies are therefore especially important, as it can be assumed that cost-effectiveness of these interventions is also favorable. There are however no studies to prove this assumption. From an economical point of view, it is also interesting to note that Vicens et al. demonstrated that the combination of a consult by a GP providing educational information and a tapering scheme, was not rendered more effective by the addition of (costly and time consuming) follow-up consultations to supervise this tapering.(24,25)

Nonetheless, it should be noted that our results have their limitations. Firstly, long term data are scarce with most studies having a follow-up time of maximum 6 to 12 months with 2 exceptions where follow-up was 21 and 36 months respectively.(16,25) Also, sample sizes were rather small: most studies had a sample size of only a few dozen or a few hundred of patients. The largest studies were conducted by Niessen et al., Gorgels et al. and Vicens et al with inclusion of respectively 8837, 4416 and 532 subjects.(15,16,25) On the contrary the smallest included study only included 53 subjects.(27) Also, heterogeneity in populations, interventions and definition of outcome measures severely limits the comparison of results of different studies. As an example: the result of ‘standard of care’, which one can assume is quite diverse in different countries with dissimilar health care systems, differs between the separate studies. Usually the group which received this ‘standard care’ was the control group and compared against the different interventional groups. Given the differences between ‘standard of care’ in 2 separate studies, this makes it quite difficult or nearly impossible to compare the difference between control and intervention group in between 2 different studies.

Given these limitations it seems fair to conclude that interventions such as tapering schemes and minimal interventions have proven their benefit, especially when combined. Addition of CBT to a tapering scheme was effective in the short term as demonstrated in the systematic review mentioned above, but its long-term effect remains uncertain (no significant effect at 12 months.(32) So, more research on this subject is definitely needed, as well as more long-term studies comparing different approaches and combinations thereof.

As most HCPs lack training or time to adequately provide CBT, a combination of a tapering scheme with a consultation or letter providing educational information about stopping BZRAs seems to be a reasonable option to help their patients in the discontinuation process, especially considering the high effectiveness rates and lower costs associated with these interventions.

Finally, the established fact that BZRA should be prescribed cautiously cannot be stressed enough, especially in risk patients, such as geriatric patients, as stopping BZRA still remains a challenge.(34)

Conclusion

Three studies showed that a combination of CBT with a tapering scheme is a promising intervention for benzodiazepine discontinuation. Four other studies found a good effect of the stop letter. However, these findings are contradicted by a minority of studies.(19,27) Further, the minimal intervention of sending the patient educational information seems to have positive results on benzodiazepine discontinuation.(21,23) Another promising approach is the combination of a tapering scheme with minimal interventions. Vicens et al. had significant results combining these. Moreover, their results were still significant after 36 months. They state that one GP consult combined with a tapering scheme and educational information is as effective as a GP consult with tapering scheme and follow-up visits.(24,25) The study of Tannenbaum et al also showed good results with a combination of a tapering scheme and educational information.(20) These studies suggest that a combination of minimal, less complex interventions could be a good, low cost solution for BZRA discontinuation.

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Conflicts of Interest

The authors declare that they have no competing interests.

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APPENDIX A

Sample syntax Pubmed

Concept 1 : benzodiazepines and z-drugs

“Benzodiazepines”[Mesh] OR “Zolpidem”[Mesh] OR “Eszopiclone”[Mesh] OR "zopiclone"[Supplementary Concept] OR "zaleplon"[Supplementary Concept]

OR Benzodiazepin*[tiab] OR Alprazolam[tiab] OR Anthramycin[tiab] OR Bromazepam[tiab] OR Brotizolam[tiab] OR Clonazepam[tiab] OR Devazepide[tiab] OR Diazepam[tiab] OR Flumazenil[tiab] OR Flunitrazepam[tiab] OR Flurazepam[tiab] OR Lorazepam[tiab] OR Nitrazepam[tiab] OR Oxazepam[tiab] OR Pirenzepine[tiab] OR Prazepam[tiab] OR Temazepam[tiab] OR Chlordiazepoxide[tiab] OR Clobazam[tiab] OR Clorazepate[tiab] OR Clotiazepam[tiab] OR Cloxazolam[tiab] OR ethyl-loflazepate[tiab] OR ketazolam[tiab] OR loprazolam[tiab] OR lormetazepam[tiab] OR nordazepam[tiab] OR Estazolam[tiab] OR Medazepam[tiab] OR Midazolam[tiab] OR Olanzapine[tiab] OR prazepam[tiab] OR Triazolam[tiab] OR Zolpidem[tiab] OR SL-800750[tiab] OR SL-80-0750[tiab] OR Zolirin[tiab] OR Zolpi-Lich[tiab] OR Zolpinox[tiab] OR Zolpimist[tiab] OR Ambien[tiab] OR Amsic[tiab] OR Bikalm[tiab] OR Stilnoct[tiab] OR Stilnox[tiab] OR Dalparan[tiab] OR Zodormdura[tiab] OR Zoldem[tiab] OR eszopiclon*[tiab] OR zopiclon*[tiab] OR Lunesta[tiab] OR Lunivia[tiab] OR Estorra[tiab] OR esopiclone[tiab] OR Zop[tiab] OR Zopicalma[tiab] OR zopiclodura[tiab] OR Zopitan[tiab] OR Zorclone[tiab] OR Imovane[tiab] OR Ximovan[tiab] OR Zimovane[tiab] OR Limovan[tiab] OR Optidorm[tiab] OR Rhovane[tiab] OR Siaten[tiab] OR Somnosan[tiab] OR Zileze[tiab] OR Zimoclone[tiab] OR Zopi-Puren[tiab] OR Zopicalm[tiab] OR zaleplon[tiab] OR L-846[tiab] OR Zelepion[tiab] OR Starnoc[tiab] OR SKP-1041[tiab] OR Sonata[tiab] OR Z-drug*[tiab] OR Z-hypnotic*[tiab] OR zaleplon*[tiab] OR andante[tiab] OR hegon[tiab] OR hipnodem[tiab] OR noctiplon[tiab] OR plenidon[tiab] OR sonata[tiab] OR zaplon[tiab] OR zerene[tiab] OR zelepion[tiab]

Concept 2 : discontinuation

“Deprescriptions”[Mesh]

OR de-prescri*[tiab] OR deprescri*[tiab] OR discontinu*[tiab] OR reduction[tiab] OR reduce[tiab] OR decrease[tiab] OR stop[tiab] OR prescription-change*[tiab] OR prescribing-intervention*[tiab] OR prescribing-restriction*[tiab]

Concept 3 : non-pharmacological intervention

“Placebos”[Mesh] OR “Counseling”[Mesh] OR “Health Education”[Mesh] OR “Psychotherapy”[Mesh] OR “Pamphlets”[Mesh] OR “Health Knowledge, Attitudes, Practice”[Mesh] OR “Attitude to Health”[Mesh:noexp] OR “Electronic Mail”[Mesh] OR “Telemedicine”[Mesh:noexp] OR “Motivation”[Mesh] OR “combined modality therapy”[Mesh:noexp] OR “Health literacy”[Mesh] OR placebo*[tiab] OR “sham treatment”[tiab] OR counsel*[tiab] OR Behavioral-Therap*[tiab] OR Behavioral-Treatment*[tiab] OR Behavioural-Therap*[tiab] OR Behavioural-Treatment*[tiab] OR Cognition-Therap*[tiab] OR Cognitive-Therap*[tiab] OR acceptance-and-commitment-therap*[tiab] OR Cognitive-remediation*[tiab] OR cognitive-enhancement-therap*[tiab] OR behaviour-modification*[tiab] OR behavior-modification*[tiab] OR behaviour-analysis*[tiab] OR behavior-

analysis*[tiab] OR Behavior-Therap*[tiab] OR Behaviour-Therap*[tiab] OR Behavior-Treatment*[tiab] OR Behaviour-Treatment*[tiab] OR Behavior-Training*[tiab] OR Behaviour-

Training*[tiab] OR Behavioural-stress-management*[tiab] OR Behavioral-stress-management*[tiab] OR CBSM[tiab] OR cognitive-interference[tiab] OR chronotherapy* OR Relaxation*[tiab] OR meditation*[tiab] OR mindfulness[tiab] OR health-campaign*[tiab] OR psychoeducation[tiab] OR Health-Promotion*[tiab] OR Promotion-of-Health[tiab] OR CBT*[tiab] OR gradual-dose-reduc*[tiab] OR education*[tiab] OR motivation*[tiab] OR disincentive*[tiab] OR expectation*[tiab] OR incentive*[tiab] OR encourag*[tiab] OR letter*[tiab] OR taper*[tiab] OR "non-pharmacological intervention"[tiab] OR psychotherap*[tiab] OR socioenvironmental-therap*[tiab] OR psychosocial-intervention*[tiab] OR psychological-intervention[tiab] OR publication*[tiab] OR poster*[tiab] OR pamphlet*[tiab] OR brochure*[tiab] OR booklet*[tiab] OR Health-Knowledge[tiab] OR Health-Attitude*[tiab] OR attitude-to-health[tiab] OR electronic-mail*[tiab] OR e-mail*[tiab] OR email[tiab] OR telemedicin*[tiab] OR tele-medicin*[tiab] OR mobile-health[tiab] OR telehealth[tiab] OR mhealth[tiab] OR ehealth[tiab] OR combined-modality-therap*[tiab] OR multimodal-treatment*[tiab] OR health-advertis*[tiab] OR health-announcement*[tiab] OR health-ads[tiab] OR messag*[tiab] OR (health-service*[tiab] AND announcement*[tiab]) OR (health[tiab] AND television-advertis*[tiab]) OR medication-knowledge[tiab] OR drug-knowledge[tiab] OR health-literacy[tiab] OR aspiration*[tiab] OR brief-intervention*[tiab] OR advice[tiab] OR minimal-intervention*[tiab] OR intervention-strateg*[tiab] OR psychosocial-support[tiab] OR caregiver-support[tiab] OR empowerment[tiab] OR teleconsultation*[tiab] OR screening[tiab] OR self-rating*[tiab]

Concept 4 : sleep disorder OR long-term/chronic use OR adult OR primary care

"Sleep Disorders, Intrinsic"[Mesh:NoExp] OR "Sleep Medicine Specialty"[Mesh] OR "Sleep Initiation and Maintenance Disorders"[Mesh] OR "Sleep Wake Disorders"[Mesh:noexp]

OR "adult"[Mesh]

OR "general practice"[Mesh]

OR sleep-medicin*[tiab] OR (sleep[tiab] AND initiati*[tiab]) OR DIMS[tiab] OR Early-Awakening[tiab] OR Sleeplessness[tiab] OR Insomni*[tiab] OR sleep-disorder*[tiab] OR Sleep-disturbance*[tiab] OR sleep-perturbation*[tiab] OR sleep-wake-disorder*[tiab] OR sleep-wake-transition-disorder*[tiab] OR hyposomnia[tiab] OR agrypnia[tiab] OR long-term[tiab] OR chronic-use[tiab] OR aged*[tiab] OR elder*[tiab] OR senior*[tiab] OR senium[tiab] OR pensioner*[tiab] OR very-old[tiab] OR older-people[tiab] OR general-medicine[tiab] OR general-practice[tiab] OR family-practice[tiab] OR primary-medical-care[tiab] OR primary-care[tiab] OR primary-health-care[tiab] OR advanced-age[tiab] OR advancing-years[tiab] OR ageing[tiab] OR aging[tiab] OR old-age[tiab] OR adult*[tiab] OR grown-up*[tiab] OR grownup*[tiab] OR middle-age*[tiab

Verslag Masterproef:
"Discontinuation of benzodiazepines by non-pharmacological interventions in primary care: a systematic review"

Voor het behalen van mijn masterproef als deel van de master in de huisartsengeneeskunde heb ik samen met Rani Peeters een systematic review gemaakt met als onderwerp de niet farmacologische interventies voor afbouw en stop van benzodiazepine receptor antagonisten (BZRA) in de eerstelijnsgeneeskunde.
Omdat het me verbaasde hoeveel mensen chronisch slaapmedicatie gebruiken, koos ik dit onderwerp . Tijdens een eerste vergadering in december 2018 samen met onze promotor en copromotor werd besproken hoe we een systematisch literatuuronderzoek moesten aanpakken en werd een eerste aanzet gegeven richting het opstellen van een onderzoeksvraag na doornemen van wat eerste literatuur. Gezien er recent nog een meta-analyse verscheen die de verschillende farmacologische interventies voor afbouw van BZRA beschreef hebben we in overleg gekozen om ons te focussen op de niet farmacologische methodes. Na een tweede vergadering in januari 2019 om dit verder te bespreken kwam uiteindelijk volgende onderzoeksvraag hieruit voor: "Welke non-farmacologische interventies in de eerstelijnszorg zijn effectief om patiënten met insomnia en/of angst te ondersteunen in de afbouw van chronisch benzodiazepine- of Z-productengebruik?". Tijdens deze vergadering werd ook een tijdslijn opgesteld en werden verdere literatuurtips gegeven. Uiteindelijk werd dan een protocol uitgewerkt in samenwerking tussen ons beiden, promotor en copromotor.
Nadien hebben we op basis van dit protocol een zoekstrategie uitgewerkt voor Pubmed, die werd geoptimaliseerd door een bibliothecaris van KU Leuven. Deze heeft ook gezorgd voor een zoekstrategie voor de andere databanken die werden gebruikt voor deze review. Hier heeft onze copromotor ons ook bij geholpen. Deze zoekstrategieën waren beschikbaar in oktober 2019, waarop zowel Rani als ikzelf deze hebben ingegeven in de databases. Na verificatie dat we beiden dezelfde resultaten hadden werden duplicaten verwijderd met Mendeley. Met ondersteuning van de copromotor kon er worden gestart met screening van de artikels met behulp van de app 'Rayyan QCRI', die dit proces veel eenvoudiger maakt. We hebben elk alle artikels gescreend om te kijken of ze al dan niet in aanmerking kwamen voor inclusie (in totaal 6868 artikels). De conflicten werden besproken met de copromotor alvorens ze te in- dan wel excluderen bij de te lezen artikels. Op deze manier bleven echter nog teveel artikels over (161), waardoor werd besloten in overleg met promotor en copromotor om de criteria in ons protocol te verstrengen. We kwamen zo tot 34 artikels. Op basis van abstract, titel en zo nodig volledige tekst werd deze lijst verder ingekort tot 13 artikels die definitief werden geïncludeerd voor de systematische review. Hierbij hebben we beiden bijgedragen.
Om de informatie die uit de artikels gehaald kon worden op een wat gestructureerde manier te kunnen verwerken werd een data extractieformulier opgesteld. Op basis van het protocol maakte ik eind januari 2020 een eerste versie van dit data extractieformulier in Excel dat dan nog werd geoptimaliseerd in overleg met promotor en copromotor.
Vervolgens hebben we de geselecteerde artikels verdeeld over ons beiden, de volledige tekst gelezen en op basis hiervan samen het dataformulier (gedeeld Excel bestand op cloud-opslag) ingevuld (periode februari-maart 2020). De resultaten werden besproken met de promotor en copromotor waarna we zijn overgegaan tot het analyseren van de data en het schrijven van de paper. Rani heeft op basis van het data extractieformulier 2 tabellen gemaakt die de resultaten mooi samenvatten (begin april 2020). Bij het schrijven van de paper (april-mei 2020 hebben we in eerste instantie de verschillende onderdelen over elkaar verdeeld. Rani heeft zoals vermeld de 2 tabellen opgemaakt en heeft het stuk 'resultaten' geschreven. Zij schreef ook grotendeels het abstract en de conclusie. Ik heb ondertussen de inleiding, methodologie en discussie geschreven. Daarnaast maakte ik de figuur met Prismaflowchart en heb ik de referenties in het ganse document verzorgd. Er werden een aantal versies over en weer gestuurd tussen ons beiden en de copromotor en op basis van

haar feedback hebben we het document bijgewerkt waarbij ik ook delen van de stukken die initieel door Rani werden gemaakt heb aangepast. Uiteindelijk denk ik dat zeker resultaten en discussie en conclusie voor een groot deel berusten op samenwerking, waarbij Rani het grootste deel van het stuk resultaten voor zich nam en ik het leeuwendeel van de discussie. Het was een zeer leerrijke ervaring om zelf een dergelijke review te maken en deze in artikelvorm te gieten. Het werk dat in een dergelijk artikel kan zitten onderschat je vaak, als je het gewoon gelezen hebt.