



Promoting benzodiazepines and z-drugs deprescribing in the community setting:

Adapting tools to better engage older adults and healthcare professionals

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Septembre 2024

Thèse présentée en vue de l'obtention du grade de
docteur en sciences de la santé publique

Secteur des sciences de la santé

« Qui veut déplacer des montagnes commence par déplacer de petites pierres »
(Confucius)

Remerciements

Quand j'ai eu la folle idée, il y a 10 ans, de reprendre des études universitaires, j'étais très loin de me douter que j'aurais plus tard une autre folle idée, celle d'entamer une thèse de doctorat. Et pourtant, après 6 ans d'efforts et de doutes mais aussi de challenge intellectuel et de découvertes enthousiasmantes, me voici arrivée au bout de cette thèse. Si les mots qui suivent semblent bien peu pour exprimer toute ma gratitude, je tiens à remercier ici les nombreuses personnes qui ont contribué de près ou de loin à cet accomplissement.

Tout d'abord, j'ai eu la chance d'avoir été accompagnée par une promotrice et une co-promotrice extraordinaires. Séverine, Anne, merci infiniment de m'avoir si bien guidée et soutenue professionnellement mais aussi humainement tout au long de ces 6 années.

Merci, Séverine, non seulement pour ta patience et ta guidance pour les analyses statistiques et la découverte de R, mais aussi, et surtout, pour ta disponibilité, ton écoute et nos réunions régulières, qui m'ont permis de garder le cap tout au long de ce parcours doctoral.

Anne, merci pour tes conseils et commentaires prodigués au fil des très nombreuses relectures et réunions, et qui toujours avec bienveillance, m'ont emmenée un pas plus loin à chaque fois.

Merci aux membres de mon comité de thèse, les Professeur·e·s et Docteur·e·s Perrine Hoet, William D'Hoore, Nathalie Dujardin et Sophie Marien pour vos feedback et conseils avisés tout au long de ce travail. To my external jury members, Professors Cathal Cadogan and Nicolas Delvaux, thank you for your critical reading of this thesis, your questions and comments that helped me improve my work.

Merci aux nombreux professionnels de la santé et patients qui ont partagé leur expérience et/ou donné de leur temps pour participer à nos différents projets de recherche. La recherche n'est pas possible sans vous.

Merci aux (anciens) collègues du CLIP, Stefanie, Pauline, Anne-Laure, Anne-Elisabeth, Sophie, Antoine, François-Xavier, Laudine, Manon, Maria, Marine, Olivia, Rostand, Vlad, Sara, Carine, Ariane et Angèle pour les échanges constructifs lors des staffs CLIP. Merci pour votre bonne humeur, votre soutien et votre solidarité qui rendent l'openspace aussi chouette à partager.

Merci à Isabelle et Murielle, nos alliées administratives et comptables pour les très nombreux services rendus pendant ces années.

On dit souvent que faire une thèse est un processus solitaire. J'ai eu le grand bonheur du contraire. Perrine, ma binôme de thèse en or massif, merci d'avoir partagé cette aventure avec moi, merci pour les si nombreuses conversations qui commençaient par « on devrait réfléchir à... », « que penses-tu si... », « tu voudrais bien relire ceci ? », et qui m'ont tellement aidée à avancer. Merci d'être aussi une amie, toujours à présente et à l'écoute dans les bons et les moins bons moments de ce parcours.

Au cours de ces 6 ans, j'ai eu la chance de partager mon temps entre la recherche et l'enseignement en travaillant comme assistante à la faculté de santé publique.

Merci aux Professeur·e·s William D'Hoore et Sophie Thunus, doyen·ne de la Faculté de Santé publique, ainsi qu'à tous les professeur·e·s dont j'ai encadré les TP de m'avoir accordé leur confiance.

Merci à mes (anciens) collègues assistant·e·s, Anne-Sophie, Carine, Héline, Pierre-Olivier, Sékou, Marine, Marlène, Nora, Carole, Madeleine, Hélène, Victoria, Jinane, Cécilia, Charlotte, Alexia, Céline, ça a été un bonheur de faire partie de l'équipe. Un merci particulier à l'équipe « quanti » et encore un autre à Anne-So, Hélène, Madeleine et Nora, vous qui m'avez entourée et soutenue chaque fois que j'en ai eu besoin.

Merci à Claire, Claudine, Gaëlle, Laetitia et Pierre, pour votre gentillesse et votre redoutable efficacité pour répondre à toutes mes questions relatives aux horaires, examens et autres programmes de cours.

Merci aux étudiant·e·s à qui j'ai eu le privilège d'enseigner.

Merci aux collègues de l'IRSS dont la présence a éclairé mon quotidien à la faveur d'une pause midi, d'une conversation au détour d'un couloir ou d'un moment informel. Merci Lucia, Thérèse, Jean, Nathalie, Nathalie, Anne, Asmaa, Lisa, Pierre, Mégane, Camille et tant d'autres qu'il m'est impossible de citer ici (j'espère que vous me pardonneriez).

Un merci special à la Professeure Isabelle Aujoulat, sans qui jamais je n'aurais poussé la porte du CLIP, preuve qu'un clic pour faire parvenir une offre d'emploi peut changer une vie. Merci Isabelle d'avoir cru en moi !

Merci à mes amis, Isabelle, Jacques, Dorothy, Aurore, Jonathan, Sylvie, Jean-Michel, Gaële, Déborah, merci pour ces moments de vie que nous partageons ensemble depuis bien des années. Plus que jamais, ils m'ont été indispensables.

Enfin, je voudrais remercier ici ma famille. Merci à ma maman et à ma sœur Florence, votre soutien inconditionnel a été une force pour traverser les tempêtes. Merci à mon beau-frère Fabrice, mes nièces Elise et Violette, pour votre présence, vous faites partie de mon essentiel. Pour terminer, merci aux trois soleils de ma vie : mon mari, Laurent, mes enfants, Eva et Dorian. Merci pour votre amour, votre soutien, votre patience et votre compréhension pour les longues heures de travail. Vous êtes l'oxygène que je respire, sans vous rien n'aurait été possible.

A toutes et tous, une fois encore, merci !

Catherine

Table of content

Jury members-----	11
Summary-----	13
List of abbreviations-----	15
GENERAL INTRODUCTION -----	17
OUTLINE OF THE THESIS AND RESEARCH OBJECTIVES -----	45
SECTION 1: Identification of local priorities for BZRA deprescribing -----	51
Chapter 1. Trends in benzodiazepine receptor agonists use and associated factors in the Belgian general older population: analysis of the Belgian health interview survey data-----	53
SECTION 2: Identification of barriers and potential interventions to BZRA deprescribing -----	77
Chapter 2. Barriers and enablers for deprescribing benzodiazepine receptor agonists in older adults: a systematic review of qualitative and quantitative studies using the theoretical domains framework -----	79
Chapter 3. Adaptation and validation of the revised Patients' Attitudes towards Deprescribing (rPATD) questionnaire for benzodiazepine receptor agonists ---	121
Chapter 4. Deprescribing benzodiazepine receptor agonists in older adults: a mixed-methods study to adapt the Canadian D-PRESCRIBE intervention to the Belgian community setting -----	149
SECTION 3: Evaluation of an implementation program to BZRA deprescribing-----	209
Chapter 5. Feasibility of the adapted D-PRESCRIBE intervention in the Belgian community setting: protocol for a cluster randomized controlled trial (END-IT CS study) -----	211
Chapter 6. Feasibility of the adapted D-PRESCRIBE intervention to favor benzodiazepine deprescribing in the Belgian community setting: results from a cluster randomized controlled trial (END-IT CS study) -----	245
GENERAL DISCUSSION -----	275
Curriculum vitae - Catherine Péteïn -----	297

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Summary

Benzodiazepine and z-drugs (BZRA) are medications mainly prescribed to treat insomnia or anxiety. However, in older adults (aged 65 or older), these medications have potentially harmful side effects, that may jeopardize older adults' safety and health. Despite guidelines to limit BZRA use to a few weeks at maximum, older adults frequently take them long-term. BZRA deprescribing in older adults is thus a priority.

This thesis aimed at developing tools to promote BZRA deprescribing in Belgian older adults living in the community setting. Before the development of these tools, we evaluated BZRA use in Belgian older adults (≥ 65 years) using data from the Belgian Health Interview Survey. This showed that BZRA use, if tending to decline, was still high in our country (18% in 2013). We also participated in a systematic review that highlighted barriers and facilitators towards BZRA deprescribing in older adults, showing numerous barriers from both the patients' and healthcare professionals' perspectives.

Because leaning on previous research might be more effective than developing new tools from scratch, we adapted three tools to promote efficient BZRA deprescribing. First, we adapted a validated questionnaire evaluating patients' attitudes towards deprescribing in general to BZRA deprescribing. If the assessment of its psychometric properties showed some statistical limitations, this questionnaire might facilitate the initiation of a conversation about BZRA deprescribing. Second, we adapted the two components of a Canadian benzodiazepine deprescribing intervention, comprising an educational brochure and a communication tool between the pharmacist and the prescriber. The feasibility of this adapted intervention was tested in a cluster-randomized controlled trial, that included 57 older adults recruited through 7 community pharmacies. The study demonstrated that implementing this intervention was feasible in the Belgian community setting, subject to some modifications in the study conduction procedures.

This thesis contributes to reinforcing the material already available in Belgium to promote BZRA deprescribing by providing tools specifically dedicated to older adults and fostering interprofessional communication around BZRA deprescribing.

List of abbreviations

ATC	Anatomical Therapeutic Chemical
aOR	Adjusted odds ratio
BCT	Behavior change technique
BEL-PEP	Belgian Psychotropic Expert platform
BHIS	Belgian Health Interview Survey
BMI	Body Mass Index
BZRA	Benzodiazepine receptor agonists
CBIP	Centre Belge d'Information Pharmacothérapeutique
CBT	Cognitive behavioral therapy
CBT-I	Cognitive behavioral therapy for insomnia
CDSS	Clinical decision support system
CI	Confidence interval
CW	Choosing Wisely
CWDIF	Choosing Wisely de-implementation framework
DSM	Diagnostic and Statistical Manual of Mental Health Disorders
EFA	Exploratory factor analysis
EQ5D-5L	EuroQol questionnaire (5 dimensions, 5 levels)
EU-PIM list	European list of potentially inappropriate medications
FAMHP	Federal Agency for Medicines and Health Products
GAD	Generalized anxiety disorder
GAI-SF	Geriatric Anxiety Inventory
GHQ-12	General Health Questionnaire
GP	General practitioner
HCP	Healthcare professionals
ICC	Intraclass correlation coefficient
ICER	Incremental cost-effectiveness ratio
ICSD	International Classification of Sleep Disorders
IQR	Interquartile range
ISI	Insomnia Severity Index
KCE	Belgian Healthcare Knowledge center
LVC	Low-value care
MMAT	Mixed Methods Appraisal Tool
MPC	Medico-pharmaceutical concertations
MRC	Medical Research Council
NA	Not applicable
NH	Nursing home
NIHDI	National Institute of Health and Disability Insurance

NPT	Normalization Process Theory
OECD	Organization for Economic Cooperation and Development
OR	Odds ratio
PATD	Patients' Attitudes Towards Deprescribing questionnaire
PC	Primary care
PD	Prevalence difference
PIM	Potentially inappropriate medication
Ph	Pharmacy
PR	Prevalence ratio
rPATD	Revised Patients' Attitudes Towards Deprescribing questionnaire
rPATD-BZRA	Revised Patients' Attitudes Towards Deprescribing questionnaire adapted for benzodiazepine receptor agonists
SCL-90-R	Symptoms Checklist-90-Revised questionnaire
SF-36	MOS 36-item Short-Form Health Survey
SNRI	Serotonin and norepinephrine reuptake inhibitor
SR	Systematic review
SSRI	Selective serotonin reuptake inhibitor
STOPP/START	Screening Tool of Older Persons' Prescription / Screening Tool to Alert to Right Treatment
TDF	Theoretical domains framework
VIF	Variance inflation factor

GENERAL INTRODUCTION

Introduction

This introduction is structured in three main parts. The first part briefly describes the state of the art regarding benzodiazepine receptor agonists, insomnia, and anxiety. The second part defines deprescribing in general and then focuses on benzodiazepine deprescribing. Finally, the third part presents benzodiazepine use in older adults as an example of low-value care.

1. **Benzodiazepine receptor agonists, insomnia, and anxiety**

1.1. Short history of benzodiazepine receptor agonists

Benzodiazepine receptor agonists (BZRA) include benzodiazepines and z-drugs. Benzodiazepines first arrived on the market in the 1960s, with for example Librium® in 1960 and Valium® in 1963, to treat insomnia or anxiety [1]. In less than two decades, they became the most prescribed drug, with 40 billion doses daily taken worldwide at the end of the 1970s [2]. However, concerns about dependence issues were raised in the 1980s, even when benzodiazepines were consumed at the prescribed dose [3]. In the 1980s, z-drugs (e.g.: zolpidem) were commercialized [4]. These medications, approved for treating insomnia only, were thought to be safer than benzodiazepines because of their shorter duration of action [4]. However, dependence issues related to z-drugs use as well were raised in the early 1990s [5]. Nowadays, BZRA are still prescribed to treat insomnia and anxiety, but current guidelines do not recommend them as a first-line treatment (see. 1.3). Since the late 1960s - early 1970s, benzodiazepines have also been prescribed for other health issues (e.g. epilepsy, neurologic spasticity) [6, 7]. However, these indications are minor, with anxiety and sleep disorders accounting for most of BZRA prescribing [8].

1.2. Insomnia and anxiety, two major mental health issues

a. Insomnia

Several different terms are used to describe insomnia (e.g.: sleep dissatisfaction, insomnia symptoms, insomnia disorder) [9]. To qualify insomnia disorders, two main definitions are used: that of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and that of the International Classification of Sleep Disorders (ICSD-3) (Table 1).

General introduction

Table 1. Definition criteria of insomnia disorders according to the DSM-5 and ICSD-3
DSM-5 [10]
A. A predominant complaint of dissatisfaction with sleep quantity or quality associated with one (or more) of the following symptoms: • difficulty in initiating sleep • difficulty in maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings. • early-morning awakening with inability to return to sleep
B. The sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning
C. The sleep difficulty occurs at least 3 nights per week.
D. The sleep difficulty is present for at least 3 months.
E. The sleep difficulty occurs despite adequate opportunity for sleep.
F. The insomnia is not better explained by and does not occur exclusively during the course of another sleep-wake disorder (e.g., narcolepsy, a breathing-related sleep disorder, a circadian rhythm sleep-wake disorder, a parasomnia).
G. The insomnia is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication).
H. Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia.
ICSD-3 (Chronic insomnia) [11]
1. A report of sleep initiation or maintenance problems
2. Adequate opportunity and circumstances to sleep
3. Daytime consequences
4. Duration: 3 months
5. Frequency: at least 3 times per week

Insomnia is frequent in the adult population but its prevalence may vary across studies, depending on which term is used and how it is measured (tool, time interval) [9]. According to the review of Morin and Jarrin in 2022, higher estimates are found for insomnia symptoms (30-36%) and sleep dissatisfaction (10-25%) than for insomnia disorder (6-10%), that answer to strict criteria [9]. Similar figures are found for Belgium, with the Belgian Health Interview Survey (BHIS) in 2013 estimating the prevalence of insomnia symptoms to 30% among the aged 15 or over [12].

The prevalence of insomnia is higher among older adults (≥ 65 years), with, according to the review of Patel *et al* in 2018, a prevalence ranging from 30 to 48% for insomnia symptoms and between 12 to 20% for insomnia disorder [13]. With age, physiologic changes occur in the architecture of sleep: sleep phases change (more time spent in light sleep and less in deep sleep) making falling asleep more difficult and increasing

the number of awakenings [14]. Older adults also frequently experience “advanced sleep phase syndrome”, which makes them falling asleep and waking up earlier [14]. Besides these physiologic changes, other environmental (e.g.: moving to a smaller place, institutionalization), social (e.g.: retirement, death of family or friends), behavioral (e.g.: change in sleep schedules, napping) and medical (onset of medical conditions, the taking of certain medications) risk factors explain the higher prevalence of insomnia in older adults [15].

b. Anxiety

Anxiety disorders include a vast spectrum of 11 different conditions, defined by the DSM-5, of which social anxiety, panic disorder, agoraphobia, or generalized anxiety disorder (GAD) [10]. Table 2 presents the DSM-5 definition criteria for GAD.

Table 2. Definition criteria for generalized anxiety disorders according to the DSM-5 [10]	
A.	Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).
B.	The person finds it difficult to control the worry.
C.	The anxiety and worry are associated with three or more of the following six symptoms (with at least some symptoms present for more days than not for the past 6 months). 1. Restlessness or feeling keyed up or on edge. 2. Being easily fatigued. 3. Difficulty concentrating or mind going blank. 4. Irritability. 5. Muscle tension. 6. Sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep).
D.	The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
E.	The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism).
F.	The disturbance is not better explained by another mental disorder (e.g., anxiety or worry about having panic attacks in panic disorder, etc.)

In 2010, anxiety disorders were the most frequent mental health disorders in the general population, with a 12-month prevalence estimated to be 14% among the European population aged ≥ 14 years, according to the systematic review of Wittchen

General introduction

et al [16]. Most likely due to differences in methods assessing anxiety disorders, figures from the Global Burden of Disease (2019) estimated the prevalence of anxiety disorders (all ages) in the European Union at 5.2% [17]. In Belgium, the 2018 BHIS found a prevalence of generalized anxiety disorder of 11.2% in the population aged 15 and older [18], when it is estimated at 5% by the Global Burden of Disease (2019) (all ages) [17].

Contrary to the prevalence of insomnia disorders that increases with older age, anxiety disorders prevalence tends to decrease. Figures from the Global Burden of Disease (2019) show a prevalence of 5.6% for older adults ≥ 70 years living in the European Union, which is less than the prevalence observed for the 60-64 years category (6.1%) [17]. When looking at the figures for Belgium specifically, the same trend is found (4.9% for older adults ≥ 70 years, 5.4% for the 64-69 years category, 5.5% for the 60-64 years category) [17]. Similarly, the 2018 BHIS showed that the prevalence of GAD tended to decrease after 65 years (7.7%) whereas it peaks at 14.6% for the 34-44 years category [18]. According to a national Australian study, many factors are associated with 12-months GAD at an older age: functional limitations, lifetime depression history, concerns about having a serious illness despite doctor's reassurance, and family history of anxiety or depression [19].

c. Health consequences of anxiety and insomnia

Both insomnia and anxiety disorders have negative consequences on mental and physical health and are associated with low quality of life [20, 21]. Long-term insomnia has been associated not only with higher risks of anxiety or depression [9], but also with higher risks of obesity, diabetes or glucose intolerance, cardiovascular diseases and hypertension, and alcohol use [22]. Individuals with anxiety disorders often present depressive disorders and vice versa [23]. Anxiety disorders are also associated with higher risks of gastrointestinal problems, hypo-hyperthyroidism, diabetes, cardiovascular disease, and respiratory problems [23]. In older adults, anxiety has been associated with higher levels of physical disability, and higher medical expenses [24]. In addition to these health-related consequences, insomnia and anxiety have also negative consequences on the social functioning of the individuals [25, 26], which may, in return, impact their mental health.

1.3. Current guidelines for the treatment of insomnia and anxiety

European guidelines recommend cognitive behavioral therapy for insomnia (CBT-I) as the first-line treatment for insomnia at any age (very strong recommendation) [27]. Indeed, CBT-I is safe and is also the only therapeutic option whose effect remains up to two years after discontinuation [28]. Pharmaceutical treatment options are limited

and may comprise BZRA and low-dose sedating antidepressants in the short-term (≤ 4 weeks) (respectively very strong and strong recommendations). Longer-term use of these medications might be considered depending on the individual situation (strong recommendation)[27]. Other medications such as antipsychotics, antihistaminic drugs, melatonin, and phytotherapy are not recommended in the treatment of insomnia, due to their potential side-effects and/or low evidence of efficacy (strong recommendation)[27]. In Belgium, the Working group Development of Primary Care guidelines (WOREL) developed similar guidelines recommending also non-pharmaceutical therapies such as CBT-I (strong recommendation) [29]. Sedative medication may be prescribed in the short-term in case of “*severe insomnia accompanied by severe suffering*” (weak recommendation) but never as first-line treatment in older adults (strong recommendation) [29]. Sedative medications should not be prescribed outside “crisis situation” (strong recommendation) and their deprescribing should be discussed at initial prescribing (strong recommendation) [29]. In addition, and specific to older adults, the Belgian “*Formulaire de soins aux personnes âgées*” from the Centre Belge d’Information Pharmacothérapeutique (CBIP) only recommends prescribing an intermediate-acting BZRA¹ such as lorazepam, for one week only [30].

For treating acute situations of anxiety disorders, the European guidelines recommend choosing a psychological or a pharmaceutical treatment based on “*clinical features, needs and preferences, and local service availability*” (p. 416), as they have the same efficacy overall. In the longer term, a pharmacological treatment found effective should be continued for up to 18 months (based on category I evidence). If a psychological treatment is chosen, CBT should be recommended (based on category III evidence). However, combining both approaches is not recommended for initial treatment (based on category I evidence). In older adults, the Belgian “*Formulaire de soins aux personnes âgées* » (CBIP) places CBT as first-line treatment for GAD. If a pharmacological treatment is chosen, both the European guidelines and the Belgian guidelines from the CBIP recommend using selective serotonin reuptake inhibitors (SSRI) as the first-line pharmaceutical treatment (based on category I evidence) [31, 32]. Serotonin and norepinephrine reuptake inhibitors (SNRI), and pregabalin are also medications found effective in the treatment of anxiety but have more side effects [31]. Belgian guidelines (CBIP) do not recommend using them in older adults [32].

¹ BZRA can be classified according to their duration of action: long-acting BZRA (half-life >20 h, e.g.: diazepam), intermediate-acting BZRA (half-life between 10 and 20h, e.g.: lorazepam, alprazolam), short-acting BZRA (half-life between 5 and 10h, e.g.: zolpidem) and ultra-short-acting BZRA (half-life <5 h, e.g.: triazolam) (source: CBIP website: www.cbip.be, accessed 11/03/2024)

General introduction

Benzodiazepine use could be considered in acute situations and limited to short-term treatment (based on category I evidence, standard of clinical care) but no guidelines indicate a specific duration [32, 33]. The European guideline recommends using tricyclic antidepressants only in a second intention, in case of non-response to SSRI and SNRI (based on category IV evidence). These medications along with beta-blockers which are also used in the treatment of anxiety are not recommended in older adults, according to the CBIP [32].

1.4. BZRA risks and benefits in older adults

The restrictions in BZRA use in the treatment of insomnia and anxiety are driven by an unfavorable benefit-risk balance in older adults.

A recent systematic review and network meta-analysis showed that compared to placebo, BZRA use improved self-reported quality of sleep in the acute treatment of insomnia disorders (moderate to high certainty of evidence) [34], and another meta-analysis found that BZRA use increased sleep duration of 25.2 minutes per night on average, and to significantly decreased the number of awakenings [35]. Sleep quality of older adults, however, does not seem to be improved, as suggested by a large Canadian study conducted in 2005-2006 [36], and the BZRA hypnotic effects were found to fade after four weeks [37]. BZRA efficacy in treating anxiety presents some limits as well: a review in 1999 found that 50% of the BZRA anxiolytic effects were related to the placebo effect [37], and another systematic review in 2020 highlighted that if BZRA were effective in the treatment of anxiety disorders in older adults the included studies were few, outdated, limited to few compounds, and not covering the whole spectrum of anxiety disorders [38]. For example, BZRA have shown effectiveness in the acute treatment of GAD, social anxiety disorder, and panic disorders, but not in post-traumatic stress disorders [39].

BZRA use involves potential important risks in older adults. In 2018, a systematic review and meta-analysis found a significant association between benzodiazepine use in older adults (≥ 60 years) and the risk of falls (OR (95% CI): 1.42 (1.22; 1.65)) [40]. According to another meta-analysis conducted in 2017, BZRA use also involves a higher risk of hip fracture (pooled relative risk (RR) for benzodiazepines: 1.52 (95%CI: 1.37; 1.68), pooled RR for z-drugs (1.90 (95%CI: 1.68-2.13)) [41]. Moreover, older BZRA users have a higher risk of being involved in a car accident leading to hospitalization [42]. Besides, if no causal association has been found between BZRA use and dementia [43], they have been associated with a higher risk of cognitive impairment [44]. All these risks can have serious impacts on hospitalizations, functional decline, and mortality [45, 46]. Besides, BZRA use is associated with tolerance (which may lead

to increased dosage but is unusually observed) and dependence (which may lead to withdrawal symptoms) [39].

1.5. BZRA use in older adults

BZRA use is high in older adults living in Western countries with a prevalence of around 12-15% in Ontario, Scotland, and the United States and 20%-25% in Switzerland and Quebec [47-51]. Among older adults, BZRA use is higher in women and the oldest age groups [8, 47, 48]. However, a trend toward a decline in BZRA use has been observed during the past decade in several countries [47, 52, 53].

In Belgium also, BZRA use is high, with 20% of the Belgian population having taken at least one BZRA in 2022. Similar to what was observed in other countries, the number of patients prescribed BZRA has overall decreased since 2018 [54]. However, a study using Belgian prescription data from general practice examined trends in BZRA prescription in the general population over a longer period (from 2000 to 2019) and mitigates this declining trend. Indeed, results showed an overall increase in BZRA prescription over the period, particularly among older long-term users (≥ 65 years), despite a significant decrease since 2006 [55].

Not only do many older adults take a BZRA, but many of them take it long-term, despite the recommendation of the guidelines (see 1.6) [56]. Indeed, in Sweden, among all new users, higher percentages of switch to long-term use are observed in older adults compared to younger BZRA new users [57]. Some prescribing patterns at initiation are associated with the switch to long-term use, like the high number of days supplied [58] and the prescription of multiple BZRA [57]. Reporting a bad sleep quality and being prescribed a sedative-hypnotic at initiation (compared to being prescribed an anxiolytic BZRA) were also associated with long-term use in older adults [57, 58]. Indeed, long-term use was found more prevalent in older adults with sleep disorders than those with anxiety disorders [59].

BZRA abuse (or sedative, hypnotic, or anxiolytic use disorder) is defined by the DSM-5, as *“a problematic pattern of sedative, hypnotic, or anxiolytic use leading to clinically significant impairment or distress, manifested by at least two symptoms (out of a list of 11, e.g.: taking the medication in larger amounts or over a longer period than was intended, craving, persistent desire or unsuccessful effort to control use), occurring within a 12-month period”*[10]. It is unusual in older adults (≥ 65 years): according to two American studies, between 0.6 and 4.2% declare using them without a prescription, or in greater amounts, more often, longer, or for any other use than prescribed during the past year [49, 60]. A systematic review including registry-based

General introduction

studies from 1994 to 2014 highlighted that low and steady dosage was the most frequent pattern of long-term use in older adults [56].

1.6. Current guidelines for BZRA use and deprescribing in older adults

Due to the unfavorable benefit-risk balance of BZRA use, lists of potentially inappropriate medications in older adults unanimously advise very limited use of them, which is in line with the guidelines for the treatment of insomnia and anxiety presented in point 1.3. For example, the American Geriatrics Society Beers criteria recommend avoiding BZRA in older adults (strong recommendation, moderate evidence) [61]. In Europe, the STOPP/START (Screening Tool of Older Person's Prescription/Screening Tool to Alert to Right Treatment) criteria recommend BZRA use to be limited to two weeks maximum when prescribed for insomnia and to four weeks maximum otherwise [62]. The EU(7)-PIM list (European list of potentially inappropriate medication) advises to use the lowest dose possible (up to half the usual dose), to progressively increase or decrease the dosage, and to limit BZRA use to the shortest possible treatment duration [63]. In addition, the evidence-based clinical guidelines of Pottie *et al*, published in 2018, recommend deprescribing BZRA in older adults taking them for insomnia (strong recommendation, low-quality evidence) [64]. The recent MAGIC guidance, published in the frame of the BE-SAFE project², also recommends considering deprescription for patients taking them for insomnia. However, the force of this recommendation is weak for several reasons: (1) little evidence of benefits on outcomes such as quality of life or sleep symptoms, (2) variation in patient preferences regarding willingness to deprescribe and avoiding long-term side-effects, (3) uncertainty on causal associations between BZRA use and long-term risks, that may vary depending on the context, and, (4) as BZRA deprescribing interventions are time-consuming, the necessity for the clinician to prioritize other more important health problems [65].

It is important to note that BZRA deprescribing is not recommended in every older adult using a BZRA. For example, the BZRA deprescribing algorithm from the Canadian Medication Appropriateness and Deprescribing Network recommends BZRA continuation if prescribed for restless legs, unmanaged anxiety, depression or physical problems or alcohol withdrawal [66].

² BE-SAFE is a European Union-funded research project aiming “to improve patient safety by addressing knowledge and practice gaps related to the reduction of benzodiazepine and sedative hypnotics used for sleep difficulties in Europe.” (source: <https://besafe-horizon.eu/en/about-be-safe/the-project>, accessed 10/03/2024)

2. Deprescribing medications

2.1. Definition

Deprescribing has several definitions: Reeve *et al.* define it in 2015 as “*the process of withdrawal of an inappropriate medication, supervised by a healthcare professional with the goal of managing polypharmacy and improving outcomes*”[67] (p.1254). Farrell *et al.* define it in 2016 as “*the planned and supervised process of dose reduction or stopping medications that may be causing harm or are no longer providing benefits*”[68] (p.2).

For this thesis, we decided to use the definition of Farrell *et al.* for three reasons:

- 1) It includes the dimension of reducing the medication, which may already be beneficial for patients taking BZRA.
- 2) Due to the tolerance and dependence phenomena and potential side effects, BZRA corresponds perfectly to the explicit definition of “*medications that may be causing harm or are no longer providing benefits*” (which are also covered by the term “inappropriate” in Reeve’s definition).
- 3) The goal of managing polypharmacy stated in the definition of Reeve *et al.*, is not 100% appropriate regarding BZRA, as BZRA use does not concern patients with polypharmacy only.

2.2. Evidence of benefits and risks of deprescribing

Many different outcomes have been studied regarding the risks and benefits of deprescribing medications. The TAILOR evidence synthesis about deprescribing in older adults living with multimorbidity and polypharmacy classified them in 4 categories: **safety** (e.g.: adverse drug effects, delirium, cardiovascular events), **clinical effects** (e.g.: hospital (re)admissions, health appointments, mortality, adherence, quality of life), **prescribing effects** (e.g.: number of drugs, medication appropriateness, drug discontinuation, drug dosage), and **acceptability** (e.g.: pursuing the offer to change drugs, or participation for patients, and communication or satisfaction with the experience for healthcare providers) [69]. Some of the clinical outcomes, such as mortality, falls or hospitalization are considered by other authors as safety outcomes as well [70].

The literature describes deprescribing interventions as safe. The TAILOR synthesis, which included 20 studies conducted in Europe, Asia, North America and Australia between 2013 and 2020, found that outcomes related to safety were overall positive, especially when structured deprescribing approaches were used [69]. As an example, the ECSTATIC non-inferiority trial showed the feasibility of deprescribing preventive

General introduction

cardiovascular medications, with no safety issues, provided appropriate monitoring [71]. To add to these results, another systematic review and meta-analysis conducted in 2023 found that deprescribing interventions had a significant positive effect on adverse drug reactions after the intervention.

Many outcomes regarding clinical effects showed no statistically significant results in different systematic reviews: hospitalization rate [72], number of emergency visits [72], mortality [72, 73], quality of life [72, 74], number of falls [72, 75]. As they may also be considered as safety outcomes, these results also show that deprescribing interventions do not lead to worse outcomes. This strengthens the conclusions about deprescribing being safe for the patient.

Regarding prescribing outcomes, percentages of potentially inappropriate medications (PIM) and potential prescribing omissions (PPO) in older adults were found to be statistically improved by deprescribing interventions [72]. However, contradictory results were found in the literature regarding the impact of deprescribing interventions on medication adherence. One systematic review concluded to no evidence of an effect of deprescribing interventions on medication adherence [76] whereas another described higher rates of medication compliance [72].

Finally, acceptability outcomes were also overall positive for healthcare providers, even if there is a lack of evidence regarding acceptability for patients [69]. However, the study of Zhang et al, who examined patients' trust level in healthcare providers after an educational deprescribing intervention in Canada, found that it was not detrimental to the patient-healthcare provider relationship [77].

All these data suggest that deprescribing allows patients to live with less but more appropriate medications without safety issues or trust issues with healthcare providers.

2.3. Shared decision-making in the deprescribing process

Shared decision-making is central in the deprescribing process and eliciting patient preferences is one of its key steps [78, 79]. Shared decision-making is defined as *“an approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences”*[80] (p.1361). A study among older adults with multimorbidity showed that shared decision-making increased the probability of deprescribing [81]. However, eliciting patients' preferences might be challenging as preferences vary between and within older adults [78]. This challenge is even more

important with patients presenting cognitive impairment. Weir et al described three patient profiles regarding attitudes towards medicines, preferences for decision-making and openness to deprescribing (see Figure 1) [82]. Authors underline that these profiles are not watertight (a patient may present characteristics from several profiles) and that attitudes may be different according to the medication considered [82].

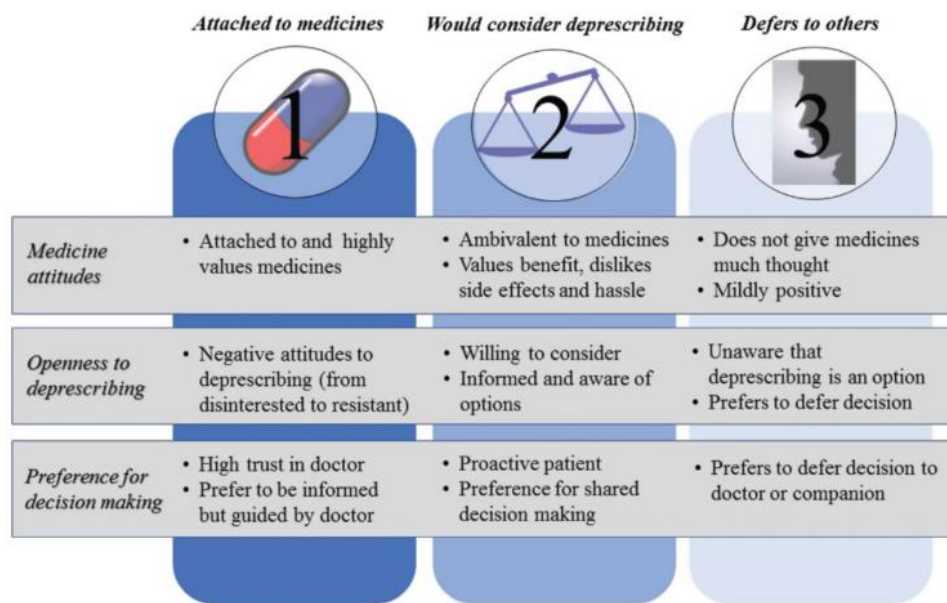


Figure 1. Typology of participants. From Weir et al. [82, p.101], reproduced with the kind authorization of the author.

2.4. Attitude of older adults towards deprescribing in general

Assessing their attitudes towards deprescribing is a first step to involving patients in shared decision-making. To explore the attitudes of older adults towards deprescribing, Reeve *et al.* developed the Patients Attitudes Towards Deprescribing questionnaire (PATD) in 2013 [83], its revised version in 2016 (rPATD) [84], and a specific version for people with cognitive impairment (rPATDcog) in 2018 [85]. A caregiver version exists for the rPATD questionnaire [84]. These questionnaires are the most frequently used tools to explore patients' attitudes towards deprescribing [86]. In 2022, Weir et al published a systematic review of studies that used these questionnaires. This review included 40 studies, mostly led in Australia, North America, and Europe [86]. Authors showed that a large majority of older adults (84%, 95% CI: 81-88%) would agree or strongly agree with the statement "If my doctor said it

General introduction

was possible, I would be willing to stop one or more of my regular medicines”. However, a large majority of older adults also agree or strongly agree with the statement “Overall, I am satisfied with my current medicines” (between 67% and 93%, across studies that used the rPATD). This demonstrates some ambivalence in older adults regarding deprescribing in general [86]. The literature describes some elements that may influence patient’s deprescribing willingness:

1. The nature of the treatment (preventive medication or medication against a specific symptom) [87, 88]. A systematic review has indeed shown that deprescribing was more successful in cardiovascular medications and less successful in proton pump inhibitors and psychotropics [89].
2. Patients’ health outcome priorities [90]. Higher deprescribing willingness (for either preventive or symptom-relief medications) was found in older adults prioritizing fewer medications [90]. On the opposite, lower deprescribing willingness regarding symptom-relief medications was found in older adults prioritizing now over the future [90].
3. The patient-doctor relationship. A study conducted in primary care has indeed shown that older adults trusted their GP to make the right decisions regarding medication deprescribing [91].

2.5. Available tools to help healthcare professionals with deprescribing in clinical practice

Based on a narrative review published in 2020, tools helping the deprescribing process may be classified into seven categories, listed below [92]:

1. **General deprescribing guidance** that provides clinicians with a general background about the necessity to consider deprescribing. Some general guidelines also include advice on how to detect eligible medications for deprescribing or provide a deprescribing framework or process [92].
2. **Generic (non-specific) deprescribing frameworks**, that guide clinicians in the deprescribing process, indicating key steps to follow during the clinical encounter [92].
3. **Drug-specific deprescribing guidelines/guides** that provide tools such as deprescribing algorithms to guide clinicians through the deprescribing process of a specific medication [92].
4. **Electronic Clinical Decision Support Systems (CDSS)**, which are “*software that designed to be a direct aid to clinical decision-making, in which the characteristics of an individual patient are matched to a computerized clinical knowledge base and patient-specific assessments or recommendations are then presented to the clinician or the patient for a decision*” [93] (p. 528). Some specific deprescribing CDSS exist such as MedStopper or MedSafer [92].

5. **Tools for identifying potentially inappropriate medications** (PIMs), that comprise explicit lists of potentially inappropriate medications such as the STOPP or Beers criteria, but also implicit criteria based on clinical judgment such as the Good Palliative-Geriatric Practice [92].
6. **Tools for engaging patients**, that comprise patient education material such as fact sheets, decision aids, option grids, and educational brochures, that help improve patient knowledge and involvement in shared decision-making [92].
7. **Pharmaceutical opinions**, which are “*documents sent from the pharmacist to the prescriber detailing a problem with a patient’s pharmacotherapy and recommending a management strategy to address the drug-related problem*” [94] (p.134). Pharmaceutical opinions were commonly used in Canada until April 2024 [95] and aimed to help prescribers to reconsider the use of specific medications.

2.6. BZRA deprescribing interventions in older adults living in the community setting

BZRA deprescribing interventions have been undertaken for decades and target patients, healthcare professionals, or both, with multiple designs and strategies [96]. The literature does not report differences in sleep quality or adverse drug withdrawal reactions, suggesting the feasibility and safety of these interventions [97]. Depending on intervention components, large discrepancies are found regarding their efficacy, with discontinuation rates ranging from 27% to 80% found in the systematic review of Reeve *et al* on BZRA and other hypnotics deprescribing interventions among older people [97]. Interventions led in the community setting comprised gradual dose reduction combined with psychological support, melatonin substitution, patient education through a booklet, and “one-off counselling” by a geriatrician. The two first showed the highest success rates (80% and 64.3%, respectively) and the two last showed the lowest success rates (27% and 35% respectively) [97]. However, as underlined by the authors, patient educational interventions “*potentially reflect real-life practice better than the controlled pharmacological substitution*” [97](p. 932). Patient education was a common component (alone or in combination) of the eight brief BZRA deprescribing interventions conducted in primary care included in the systematic review of Lynch *et al*, whose population target was long-term adult users (≥ 18 years old). Pooled results indicated that the intervention group had more than twice the probability of BZRA deprescribing compared to the control group (receiving usual care), showing interest for brief interventions [98].

The recent MAGIC guideline provided recommendations on the nature of components to integrate into a BZRA deprescribing intervention: recommended components

General introduction

comprise patient education, physician education, tapering, and CBT-I (weak recommendations) [65]. The MAGIC guideline, however, does not recommend using pharmacological substitution (weak recommendation), due to low evidence of their efficacy, potential side-effects, and variation in patient values and preferences [65]. Because they may be more effective in promoting BZRA deprescribing, the MAGIC guideline recommends favoring a multi-component approach rather than a single-component intervention (weak recommendation). This choice, however, must consider the context, as well as preferences and values of the patient, to avoid overburdening the physician and/or the patient [65].

If safe and feasible, the current evidence on the benefits of BZRA deprescribing on patients' outcomes is, however, limited. For example, a Finnish study showed that sleep quality and quality of life in older adults were improved after BZRA deprescribing [99]. Regarding falls, a systematic review on "fall-risk increasing drugs" comprising sedative-hypnotics, showed that deprescribing alone did not reduce the risk of fall or fall-related injuries [100]. However, an emulated trial among older patients with cirrhosis showed a lower risk of fall and fractures in patients deprescribed zolpidem but no difference for patients deprescribed benzodiazepines [101].

2.7. Policies related to BZRA use and BZRA deprescribing interventions in Belgium

In 2024, 22 different compounds (20 benzodiazepines and 2 z-drugs) are authorized on the Belgian market [102]. BZRA use requires a medical prescription. However, BZRA are not covered by the National Institute of Health and Disability Insurance (NIHDI), meaning that the cost of these medications is entirely supported by the patient [103]. The absence of NIHDI coverage makes BZRA use monitoring difficult. Indeed, only reimbursed medication dispensed in public pharmacies is encoded in the national database Pharmanet [104]. This database allows the NIHDI to analyze and compare the prescribing behavior of physicians, but this is not possible regarding BZRA [104]. At the beginning of this thesis (September 2018), no study had been conducted yet to assess the prevalence of BZRA use in the general older population.

Since 2002, several national awareness campaigns have been launched, aiming to reduce BZRA use in the Belgian population. At the beginning of this thesis, the latest campaign "*Somnifères et calmants, pensez d'abord aux autres solutions*" was launched in February 2018³. This campaign provided GPs and community pharmacists

³ See the following webpage: <https://www.health.belgium.be/fr/sante/prenez-soin-de-vous/medication/somniferes-et-calmants>

with several materials such as a poster, a brochure, and a screen video to sensitize patients in waiting rooms or pharmacies, or practical tools such as sleep diaries or practical sheets with tips to engage the conversation about dependence issues or about the use of alternatives. Not specific to older adults, the Big Bird trial began (in August 2019), aiming to recruit 1200 participants in general practice to test the efficacy of a BZRA deprescribing intervention combining face-to-face contacts patient/GP and a web-based learning interface [105]. Other initiatives have been taken during the time course of this thesis (2018-2024); they will be addressed in the discussion part of this thesis.

3. BZRA deprescribing as an example of de-implementation of low-value care

Given all the previous information on BZRA in older adults, its deprescribing fits a larger perspective which is the de-implementation of low-value care.

3.1. Definitions

Low-value care (LVC) is defined as “*care that is unlikely to benefit the patient given the harms, cost, available alternatives, or preferences of the patient*” [106](p. 737). De-implementing low-value care is abandoning those care practices [107].

Deprescribing is important in the field of de-implementation of LVC. Indeed, among all LVC practices (e.g. laboratory testing, imaging, medication use, etc.), reducing inappropriate medications represented more than half of the studies included in the systematic review of Parker *et al.* [108]. Considering the limited benefits of BZRA use and its potential associated risks described in point 1.4., long-term BZRA use matches the definition of low-value care for many patients. Nevertheless, one may argue that BZRA use does not fully match the definition of low-value care. Indeed, a Belgian qualitative study highlighted that patients believed that “hypnotic medication use is harmless”[109]. Another Canadian qualitative study showed that patients prioritized sleep over BZRAs’ harms [110]. The authors also suggested that patients are insufficiently informed about the limited effectiveness of BZRA, which may impact their attitude towards BZRA deprescribing [110]. In this regard, BZRA use might not be perceived as LVC for patients, especially if they are not fully informed.

3.2. Why is de-implementing low-value care important?

First, the range of negative consequences of LVC for patients is wide. In point 1.4 we already discussed the risks of BZRA use in older adults. Korenstein *et al* mapped the potential negative consequences of LVC into 6 domains listed by order of frequency:

General introduction

physical effects, psychological effects, treatment burden, financial effects, dissatisfaction with the healthcare system, and social effects [111]. Authors underline that LVC often leads to an “overuse cascade” (i.e.: more healthcare use) that may also result in these negative consequences for the patient [111]. In addition, Baron et al call overuse “an inequity issue” as people from ethnic minorities are more likely to receive LVC [112].

Second, LVC has negative economic and environmental consequences. In the United States, annual costs related to LVC were estimated between \$75.7 to \$101.2 billion and potential savings between \$12.8 to \$28.6 billion if effective interventions were scaled up nationally (e.g.: medication use optimization) [113]. Besides, in the context of climate change, the environmental impact of LVC cannot be ignored. Pilcher et al estimated that healthcare systems were responsible for 5.5% of the carbon footprint in OECD (Organization for Economic Cooperation and Development) countries, which was equivalent to the footprint of the food sector [114]. In addition to the carbon impact, healthcare systems are also accountable for air and water pollution [115]. De-implementing LVC is thus a necessity for an economically and environmentally sustainable healthcare system. We believe that BZRA deprescribing contributes to this objective.

3.3. The Choosing Wisely initiative

The Choosing Wisely (CW) initiative started in 2012 in the United States with nine medical specialty societies joining the first phase of the CW initiative and each publishing their Top Five list of tests, treatments, or services whose use should be reconsidered by both patients and clinicians [116]. The CW initiative has rapidly expanded and reaches today more than 30 countries and 80 medical societies, and lists more than 700 overused or unnecessary tests, treatments, or services [117].

Statements against the use of BZRA figure in CW priorities. As an example, “Don’t use benzodiazepines or other sedative-hypnotics in older adults as first choice for insomnia, agitation or delirium” is one of the CW recommendations in the United States, Canada, and Italy [118-120], and Top-10 CW Australian recommendations include “Avoid prescribing benzodiazepines to patients with a history of substance misuse (including alcohol) or multiple psychoactive drug use” [121]. Beyond providing recommendations, Choosing Wisely Canada published a toolkit called “Drowsy without feeling lousy: A toolkit for reducing inappropriate use of benzodiazepines and sedative-hypnotics among older adults in primary care” in April 2023 [122]. For example, the toolkit explains how to take advantage of a renewal consult to discuss BZRA deprescribing, informs on alternatives to BZRA use, or describes measures allowing monitoring BZRA deprescribing efforts [122].

3.4. De-implementation theories, models, and frameworks

In implementation science, it is widely acknowledged that using theoretical approaches allows “*a better understanding and explanation of how and why implementation succeeds or fails*” [123](p.1). Guidance from the Medical Research Council framework indeed encourages the use of theory in developing and evaluating complex interventions [124, 125]. If de-implementation is a new but expanding field [108], it can rely on the numerous frameworks, models, and theories from related implementation science [126].

To better understand how theoretical approaches may help de-implementation, we would like to define the terms “theory”, “model”, and “framework”. Nilsen defines a theory as “*a set of analytical principles, or statements designed to structure our observation, understanding and explanation of the world*” [123](p. 2). Models “*involve a deliberate simplification of a phenomenon or a specific aspect of a phenomenon*” [123](p.2). If theories aim to describe and explain the world, models have a narrower scope and only have a describing purpose [123]. Frameworks “*denote a structure, overview, outline, system or plan consisting of various descriptive categories, e.g. concepts, constructs or variables, and the relation between them are presumed to account for a phenomenon*”[123]. Nilsen classified the use of theories, models, and frameworks in implementation science into three main aims: 1) describing and/or guiding the process of translating research into practice (i.e: process models); 2) understanding and/or explaining what influences implementation outcomes (i.e.: determinants frameworks, classic theories from psychology or sociology, implementation theories developed by researchers); and 3) evaluating implementation (i.e. evaluation frameworks) [123]. (see Fig 2.)

General introduction

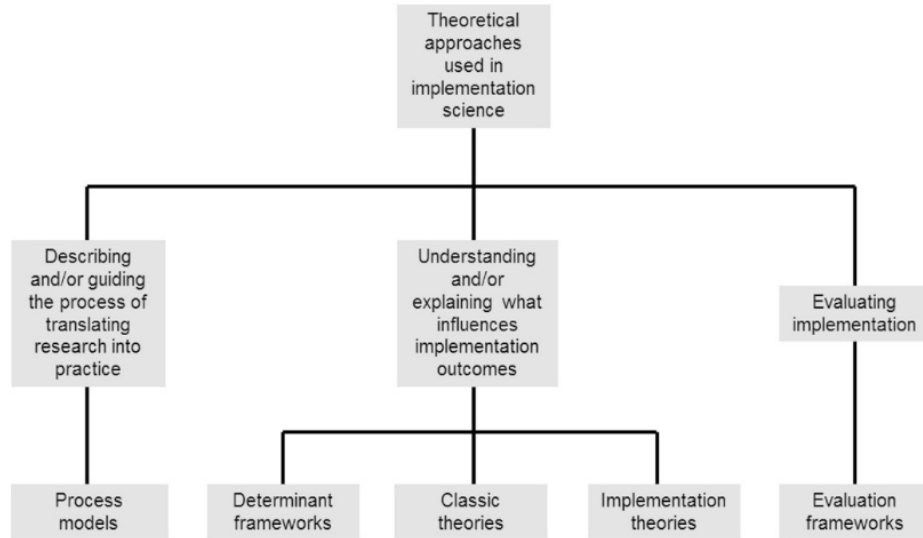


Figure 2. Three aims of the use of theoretical approaches in implementation science and the five categories, models and frameworks. From Nilsen [123], p.4, reproduced with the kind authorization of the author.

In this thesis, we will rely on a process model, the **Choosing Wisely De-Implementation Framework** (CWDIF) [127], that will structure our manuscript. The CWDIF comprises 5 phases (see Figure 3) [127].

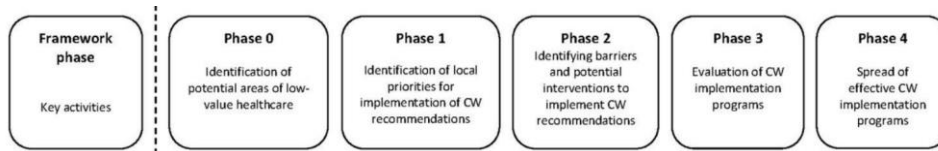


Figure 3. The Choosing Wisely De-implementation Framework (CWDIF). From Grimshaw *et al.* [127], p. 411, reproduced with the kind authorization of the author.

Phase 0 aims to *identify potential areas of LVC*. These potential areas of LVC are identified for example in lists of CW recommendations regarding tests, treatments, and services. **Phase 1** aims to *identify local priorities for implementation of CW recommendations*. As the authors underline, all CW recommendations cannot be addressed at once. Therefore, this step aims to demonstrate the need for addressing

the chosen CW recommendation. **Phase 2** aims to *identify barriers to implementing the chosen CW recommendation*. In this step, Grimshaw et al. recommend using the TDF, which is, in the taxonomy of Nilsen, a determinant framework. Phase 2 also aims to *identify potential interventions* that would address these barriers. **Phase 3** aims to *evaluate the implementation of a CW program*, with cluster-randomized controlled trial being the gold standard to do so. However, the authors highlight the importance of process evaluation and economic evaluation to inform sufficiently. Finally, **Phase 4** aims to *spread effective CW implementation programs* at a large scale.

If this model provides a useful step-by-step process to “*de-implement LVC in a systematic and rigorous manner*” [127](p.414), we acknowledge that it was not the initial purpose of this thesis and that this model was chosen “*a posteriori*”. In this thesis, Sections 1, 2, and 3 correspond to Phases, 1, 2, and 3 of the CWDIF.

In Chapter 2, we will use the Theoretical Domains Framework, as recommended by Grimshaw *et al.* This is the determinant framework that is the mostly used in empirical studies aiming to understand what influences de-implementation outcomes [108].

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OUTLINE OF THE THESIS AND RESEARCH OBJECTIVES

Outline of the thesis and research objectives

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This thesis aimed to develop tools to promote BZRA deprescribing in Belgian older adults in the community setting. Beyond developing these tools, other work has been done to broaden our knowledge and understanding of BZRA use and deprescribing in older adults. As previously stated, I structured this thesis according to the CWDIF. It comprises 3 sections, each corresponding to one phase of the CWDIF (Figure 1). Inside each section, I present different chapters, each answering a specific research objective.

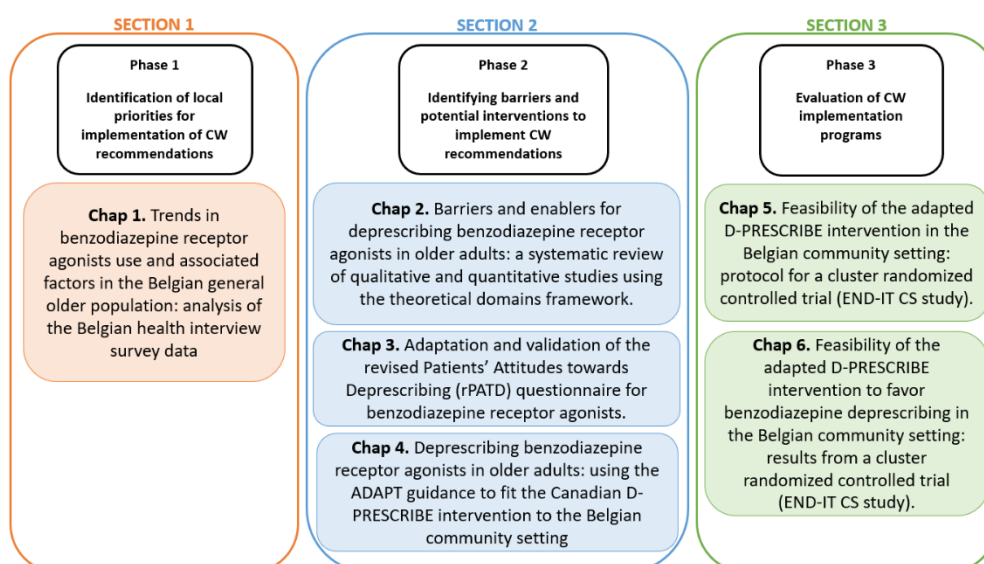


Figure 1. Structure of the thesis according to the CWDIF phases

SECTION 1: Identification of local priorities for BZRA deprescribing

Research objective:

1. To describe trends in BZRA use in Belgian older adults and factors associated with BZRA use.

This section comprises one chapter (**Chapter 1**), in which I describe 1) national trends of BZRA use in Belgium from 2004 to 2013 in older adults (≥ 65 years), and 2) factors associated with BZRA use in 2013 using the data of the Belgian health interview survey.

Outline of the thesis and research objectives

The results will help to better characterize the need for BZRA deprescribing in our population of interest.

SECTION 2: Identification of barriers and potential interventions to BZRA deprescribing

Research objectives:

1. To identify barriers and enablers to BZRA deprescribing in older adults;
2. To develop a questionnaire to assess the attitudes of older adults towards BZRA deprescribing;
3. To develop an intervention to favor BZRA deprescribing in older adults living in the community setting.

This section comprises three chapters (**Chapter 2**, **Chapter 3**, and **Chapter 4**) each answering to one research objective.

Chapter 2 presents the results of a systematic review (SR) aiming to identify barriers and enablers toward BZRA deprescribing in older adults and to map them into Theoretical Domains Framework (TDF) domains.

Chapter 3 focuses on the attitude of older adults towards BZRA deprescribing which may be an important barrier or enabler towards BZRA deprescribing. High levels of willingness toward deprescribing in general were found in the literature (84% would be willing to have a medication deprescribed if the doctor said it was possible)[1]. However, no questionnaire specifically assessed older adults' attitudes toward BZRA deprescribing. **Chapter 3** describes the adaptation of the revised Patient Attitude Towards Deprescribing questionnaire (rPATD) [2] to BZRA and the evaluation of its psychometric properties. Using the data collected for the questionnaire validation, this chapter also presents a short description of attitudes towards BZRA deprescribing of our participants.

Chapter 4 describes the adaptation process of the Canadian D-PRESCRIBE intervention to the Belgian community setting. The D-PRESCRIBE intervention comprised two components: an educational leaflet, called the EMPOWER brochure, distributed by the pharmacist to the patient, and the sending of a pharmaceutical opinion from the pharmacist to the prescriber [3]. The adaptation process was guided by recommendations from the ADAPT guidance and from the new Medical Research Council framework for developing and evaluating complex interventions [4, 5].

Outline of the thesis and research objectives

SECTION 3: Evaluation of an implementation program to BZRA deprescribing

Research objectives:

1. To elaborate a research protocol for evaluating the feasibility of the adapted D-PRESCRIBE intervention in the Belgian community setting.
2. To assess the feasibility of the adapted D-PRESCRIBE intervention in the Belgian community setting.

This section comprises 2 chapters (Chapter 5 and Chapter 6).

Chapter 5 presents the protocol of the cluster randomized controlled trial assessing the feasibility of the adapted D-PRESCRIBE intervention in the Belgian community setting (END-IT CS study). **Chapter 6** presents the first results of the feasibility study.

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SECTION 1: Identification of local priorities for BZRA deprescribing

Chapter 1. Trends in benzodiazepine receptor agonists use and associated factors in the Belgian general older population: analysis of the Belgian health interview survey data

Chapter 1. Trends in benzodiazepine receptor agonists use and associated factors in the Belgian general older population: analysis of the Belgian health interview survey data

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Adapted from the article published in *Therapeutic Advances in Psychopharmacology* (2021)

DOI: <https://doi.org/10.1177/20451253211011874>

Section 1

AUTHORS' CONTRIBUTIONS

CP and SH were involved in the conception of the work. CP performed the statistical analysis under the supervision of SH. SH and AS were involved in the interpretation of the results. CP drafted the first version of the manuscript. SH and AS revised the manuscript critically for important intellectual content. All authors approved the final version.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

DECLARATION OF INTEREST

None.

ABSTRACT

BACKGROUND. Benzodiazepine receptor agonists (BZRA), which include benzodiazepines and z-drugs, are commonly prescribed for insomnia and anxiety in older adults, and used often long-term. Yet, the risk-benefit ratio of BZRA use in older adults may be unfavorable and many recommendations suggest avoidance or a maximal treatment duration of 4 weeks. The aim of this study was to describe trends of BZRA use in older adults and associated factors.

METHODS. Using data from the Belgian Health Interview Survey in 2004 (n= 3594), 2008 (n= 2917), and 2013 (n=2048), prevalence standardized for age, sex, and region were calculated to assess trends of BZRA use in people ≥ 65 years. Analysis of associated factors to BZRA use was performed using a sub-sample of 2013 data for which variables assessing sleeping disorder and anxiety disorder were not missing (n=1286). Variables from seven main topics were explored using multivariate logistic regression: socio-demographic factors, geriatric factors, comorbidities, subjective health and mental health indicators, social health indicators, medication use and healthcare services use.

RESULTS. Overall, standardized prevalence of BZRA use decreased significantly between 2004 and 2013 (22% to 18%, prevalence difference (95%CI): -4.0% (-6.8; -1.3)). Factors associated with BZRA use in multivariable analysis included female gender (adjusted odds ratio (aOR) (95%CI) : 1.62 (1.14; 2.29)), poor mental health (aOR (95%CI): 1.73 (1.13-2.63)), a fall in the past 12 months (aOR (95%CI): 1.52 (1.02; 2.26)), reporting a sleeping disorder (aOR (95%CI): 1.92 (1.35; 2.72)), polypharmacy (aOR (95%CI): 2.51 (1.75; 3.60)) and trazodone use (aOR (95%CI): 4.05 (1.64; 10.21)).

CONCLUSION. Despite an encouraging decline observed from 2004 to 2013, BZRA use remained highly prevalent in Belgian older adults. Promotion of alternatives to BZRA in treatment of sleeping problems needs to be continued. Among BZRA older users, women, the oldest (≥ 85 years) and high-risk subgroups should be targeted in deprescribing interventions.

Section 1

INTRODUCTION

Benzodiazepine receptor agonists (BZRA) are anxiolytics and sedative drugs commonly prescribed to treat insomnia and anxiety and comprised benzodiazepines and Z-drugs. In Europe and North-America, these medications are frequently taken by older adults, often long-term [1-3]. However, the risk-benefit balance of BZRA use in older adults may be non-favorable. Indeed, BZRA use in older people is associated with an increased risk of falls, especially when combined with other drugs or when prescribed to people with dementia [4], and hip fracture [5], leading to a greater risk of institutionalization [6] and mortality [7]. Long-term BZRA use is also associated with poorer cognitive performance [8], tolerance, and dependence [9]. In contrast, the benefits of BZRA use are limited as sleep improvement fades after four weeks [10]. Therefore guidelines recommend that BZRA should be avoided or stopped after four weeks in older adults [11, 12], although maintenance of BZRA treatment beyond four weeks may be appropriate in particular cases (e.g. severe generalized anxiety disorder or alcohol withdrawal), with assessment of the risk-benefit ratio [9, 11, 13].

Since 2002, the Belgian Federal Public Service of Public Health has launched several awareness campaigns aimed at patients, pharmacists and physicians, in order to decrease sedative/hypnotic consumption in Belgium [14]. Indeed, national reports, based on the Belgian Health Interview Survey (BHIS) data, have shown that sedative or hypnotic use was frequent in the Belgian population, especially among older adults [15]. However, these reports did not focus specifically on BZRA. If previous studies estimated the BZRA use prevalence to 52-53% of the Belgian nursing home residents [16, 17], to our knowledge, no study has yet assessed BZRA use prevalence in the general older population and its evolution over time.

In the literature, several factors were found to be associated with BZRA use in older people in different countries and included female gender, depression, polypharmacy, negative health perception, insomnia, mental health diseases and chronic diseases [18-20]. In the Belgian nursing home setting, the recent study of Evrard *et al* showed that a history of fall in the past 3 months, chronic obstructive pulmonary disease, polypharmacy, insomnia, and antidepressant use were factors associated with BZRA use [17]. On the contrary, dementia and trazodone use were factors negatively associated with BZRA use [17]. However, no study has been conducted to identify factors associated with BZRA use in older people from the general Belgian older population.

The aim of this study was to describe national trends of BZRA use in older adults ≥ 65 years using the BHIS data for 2004, 2008, and 2013 and to assess associated factors in 2013, last data available.

METHODS

General design and population survey of the BHIS

Data from the BHIS were used [21]. BHIS is a repeated cross-sectional survey that collects socio-demographic and health data every 4 or 5 years among a representative sample of approximately 10,000 individuals in Belgium selected according to a stratified clustered multistage sampling, using the National Population Registry as sampling frame [22]. The precise design of the BHIS has been described elsewhere [22]. Briefly, the 10,000 interviews are distributed between the 3 regions (3500 for the Flemish Region, 3500 for the Walloon Region and 3000 for the Brussels Region) [22]. The target number of interviews for each region is split into groups of 50 individuals [22]. Then, the number of groups is distributed between provinces (except for the Brussels Region where this administrative delimitation does not exist) according to their population size [22]. Within provinces, municipalities are selected following a procedure integrating probability proportional to size and systematic sampling [22]. Within municipalities, households are selected according to a systematic sampling [22]. For each household selected, a maximum of four individuals are invited to participate [22]. All Belgian residents can be selected, including individuals living in a nursing home [22]. There are no exclusion criteria of age or nationality. Selected individuals are contacted by mail with a letter explaining the survey. Participation is voluntary, in case of refusal, a matched substitute for the household is invited to participate until the planned number of interviews is reached [22].

The data are gathered at the residency of the participant through a face-to-face interview and the auto-completion of a questionnaire for sensitive subjects [22]. In situations where participants are not able to answer (e.g. due to mental or functional limitations), a proxy is allowed to respond on their behalf, except for the auto-questionnaire [23].

The sampling procedure was the same for each year considered for our analysis except that the older population above 75 years was oversampled in 2008 at the request of the Social Affairs Ministry and a specific recruitment of people 85 years or older was organized in 2004 and 2008 [22].

Section 1

The Health Interview Survey has been approved by the Commission for the protection of private life and the Ethical Committee of Ghent University Hospital (advice EC UZG 2012/658), which guarantees that the survey procedures are in line with the privacy legislation. As our study is a secondary analysis of those data, no informed consent was required from the participants for this study but data transfer was approved by the Sectoral Committee of Social Security and Health.

Trends in BZRA use analysis

- Selected population

For this part of our analysis, we used databases from years 2004, 2008, and 2013 and selected participants aged 65 years or more. That led to samples of 3594, 2917, and 2048 individuals, respectively.

- BZRA use assessment

In the BHIS, information on medication use is collected during the interview by asking the participant to show the boxes of all medications used during the latest 24h, with no distinction between their regular or “as needed” character. Medications are then converted in Anatomical Therapeutic Chemical (ATC) code up to the chemical substance level [24].

For our analysis, BZRA drugs included ATC codes N05CB (sedative benzodiazepines), N05CF (sedative z-drugs), and N05BA (anxiolytic benzodiazepines). We analyzed trends in BZRA use up the molecule level and stratified our results according to age, gender, and number of BZRA taken. In addition, concomitant use of antidepressant (ATC code N06A) and opioids (ATC code N02A) with BZRA were assessed.

- Statistical analysis

Trends in medication use over years were assessed using standardized prevalence. The prevalence of medication use was standardized according to the age (by 5-year age groups), gender, and region by using the Belgian population on 1st January 2013 as the reference population in order to allow comparison across the years. Differences between years were assessed through the standardized prevalence differences (PD) and the standardized prevalence ratios (PR). This analysis was performed using R software 29 (version 3.5.1) and the package *dsr*, which computes directly standardized rates and their confidence interval [25].

Factors associated with BZRA use analysis

- Study population

This analysis was performed on a sub-sample of the 2013 data. In the subsample, we have included only people with no missing data for the variables assessing sleeping disorders and anxiety disorders as they are the main indications for BZRA use. Consequently, on the 2048 observations available for the ≥ 65 years older adults, we limited our analysis to 1286 individuals.

- Main outcome

The dependent variable was BZRA use; this variable encompassed ATC codes N05CD, N05CF, and N05BA.

- Explanatory variables

The BHIS collects many health data. A first selection was done on all the variables available based on a previous literature review. The selected variables were grouped into seven main topics: socio-demographic factors, geriatric factors, comorbidities, subjective health and mental health indicators, social health, medication use, and healthcare services use.

Information on social-demographic and geriatric factors, on comorbidities and on healthcare services use were gathered during the interview. The interviewer asked the question and encoded the corresponding answer directly in the computer. Data on subjective, mental, and social health figured among data collected through the self-completed paper questionnaire [23].

Socio-demographic factors included age, gender, region, civil status, educational level, country of birth, and household income.

Geriatric factors included urinary incontinence or problems controlling the bladder, falls, osteoporosis, hip fracture, Parkinson's disease, multimorbidity, low Body Mass Index (BMI) and functional limitations. Multimorbidity was assessed through the variable "number of chronic conditions (on a total of 25 conditions)" and was defined as the presence of at least two chronic conditions. A BMI inferior to 21kg/m^2 was considered low. Functional limitations were assessed through three different variables: the severity of the handicap in mobility, severity of restrictions in performing daily activities, and severity of restrictions in performing household activities.

Section 1

Comorbidities comprised low back disorder, osteoarthritis, diabetes, myocardial infarction, coronary heart disease (angina pectoris), and high blood pressure. In this category, we also included the level of pain assessed by the MOS 36-item Short-Form Health Survey (SF-36) Bodily pain score [26].

The EuroQol-5D-5L scale (EQ5D-5L) score was an indicator for people's subjective health [27]. The mean score of the General Health Questionnaire (GHQ-12) and the Vitality Index of the MOS 36-item Short-Form Health Survey (SF-36) score were used to assess mental health [26, 28]. Finally, subscales of the Symptoms Checklist-90-Revised questionnaire (SCL-90-R) were used to assess depression, anxiety and sleeping problems [29]. For each of these subscales, the average scores were transformed in a binary variable with a cut-off point set at two and more to classify the participant as reporting depression, anxiety, or sleeping problems.

Three indicators of social health were explored: the appreciation of social contacts (based on the question "How do you find your social contacts?"), the frequency of social contacts, and the perceived quality of social support. This latter indicator is based on the three questions of the Oslo Social Support Scale [30].

Factors related to medication use encompassed opioid use (ATC code N02A), antipsychotic use (ATC code N05A), antidepressant use (ATC code N06A), selective serotonin reuptake inhibitors (SSRI) use (ATC code N06AB), tricyclic antidepressant or mirtazapine use (ATC code N06AA or N06AX11), trazodone use (ATC code N06AX05), and other antidepressant use (antidepressants except SSRI, trazodone and tricyclic antidepressant or mirtazapine). SSRI were analyzed separately as they are the recommended treatment for generalized anxiety disorders in older adults by Belgian guidelines [31]. Trazodone use was also categorized separately due to its frequent off-label use at a low dosage in the treatment of insomnia [32]. Tricyclic antidepressant use was analyzed together with mirtazapine use (because of very little mirtazapine use in our sample) as they also have sedative effects [33]. In addition, the total number of medications taken during the last 24h, excluding BZRA, was taken to assess level of polypharmacy categorized in three levels: 0-4 medications, 5-9 medications (polypharmacy), and 10 or more medications (severe polypharmacy).

Finally, healthcare service use included having a regular GP, the number of contacts with the GP in the past 2 months, visit to a psychologist or a psychotherapist, inpatient hospitalization, and contact with emergency department in the past 12 months.

- Statistical analysis

For all explanatory variables described in *Explanatory variables*, categorical variables were expressed as numbers and percentages and compared between groups using a Pearson's chi-squared test or a Fisher exact test according to the condition of validity of each test. The association between all the variables and BZRA use in 2013 was assessed using a logistic regression model. First, a univariate model was performed. All variables with a p value < 0.15 in the univariate model were included in a multivariable model as candidates for the final multivariable selection. Collinearity was assessed by computing the variance inflation factor (VIF). Variables obtaining a VIF above five were excluded from the model. A stepwise selection using the Akaike information criteria was applied on the multivariable model containing all candidate variables to select the final multivariable model.

All statistical analyses were performed using R software (version 3.5.1) and the following packages: questionr, car, ResourceSelection, and ROCR [34-38]. A p value < 0.05 was considered statistically significant.

RESULTS

Trends in standardized prevalence rates of BZRA use

Table 1 shows standardized prevalence of BZRA use in older adults in 2004, 2008, and 2013. Sample sizes and crude prevalence are presented in Supplemental Table S1. Between 2004 and 2013, the standardized prevalence of BZRA use in Belgian older adults decreased from 22% to 18% (PD (95%CI): -4.0% (-6.8%; -1.3%)). Across the years considered, BZRA use was more prevalent in women (21.6% in 2013) and with increasing age (24.6% for the 85+ years age group in 2013) and mostly limited to the use of one BZRA. The use of a single BZRA decreased significantly from 2004 to 2013 (PD (95%CI): -3.8% (-6.5%; -1.2%)) whereas the use of two or more BZRA did not (PD (95%CI): -0.2% (-1.1%; 0.7%)).

Stratification by medication class showed that, over the years considered, benzodiazepines (N05BA and N05CD) prevalence were higher than z-drugs (N05CF) (Table 1). The prevalence of z-drugs users remained stable across the years around 3% of the older population while the prevalence of benzodiazepines users fell significantly from 19.5% in 2004 to 14.9% in 2013 (PD (95%CI): -4.6% (-7.1%; -2.0%)). Further stratification showed that anxiolytic BZRA (N05BA) were more commonly used than sedative BZRA (N05CD and N05CF). A significant decrease was observed from 2004 to

Section 1

2013 for anxiolytic BZRA (from 13.9% to 10.8%, PD (95%CI): -3.1% (-5.3%; -1.0%)) but not for sedative BZRA (from 9.6% to 8.5%, PD (95%CI): -1.1% (-3.0%; 0.8%)). In 2004, 2008, and 2013, the most frequently used BZRA were alprazolam, bromazepam, lorazepam, lormetazepam, and zolpidem. All other BZRA, grouped together, were used in at most 5.1% (in 2004) of older adults. Stratification up to the molecule level showed that only lorazepam and the group of other BZRA declined significantly between 2004 and 2013.

Table 1. Trends in benzodiazepines and z-drugs use in older adults (standardized prevalence^a) in 2004, 2008 and 2013

Variable	Standardized prevalence (%) [95% CI]			Comparison years 2004 and 2013		Comparison years 2008 and 2013	
	Year 2004 (N=3594)	Year 2008 (N=2917)	Year 2013 (N=2048)	PR (95%CI) (%) 2013/2004	PD (95%CI) 2013-2004	PR (95%CI) (%) 2013/2008	PD (95%CI) 2013-2008
Total BZRA use	22.0 (20.2; 23.9)	19.6 (17.7; 21.6)	18.0 (15.9; 20.2)	0.82 (0.67; 0.96)	-4.0 (-6.8; -1.3)	0.92 (0.77; 1.07)	-1.6 (-4.4; 1.2)
Number of BZRA taken							
1	19.9 (18.2; 21.7)	17.3 (15.5; 19.2)	16.0 (14.1; 18.1)	0.81 (0.66; 0.96)	-3.8 (-6.5; -1.2)	0.93 (0.77; 1.09)	-1.2 (-3.9; 1.4)
2	2.1 (1.6; 2.8)	2.3 (1.7; 3.0)	1.9 (1.3; 2.8)	0.91 (0.45; 1.36)	-0.2 (-1.1; 0.7)	0.84 (0.39; 1.30)	-0.4 (-1.3; 0.6)
Total BZRA use by age group							
65-74 years	17.1 (14.9; 19.6)	16.1 (13.4; 19.1)	14.7 (12.2; 16.7)	0.86 (0.63; 1.08)	-2.4 (-5.9; 1.1)	0.92 (0.66; 1.17)	-1.3 (-5.2; 2.5)
75-84 years	25.2 (21.7; 29.2)	21.5 (18.2; 25.1)	19.9 (16.5; 23.8)	0.79 (0.56; 1.02)	-5.3 (-10.4; -0.2)	0.93 (0.69; 1.17)	-1.5 (-6.5; 3.4)
85 or more years	31.2 (27.2; 35.5)	27.2 (24.0; 30.8)	24.6 (18.3; 32.4)	0.79 (0.49; 1.09)	-6.5 (-14.4; 1.3)	0.90 (0.60; 1.21)	-2.6 (-10.1; 5.0)
Total BZRA use by gender							
Female	26.5 (24.6-28.3)	25.0 (22.3; 28.0)	21.6 (18.6; 24.9)	0.82 (0.64; 0.99)	-4.9 (-8.9; -0.8)	0.86 (0.68; 1.04)	-3.5 (-7.7; 0.7)
Male	16.0 (13.7; 18.7)	12.2 (9.9; 14.9)	13.2 (10.7; 16.0)	0.82 (0.57; 1.07)	-2.9 (-6.5; 0.7)	1.08 (0.80; 1.36)	0.9 (-2.6; 4.5)
BZRA use by class							
Benzodiazepine use (N05BA or N05CD)	19.5 (17.8; 21.3)	17.1 (15.4; 19.0)	14.9 (13.1; 17.0)	0.77 (0.61; 0.92)	-4.6 (-7.1; -2.0)	0.87 (0.71; 1.04)	-2.2 (-4.8; 0.4)
Z-drugs use (N05CF)	3.0 (2.4; 3.8)	3.2 (2.4; 4.1)	3.2 (2.4; 4.2)	1.05 (0.70; 1.41)	0.2 (-1.0; 1.3)	1.00 (0.63; 1.37)	0.0 (-1.2; 1.2)
Sedative BZRA use (N05CD or N05CF)	9.6 (8.4; 10.9)	8.9 (7.6; 10.3)	8.5 (7.1; 10.1)	0.89 (0.68; 1.10)	-1.1 (-3.0; 0.8)	0.96 (0.74; 1.19)	-0.3 (-2.3; 1.6)
Anxiolytic BZRA use (N05BA)	13.9 (12.5; 15.4)	12.2 (10.7; 13.7)	10.8 (9.2; 12.5)	0.78 (0.59; 0.96)	-3.1 (-5.3; -1.0)	0.89 (0.69; 1.08)	-1.4 (-3.6; 0.8)
BZRA use at molecule level							
Alprazolam	2.9 (2.3; 3.7)	3.1 (2.4; 4.0)	3.3 (2.5; 4.3)	1.13 (0.79; 1.47)	0.4 (-0.7; 1.5)	1.06 (0.71; 1.42)	0.2 (-0.9; 1.3)
Bromazepam	2.6 (2.0; 3.3)	2.8 (2.1; 3.6)	1.7 (1.1; 2.4)	0.64 (0.20; 1.09)	-0.9 (-1.8; 0.0)	0.60 (0.15; 1.06)	-1.1 (-2.1; -0.1)
Lorazepam	5.9 (5.0; 6.9)	5.2 (4.3; 6.3)	4.2 (3.3; 5.4)	0.72 (0.43; 1.00)	-1.7 (-3.1; -0.3)	0.81 (0.51; 1.11)	-1.0 (-2.4; 0.4)
Lormetazepam	4.6 (3.8; 5.5)	4.0 (3.2; 5.0)	4.3 (3.3; 5.5)	0.93 (0.62; 1.24)	-0.3 (-1.7; 1.1)	1.06 (0.73; 1.39)	0.2 (-1.1; 1.6)
Zolpidem	2.3 (1.7; 2.9)	2.4 (1.8; 3.3)	2.9 (2.1; 3.9)	1.28 (0.89; 1.68)	0.6 (-0.4; 1.7)	2.89 (0.77; 1.60)	0.5 (-0.7; 1.6)
Other	5.1 (4.3; 6.0)	4.2 (3.4; 5.1)	3.2 (2.4; 4.2)	0.63 (0.31; 0.94)	-1.9 (-3.1; -0.7)	0.76 (0.43; 1.10)	-1.0 (-2.2; 0.2)
Concomitant use of BZRA & other drugs							
Concomitant antidepressants use	5.7 (4.8; 6.6)	4.9 (4.0; 5.9)	4.8 (3.8; 6.0)	0.85 (0.57; 1.12)	-0.9 (-2.3; 0.5)	0.98 (0.69; 1.27)	-0.1 (-1.5; 1.3)
Concomitant opioid use	2.0 (1.4; 2.6)	2.5 (1.9; 3.2)	1.5 (1.0; 2.2)	0.77 (0.31; 1.23)	-0.5 (-1.2; 0.3)	0.61 (0.16; 1.05)	-1.0 (-1.8; -0.1)

Abbreviations: BZRA, Benzodiazepine receptor agonists; 95%CI, 95% confidence interval; PD, standardized prevalence difference; PR, Standardized prevalence ratio

^a Standardized prevalence: prevalence standardized for age, gender and region

Section 1

In 2013, 4.8% of the older adults in the general population used concomitantly a BZRA and an antidepressant. If looking at BZRA users specifically, we observe that 26% of them took also an antidepressant (Table 1). The concomitant use of a BZRA and an opioid concerned 1.5% of the older population in 2013, 10% of the BZRA users. No significant reductions in this concomitant use with BZRA were observed between 2004 and 2013, or between 2008 and 2013. In parallel, antidepressants and opioids use did not show any significant trend between 2004 and 2013 (data not shown). Antidepressant use remained stable around 10% of the older adults, and opioids use around 4%. Trazodone use increased slightly from 2% to 2.7% but this increase was not significant.

Factors associated with BZRA use in 2013

As previously explained, a subsample of 2013 data (1286 observations out of the 2048 available) was used for this analysis. The main characteristics of included participants are described in Table 2. Slightly more than half of them were women (53.1%) and 56.9% were aged <75 years; 53% reported suffering from two or more chronic conditions (Table 2). Of the 1286 included participants, 217 (16.9%) were BZRA users (Table 2). Regarding potential indication for a BZRA use, nearly half of the BZRA users reported a sleeping disorder and 15.7% reported an anxiety disorder against respectively 26.7% and 7.2% of the non-users (Table 2).

Table 2. Main characteristics of the included participants for the analysis of associated factors				
Variable	Total (N=1286) n (%)	BZRA use (N=217) n (%)	No BZRA use (N=1069) n (%)	p- value^a
Age				0.004
65-74 years	732 (56.9)	102 (47.0)	630 (58.9)	
75-84 years	439 (34.1)	89 (41.0)	350 (32.7)	
85 years or more	115 (8.9)	26 (12.0)	89 (8.3)	
Gender				<0.001
Female	683 (53.1)	138 (63.6)	545 (51.0)	
Household income				<0.001
Quintile 1 (lowest quintile)	192 (14.9)	28 (12.9)	164 (15.3)	
Quintile 2	307 (23.9)	61 (28.1)	246 (23.0)	
Quintile 3	248 (19.3)	55 (25.3)	193 (18.1)	
Quintile 4	203 (15.8)	30 (13.8)	173 (16.2)	
Quintile 5 (highest quintile)	195 (15.2)	21 (9.7)	174 (16.3)	

Missing data	141 (11.0)	22 (10.1)	119 (11.1)	
Reporting an anxiety disorder				<0.001
Yes	111 (8.6)	34 (15.7)	77 (7.2)	
Reporting a sleeping disorder				<0.001
Yes	390 (30.3)	105 (48.4)	285 (26.7)	
Mean score of positive mental health				<0.001
≥50	862 (67.0)	107 (49.3)	755 (70.6)	
<50	261 (19.6)	82 (36.9)	179 (16.1)	
Missing	163 (12.7)	28 (12.9)	135 (12.6)	
EQ-5D-5L score, median	0.76	0.66	0.77	<0.001
[P₂₅; P₇₅]^b	[0.64; 1.00]	[0.49; 0.76]	[0.68; 1.00]	
Mean number of chronic conditions^c				<0.001
0 to 1	590 (45.9)	66 (30.4)	524 (49.0)	
2 to 5	614 (47.7)	125 (57.6)	489 (45.7)	
6 or more	77 (6.0)	25 (11.5)	52 (4.8)	
Fall in the past 12 months				<0.001
Yes	226 (17.6)	66 (30.4)	160 (15.0)	
Number of medications excluding BZRA				<0.001
0 to 4	942 (73.3)	109 (50.2)	833 (77.9)	
5 to 9	302 (23.5)	90 (41.5)	212 (19.8)	
10 or more	42 (3.3)	18 (4.6)	24 (2.2)	
Number of contacts with GP in the past 12 months				<0.001
0	449 (34.9)	36 (16.6)	413 (38.6)	
1	527 (41.0)	91 (41.9)	436 (40.8)	
≥2	310 (24.1)	90 (41.5)	220 (18.7)	
Abbreviations: BZRA , Benzodiazepine Receptor Agonists (ATC N05BA, N05CD and N05CF); EQ-5D-5L : EuroQol 5 dimensions, 5 levels				
^a Comparison BZRA use vs No BZRA use: Pearson chi-square test, Fisher exact test or Mann-Whitney test				
^b 52 missing values (n= 52/1286, 4%)				
^c 5 missing values (n=5/1286; 0.4%)				

Table 3 presents factors associated with BZRA use in older adults in 2013 in univariate and multivariable logistic regression. Detailed results of the univariate analysis can be found in Supplemental Table S2. In total, 46 potential associated variables were

Section 1

explored in the univariate analysis of which a large majority was significant and thus candidate for the multivariable analysis (all candidate variables for the multivariable analysis are listed in Supplemental Table S3).

Among all sociodemographic factors included, only female gender was significantly associated with BZRA use in older adults in the final multivariable model (adjusted odd ratio (aOR) (95%CI): 1.62 (1.14; 2.29), $p=0.007$) (Table 3). Age was not retained in the final model and neither was multimorbidity nor any specific comorbidities. Regarding geriatric factors, a low BMI was significantly associated with BZRA intake (aOR (95%CI): 2.02 (1.13-3.50), $p= 0.015$) as well as reporting a fall in the past 12 months (aOR (95%CI): 1.52 (1.02; 2.26), $p=0.037$). Two mental health indicators were associated with BZRA use in older adults: a mean score of positive mental health (of the MOS SF-36 Vitality scale) below 50 (aOR (95%CI): 1.73 (1.13; 2.63), $p=0.011$) and reporting having a sleeping disorder (aOR (95%CI): 1.92 (1.35; 2.72), $p<0.001$). Reporting having anxiety or depressive disorder were not retained in the multivariate analysis. BZRA use was also associated with polypharmacy (aOR: 2.51 (1.75; 3.60), $p<0.001$) and excessive polypharmacy (aOR: 2.82 (1.30; 6.04), $p= 0.008$), trazodone use and other antidepressant use (antidepressants excluding SSRIs, trazodone and tricyclic antidepressants or mirtazapine). Of the variables assessing healthcare services use, only the number of contacts with the GP in the past 2 months was associated with BZRA use. The higher the number of visits, the higher the aOR.

Table 3. Factors associated with benzodiazepine and z-drugs use in older adults in 2013 in univariate and multivariable logistic regression ^a				
Variables	Univariate model (N=1286)		Multivariable model (N=1225)	
	OR (95%CI)	p-value	aOR (95%CI)	p-value
Socio-demographic factors				
Female	1.68 (1.25; 2.28)	<0.001	1.62 (1.14; 2.29)	0.007
Geriatric factors				
Low Body Mass Index (<21 kg/m ²)	1.64 (0.98; 2.64)	0.051	2.02 (1.13; 3.50)	0.015
Fall in the past 12 months	2.48 (1.77; 3.46)	<0.001	1.52 (1.02; 2.26)	0.037
(Mental) health indicators				
Reporting sleeping disorder ^b	2.58 (1.91; 3.48)	<0.001	1.92 (1.35; 2.72)	<0.001

Mean score of positive mental health (SF-36 Vitality Index)				
≥50	1.00		1.00	
<50	3.23 (2.32; 4.50)	<0.001	1.73 (1.13; 2.63)	0.011
Missing data (n=163)	1.46 (0.91; 2.28)	0.101	1.18 (0.68; 1.98)	0.552
EQ-5D-5L score ^c	0.05 (0.02; 0.09)	<0.001	0.35 (0.14; 0.84)	0.019
Medication use				
Number of medications BZRA excluded				
0 to 4	1.00		1.00	
5 to 9 (polypharmacy)	3.24 (2.36; 4.46)	<0.001	2.51 (1.75; 3.60)	<0.001
≥10 (severe polypharmacy)	5.73 (2.98; 10.86)	<0.001	2.82 (1.30; 6.04)	0.008
Trazodone use	7.01 (3.28; 15.37)	<0.001	4.05 (1.64; 10.21)	0.003
Other antidepressants use (antidepressants except trazodone, SSRI and tricyclic antidepressant or mirtazapine)	4.80 (2.20; 10.42)	<0.001	2.91 (1.16; 7.39)	0.022
Healthcare services use				
Number of contacts with GP in the past 2 months				
0	1.00		1.00	
1	2.39 (1.60; 3.64)	<0.001	1.89 (1.22; 3.02)	0.004
≥2	4.69 (3.11; 7.22)	<0.001	2.15 (1.33; 3.51)	0.002
Abbreviations: aOR, adjusted odds ratio; BZRA, Benzodiazepines Receptors Agonists (ATC N05BA, N05CD and N05CF); 95%CI, 95% confidence interval; EQ-5D-5L, EuroQol 5 dimensions, 5 levels; GP, General Practitioner; OR, Odds Ratio; SSRI, Selective Serotonin Reuptake Inhibitor ^a The complete univariate analysis is available in Supplementary table S2. All variables that were candidate for the final model are listed in Supplementary table S3 ^b 2 missing values (n=2/1286; 0.2%); ^c 52 missing values (n=52/1286; 4.0%)				

Section 1

DISCUSSION

BZRA use remained highly prevalent in Belgian older adults even if it declined significantly from 22% in 2004 to 18% in 2013. This latter percentage was comparable to other European studies among older adults, with 20% reported in a Swiss study using data from 2017 and between 15 to 20% in a German study using data gathered from 2010 to 2014 [1, 39]. Consistent with other studies, BZRA use was found to be more prevalent with increasing age and in women [1, 39, 40].

A similar trend toward a reduction in BZRA use by older adults was observed in other countries. In Canada, a population-based study among Ontarian residents aged 65 years or more showed that benzodiazepine use decreased from 23% to 15% between 1998 and 2013 [40]. In Europe, a Danish study also reported a reduction of benzodiazepine use from 1998 to 2008 in the older groups of the population: from 26% to 19% for the 65-74 years, 36% to 26% for the 75-84 years and 42% to 30% for the 85 or more years [41]. This trend toward a decline in benzodiazepine use might indicate a change in prescribing culture supported by local policies in these countries [40, 41]. Similarly, the reduction in BZRA use in Belgium might be the result of several national campaigns targeting physicians, pharmacists, and patients to promote a rational use of BZRA and encourage non-pharmacological alternatives to anxiety and sleep problems [14]. However, these campaigns did not target specifically older adults whereas previous research has shown that the vast majority of older adults are unworried about BZRA long-term side effects and unaware of the potential harmful consequences [42]. Greater reduction in BZRA use might be achieved with awareness campaigns targeted to older adults.

If encouraging, the decline in BZRA use in Belgium was not homogenous. Indeed, while benzodiazepine use declined, z-drugs use remained stable across the considered years. This was also observed in Denmark and in Canada where z-drugs use even rose concurrently to benzodiazepine use reduction [41, 43]. Previous literature has shown that doctors perceived z-drugs safer in general than benzodiazepines [44, 45]. This might be one factor explaining the absence of decrease observed in our country. Since 2017, the French regulations for zolpidem prescription impose the use of secure prescription booklets, a thorough specification of dosage and quantity, and maximal 4 weeks treatment duration [46]. An evaluation of these measures has demonstrated efficacy, with a drastic decrease of zolpidem use in the general population [46]. This might be an interesting lead for future health policies in our country.

In 2013, 27% of BZRA users also took an antidepressant and 10% took an opioid. These results are consistent with those of Maust *et al*, who studied older adult's visits to

ambulatory care services [47]. They found that 25% of the visits that implied a BZRA prescription also included prescription of an antidepressant, and that concurrent prescription of a BZRA and an opioid concerned 10% of visits [47]. Antidepressant use in older adults has been associated with a higher risk of falls and opioid use with a higher risk of fractures [48, 49]. These risks may increase those potentially induced by BZRA intake. Moreover, the updated Beers Criteria published in 2019 strongly recommend avoidance of opioid use with a BZRA due to increased risk of overdose [11]. The fact that no significant decrease between 2004 and 2013 was found in concomitant users of BZRA and antidepressant or opioid in our study is thus of concern as it also concerns a sizeable proportion of older BZRA users. A similar preoccupation is for older adults taking ≥ 2 BZRA (10% of BZRA users in 2013). Indeed, the concomitant use of several psychotropic medications was associated with a greater risk of fall injuries, hospitalization, and death [50].

Our analysis of associated factors showed that female gender was associated with BZRA use, which was consistent with previous research [39, 47]. Also similar to previous research conducted among older adults [18, 20, 51], our results showed that polypharmacy (taking 5-9 medications) and excessive polypharmacy (taking 10 or more medication) were associated with BZRA use. These subgroups would particularly benefit from deprescribing, which is “the planned and supervised process of dose reduction or stopping medication that may be causing harm or are no longer providing benefits” [52]. A recent systematic review has shown that successful BZRA deprescribing in older adult could be achieved using various interventions, ranging from pharmacological substitution to patient education [53].

Falls were found to be associated with BZRA use, consistently with a meta-analysis of 2018 [54]. In contrast, neither multimorbidity nor specific comorbidities were significantly associated with BZRA, contrary to previous literature showing that BZRA users were more likely to suffer from chronic diseases [47]. However, the number of general practitioner (GP) contacts was associated with BZRA use, which, with polypharmacy, indirectly suggests poor health in BZRA users. The fact that BZRA users are more likely to see their GP could be an opportunity to design deprescribing interventions by involving GPs in the process. In Canada, the D-PRESCRIBE trial, involved both a community pharmacist and a GP, yielded 43% of discontinuation rate in BZRA use in older adults *versus* 9% in the control group [55], showing the efficacy of a partnership with the GP.

Reporting a sleeping disorder was associated significantly with BZRA use but not with reporting an anxiety disorder or a depressive disorder. This was similar to the study of Gerlach *et al.* [56], conducted among American low-income older adults between 2008

Section 1

and 2016 even though participants to the BHIS are from all socio-economic backgrounds. In contrast, a study among Taiwanese older outpatients found that BZRA prescription was associated with anxiety and depression as well as insomnia [19]. An explanation for this difference might be that our study was based on self-reported answers to validated scales that have no medical diagnosis value. Another explanation might be related to the importance of sleeping problems in a patient's life. A recent qualitative meta-synthesis, including 9 publications from 2000 to 2015 in Western countries, explored patient's perceptions of BZRA use and factors that influenced BZRA continuation in older adults [57]. Authors explained that patients perceive insomnia as highly disruptive to the quality of life and report anxiety and depression as consequences or causes of a lack of sleep [57]. This could explain why, in contrast to reporting anxiety disorder or depressive disorders, reporting a sleeping disorder was strongly associated with BZRA use in our study. It might also indicate that anxiety and depression may hide behind the report of a sleeping problem. This might also explain why antidepressant use was significantly associated with BZRA use while reporting depression was not.

Whereas previous studies among older adults have shown that BZRA use was associated with age [51, 58], this result was not found in our multivariable analysis. An explanation might be the inclusion in our analysis of variables assessing health-related quality of life, mental health status, and pain that may better explain BZRA use than age itself. Contrasting with a systematic review that showed significant results concerning association between income and BZRA use [2], we found no association with income in the multivariable analysis, despite the non-reimbursement of BZRA in our country. This could mean that perceived benefits of BZRA use may outweigh the costs even for older adults with a low socio-economic status.

Finally, while many variables were statistically significant in the univariate analysis, only a few were retained and significant in the final multivariable model. It suggests that older adult's profile is more likely to predict BZRA use than isolated characteristics.

Our study has several limitations. Firstly, information on medication use was obtained by asking the participants to show all the boxes of all medication taken in the last 24h. Although this produces more reliable data than self-reported information, it also excludes some medications taken at an "as needed" frequency. BZRA use prevalence might thus be underestimated. No information on the duration of the BZRA use was available in the study. Our study is thus not able to estimate the extent of potentially inappropriate BZRA use based on the guideline of a maximum duration of 4 weeks. Moreover, our study was not able to assess if the observed decrease was due to less BZRA initiation or to BZRA deprescribing. No information on the place of living of the

participant was available, so that no distinction between older adults living at home or in a nursing home was possible. Secondly, observed trends need to be confirmed with more recent data. Indeed 2013 was the last data available for our analysis, though BZRA deprescribing has gained attention in the scientific literature in recent years [59-61].

Finally, missing data are a frequent problem in using surveys databases because of incomplete cases. A quite large fraction (37%) of the original sample had to be excluded from the analysis due to missing data present in the indications for BZRA use, that is, reporting anxiety or sleeping disorder, that were expected to be associated with BZRA use. These two variables are comprised in the Mental Health section of the BHIS. As a sensitive subject, the questionnaire regarding this section is self-administered [23]. Moreover, the proxy is not allowed to answer the self-administered questionnaire on behalf of the participant [23]. This could explain the presence of the large amount of missing values in our data. Significant sociodemographic differences existed between included and excluded observations and are presented in Supplemental Table S4. Our results, even if in line with previous literature, have thus to be taken with caution.

However, to our knowledge, this is the first study to assess BZRA use prevalence rates in the older Belgian general population. As they are not reimbursed in Belgium, no data about BZRA use is collected systematically, making monitoring of their consumption difficult. Using Health Interview Survey data allowed to work on representative data of the Belgian older population and to perform an in-depth analysis of BZRA use associated factors by including a large panel of explanatory variables.

CONCLUSION

Despite a significant and encouraging decrease in BZRA use in the general older population in Belgium between 2004 and 2013, it still extended to 18% of them in 2013. Efforts to reduce BZRA use in older adults should be enhanced by specifically targeting them in awareness campaigns, as the risk-benefit balance of BZRA use may not be positive in this population. Promotion of alternatives to BZRA in treatment of sleeping problems needs to be continued. Deprescribing interventions in older BZRA users should target women and the oldest (≥ 85 years) among whom BZRA use remains particularly prevalent as well as multiple BZRA users, concomitant users of antidepressants or opioids and older adults under polypharmacy, high-risk subgroups for whom medication safety would be greatly improved.

Section 1

Supplemental material

Supplemental material can be accessed online and comprise:

- Supplemental Table S1. Trends in benzodiazepines and z-drugs use (crude prevalence) in older adults in 2004, 2008, and 2013
- Supplemental Table S2. Factors associated with benzodiazepine and z-drugs use in older adults in 2013 in univariate and multivariable logistic regression (with detailed univariate analysis)
- Supplemental Table S3. Factors candidate for the final multivariable model
- Supplemental Table S4. Characteristics of the included and excluded observations

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SECTION 2: Identification of barriers and potential interventions to BZRA deprescribing

Chapter 2. Barriers and enablers for deprescribing benzodiazepine receptor agonists in older adults: a systematic review of qualitative and quantitative studies using the theoretical domains framework.

Chapter 3. Adaptation and validation of the revised Patients' Attitudes towards Deprescribing (rPATD) questionnaire for benzodiazepine receptor agonists.

Chapter 4. Deprescribing benzodiazepine receptor agonists in older adults: using the ADAPT guidance to fit the Canadian D-PRESCRIBE intervention to the Belgian community setting

Chapter 2. Barriers and enablers for deprescribing benzodiazepine receptor agonists in older adults: a systematic review of qualitative and quantitative studies using the theoretical domains framework

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Article published in *Implementation Science* (2022)

DOI: <https://doi.org/10.1186/s13012-022-01206-7>

Section 2

AUTHORS' CONTRIBUTIONS:

PE and AS imagined and wrote study protocol, which was then amended by all authors (PE, CP, JBB and AS). PE and CP both independently screened and selected papers, before qualitatively analysing extracted data. For these two steps, AS was consulted in case of disagreement. Data extraction was performed by PE and checked by CP. Studies quality evaluation were independently performed by PE and CP. Data analysis was prepared by PE and CP, and interpretation was discussed at a meeting with all authors (PE, CP, JBB and AS). PE wrote the manuscript first draft, which was then amended by all authors (PE, CP, JBB and AS). The authors read and approved the final manuscript.

ACKNOWLEDGEMENTS

The authors would like to thank Dr Marie de Saint Hubert and Dr Olivia Dalleur for reviewing study protocol; Marie Longton, medical librarian for her help in search equation elaboration; and Dr Jeremy Grimshaw and Dr Andrea Patey, for assisting TDF use.

FUNDING

This research received no external funding.

DECLARATION OF INTEREST

None.

ABSTRACT

BACKGROUND. Many strategies aimed at deprescribing benzodiazepine receptor agonists (BZRA) in older adults have already been evaluated with various success rates. There is so far no consensus on which strategy components increase deprescribing the most. Yet, despite an unfavourable benefit-to-risk ratio, BZRA use among older adults remains high. We systematically reviewed barriers and enablers for BZRA deprescribing in older adults.

METHODS. Two reviewers independently screened records identified from five electronic databases—Medline, Embase, PsycINFO, CINAHL and the Cochrane library—and published before October 2020. They searched for grey literature using Google Scholar. Qualitative and quantitative records reporting data on the attitudes of older adults, caregivers and healthcare providers towards BZRA deprescribing were included. Populations at the end of life or with specific psychiatric illness, except for dementia, were excluded. The two reviewers independently assessed the quality of the included studies using the mixed-methods appraisal tool. Barriers and enablers were identified and then coded into domains of the theoretical domains framework (TDF) using a combination of deductive and inductive qualitative analysis. The most relevant TDF domains for BZRA deprescribing were then identified.

RESULTS. Twenty-three studies were included 13 quantitative, 8 qualitative and 2 mixed-method studies. The points of view of older adults, general practitioners and nurses were reported in 19, 9 and 3 records, respectively. We identified barriers and enablers in the majority of TDF domains and in two additional themes: “patient characteristics” and “BZRA prescribing patterns”. Overall, the most relevant TDF domains were “beliefs about capabilities”, “beliefs about consequences”, “environmental context and resources”, “intention”, “goals”, “social influences”, “memory, attention and decision processes”. Perceived barriers and enablers within domains differed across settings and across stakeholders.

CONCLUSION. The relevant TDF domains we identified can now be linked to behavioural change techniques to help in the design of future strategies and health policies. Future studies should also assess barriers and enablers perceived by under-evaluated stakeholders (such as pharmacists, psychiatrists and health care professionals in the hospital setting).

TRIAL REGISTRATION. This work was registered on PROSPERO under the title “Barriers and enablers to benzodiazepine receptor agonists deprescribing”. Registration number: CRD42020213035

Section 2

BACKGROUND

Benzodiazepine receptor agonists (BZRA, namely benzodiazepines and Z-drugs such as zolpidem, zopiclone and zaleplon) are widely prescribed for the management of insomnia and anxiety. However, their benefit-to-risk ratio is unfavourable in older adults (aged 65 or older) [1]. Indeed, BZRA offer only modest, short-term benefits, and adverse effects can include over-sedation, dependence, increased risks of falls and fractures, and cognitive impairment [2-4]. In Europe and the USA, recent studies have reported that around one in five adults aged 65 and older use BZRA [5-8]. Moreover, the proportion of long-term users among older individuals is estimated to be 47% [9]. In the nursing home (NH) setting, the prevalence of use is likely even higher, with reported rates between 14.6 and 54.4% [10-13]. For all these reasons, the American Geriatrics Society has included BZRA on the potentially inappropriate medications list [14] and the Screening Tool of Older Persons' Prescriptions (STOPP) list version 2 recommends limiting their use to 4 weeks [15]. Moreover, several organisations such as the Canadian deprescribing network or Choosing Wisely recommend that deprescribing be offered to older adults who take BZRA [16, 17].

Deprescribing is the process of “withdrawal of an inappropriate medication, supervised by a healthcare professional with the goal of managing polypharmacy and improving outcomes” [18]. Many approaches to enhance implementation of BZRA deprescribing have already been evaluated, encompassing medication review, educational programmes, substitution or multi-faceted strategies [19-22]. These strategies were associated with discontinuation rates ranging from 27 to 80% [21]. However, routine implementation of such deprescribing strategies is limited, and deprescribing policies vary across countries [23]. Moreover, data remain limited on how to best achieve BZRA deprescription or which components of a strategy are the most effective.

Improving knowledge about the barriers and enablers of BZRA deprescribing could enhance the probability of success of strategies. Different stakeholders can be involved in BZRA deprescribing (e.g., the patient, relatives and informal caregivers, general practitioner (GP), nurses, pharmacist). Each of these stakeholders may perceive different barriers and enablers, which should all be assessed and taken into consideration [24]. A recent systematic review evaluated barriers and enablers for BZRA deprescribing in older adults [25]. Based on 10 included studies, the authors reported barriers such as the perceived efficacy and safety of BZRA, lack of knowledge, work environment and procedure, and ageism. Reported enablers were education, patient motivation, multidisciplinary collaboration and awareness of adverse effects. Although this systematic review was a first step towards BZRA deprescribing

enhancement, it only included qualitative studies and was not based on any theoretical framework. Conducting a systematic review, including both qualitative and quantitative evidence, can help further investigate complex processes and systems in health and social care [26]. Moreover, psychological theories can provide a framework for the evaluation of behaviour predictors and to tailor specific interventions [27].

The primary aim of this systematic review was to identify and synthesise barriers and enablers of BZRA deprescribing in older adults and to map them into a theoretical framework. Secondary objectives were the identification of settings or stakeholders for which information is lacking, and the identification of differences in barriers and enablers between different settings.

METHODS

The systematic review protocol was developed based on PRISMA-P guidelines [28] and on the toolkit for mixed-methods studies review by Pluye et al. [29]. It was registered on PROSPERO under the name “Barriers and enablers to benzodiazepine receptor agonists deprescribing” (CRD42020213035). Report follows the 2020 PRISMA checklist for reporting systematic reviews (See additional file 1) [28].

We conducted a systematic search of qualitative, quantitative and mixed-methods studies exploring the views of different stakeholders on BZRA deprescribing in older adults. Five electronic databases were searched from their inception until October 13, 2020: MEDLINE, EMBASE, PsychINFO, CINAHL and CENTRAL. The search strategy was developed with the help of a medical librarian and focused on the three aspects of our question: (i) the studied population, i.e., adults over 65 and their formal and informal caregivers; (ii) the measurement, i.e., perceived barriers and enablers for the studied phenomenon; and (iii) BZRA deprescribing. For each of these aspects, a list of synonyms was constructed with the aim of being as sensitive as possible. Search terms were then combined into a research equation (See additional file 2) that we transcribed for each database. To supplement the database search, we hand-searched the 100 first hits on Google Scholar for grey literature. References from included papers and those citing included papers were also checked for eligibility.

Search results were introduced into the reference management software Endnote X8®, Clarivate Analytics, Philadelphia. Two reviewers (PE and CP) independently screened titles and abstracts for eligibility, using the systematic reviews web application Rayyan [30]. The full texts of potentially eligible studies were read before a final decision was made regarding their eligibility. Disagreements were resolved through discussion with a third reviewer (AS). We included empirical studies using quantitative (interventional

Section 2

or observational), qualitative or mixed-methods designs and published in the English language. Relevant reviews were not included, but their reference lists were checked for studies that had been missed in the database search. Studies assessing barriers and enablers of psychotropic deprescribing in older adults were only included if data on BZRA were presented separately, and then, only these data were extracted. Qualitative studies on BZRA prescribing were only included if they addressed factors related to deprescribing, and only these data were then extracted. We excluded studies with only abstracts available, studies conducted on populations with less than 75% of patients aged over 65 (or caregivers of this population), and studies conducted in populations with specific psychiatric disorders (except for dementia), receiving palliative care, or mentioned as being at the end of life. Eligibility criteria were pilot tested by the two reviewers on a sample of 20 studies. Results of the pilot test were discussed with a third reviewer (AS), and criteria were further adjusted.

The quality of the included studies was independently assessed by two reviewers (PE and CP), using the Mixed Methods Appraisal Tool (MMAT), version 2018 [31]. The MMAT was selected because it enables quality assessment for all three study types (qualitative, quantitative and mixed-methods). We did not exclude any study based on quality assessment, but results are taken into consideration in the discussion section.

One reviewer (PE) extracted the data from the included studies, using an extraction form that had been previously pilot tested by three reviewers (PE, CP and AS) on one qualitative, one quantitative and one mixed-methods study. A second reviewer (CP) then checked data extraction for accuracy. Extracted data included participants' quotations from qualitative studies and identified themes underlying BZRA deprescribing, quantitative findings from surveys or questionnaires, and the authors' conclusions. Predictors of and factors associated with BZRA deprescribing in quantitative studies (interventional or observational) were also extracted. Data extraction form is available in additional file 3.

The theoretical domains framework (TDF), used for data analysis, is a framework that can be used to classify the different determinants of a behaviour [32]. It is particularly relevant for the evaluation of barriers and enablers of performing a behaviour [33]. The validated TDF version 2 encompasses 84 theoretical constructs, divided into 14 domains: Knowledge; Skills; Social/Professional Role and Identity; Beliefs about Capabilities; Optimism; Beliefs about Consequences; Reinforcement; Intentions; Goals; Memory, Attention and Decision Processes; Environmental Context and Resources; Social Influences; Emotions; Behavioural Regulation [34].

We performed data analysis using a data-based convergent design [35], meaning that results from different study designs were analysed together using a single method, here qualitative. Quantitative results were therefore coded as qualitative data with regards to their interpretation. First, two independent coders (PE and CP), who received training on TDF use, deductively coded the extracted data into TDF domains. Coding disagreements were resolved through discussion and intervention of a third coder (AS). To ease data management, we used NVivo® software, QSR international, Boston. Second, one researcher (PE) identified the most relevant TDF domains for BZRA deprescribing based on the three criteria proposed by Atkins et al.: (i) frequency of the belief; (ii) presence of conflicting beliefs; and (iii) perceived importance of the belief [33]. This selection of relevant domains was then checked by a second researcher (CP) for accuracy, and results were discussed within the research team.

RESULTS

Search

The electronic database search identified 8780 records. After removing duplicates, 6498 records were screened, and 153 examined in further detail. Of these, we included 20 reports in the present study. We also identified one report through Google Scholar and two through citation searching. Overall, we included 23 reports, from 22 studies (Fig. 1).

Section 2

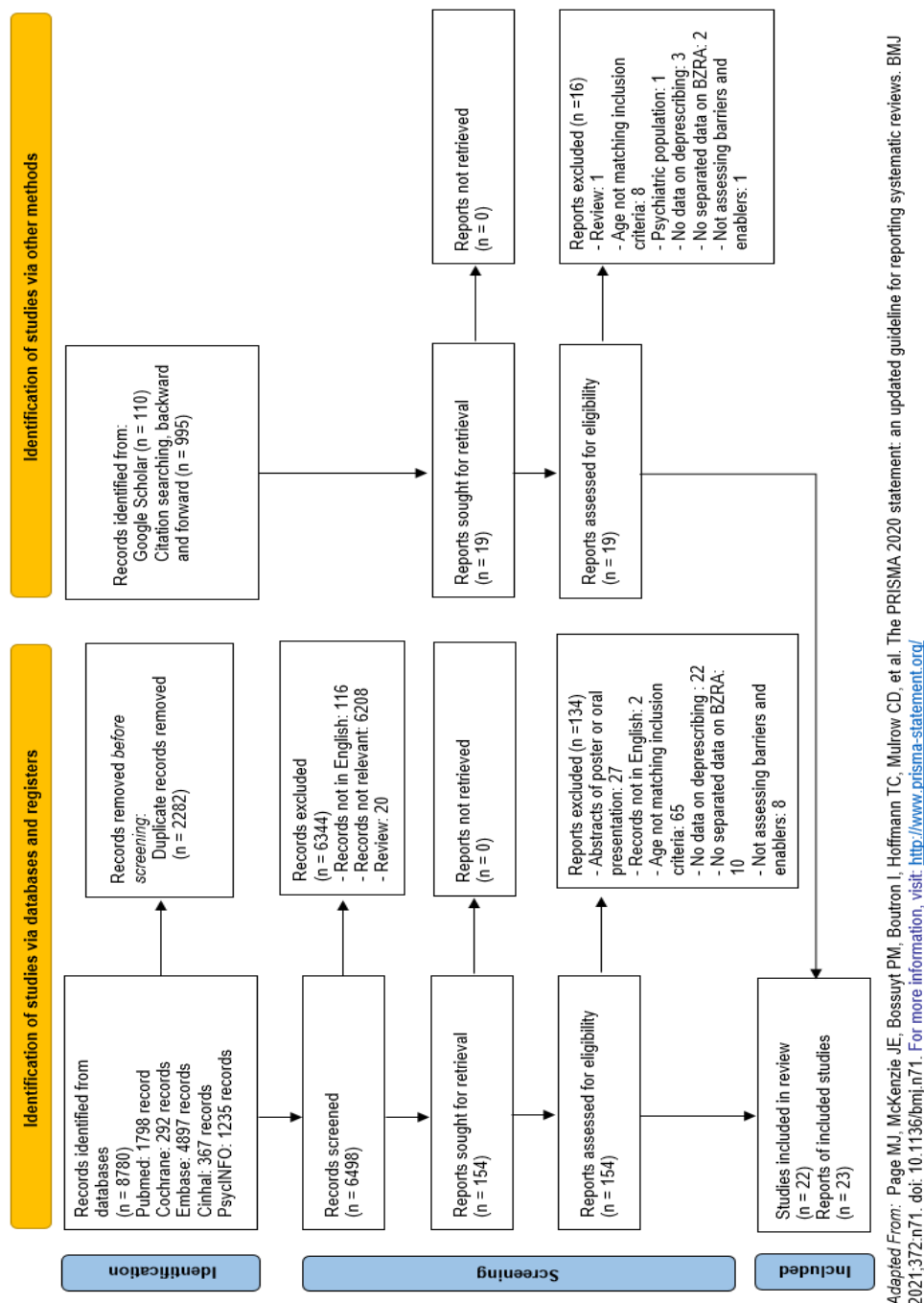


Fig. 1. Flowchart of studies screening and selection

Adapted From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: <http://www.prisma-statement.org/>

Study characteristics

Of the 23 studies, there were 13 quantitative, 8 qualitative and 2 mixed-methods studies. Two studies reflected on the point of views of different stakeholders from the same sample. The most studied setting was ambulatory, reported in 14 records. NH and hospital settings were explored in 8 and 1 records, respectively. The points of view and/or characteristics of patients, GPs and nurses were assessed in 19, 9 and 3 reports, respectively. A summary of study characteristics and extracted results is provided in Table 1. For 7 of the 23 reports, the data were missing to assess the quality of at least one of the MMAT criteria, and for 2 of these studies, the data were missing for 2 or more criteria. The quality of the majority of the included studies was good, but 2 studies [36, 37] were of poor quality (see Additional file 4).

Section 2

Table 1: Description of characteristics of included studies, significant results and related TDF domains						
Author, Year	Country	Type of study	Population	Measures/ themes explored	BZRA deprescribing definition	Main extracted results
Studies conducted in the NH setting						
Anthierens, 2009 (45)	Belgium	Qualitative	33 NH nurses, in 5 NHs	Focus group and face-to-face interviews exploring BZRA use in NH, perceived role of nurses and their attitudes and feelings	Not reported	Different themes and subthemes: Nurses' individual attitudes and perceptions: - Routine approach - Nurse as 'sleep guardian' Pharmacological knowledge Organisational factors: - Traditional doctor-nurse relationship - Organisational requirements - Smooth running of the NH Team meetings
Bourgeois, 2014 study A (51)	Belgium	Quantitative, BZRA deprescribing feasibility study, uncontrolled	135 NHRs in 5 NHs	GPs and NHRs willingness to prescribe Feasibility of deprescribing	BZRA discontinuation	Willingness for discontinuation: GPs refused deprescribing for 71 NHRs Reasons: - Unmotivated patient: 40 - Previous attempt failed: 13 - Other reasons (too old): 9 - Medical cause of sleeplessness: 8 - BZRA not indicated for sleep problems: 6 - Psychiatric history: 5 - Discontinuation started before inclusion possibility: 4 - Stopped BZD but switched to something else: 2 - Discontinuation but no agreement to start in study: 2 13 NHRs out of 51 refused Main reason: reluctance towards change Feasibility of discontinuation: Of 38 NHRs, 66.0 % were successful in completely discontinuing BZRA use at 8 months. The reasons why NHRs were not successful in their discontinuation was because of sleep problems during the discontinuation (n=6/13) and overall loss of motivation (n= 5/13)

Bourgeois, 2014 Study B (39)	Belgium	Quantitative cross-sectional study: GP and nurse questionnaire	25 GPs and 16 nurses in 5 NHs	Initiation, indication and previous attempts to stop chronic BZRA use Benefit and harm of BZRA use Willingness to stop BZRA use Resident-specific barriers General attitudes towards BZRA discontinuation	BZRA discontinuation	<u>Previous attempts</u> The GPs and the nurses indicated that they had already attempted a withdrawal in the past in 26% and 12% of the residents, respectively In general, chronic BZRA use was perceived as effective, and only few adverse effects were noted <u>Willingness to stop</u> GPs and nurses indicated willingness to stop chronic BZRA use in respectively 33 and 21% of NHRs <u>Resident-specific barriers</u> most common barriers among the GPs were: - Fear of resistance from the resident - Preference of a pharmacological treatment above a non-pharmacological treatment - Fear that in these resident initial problems would come back - Fear of an increase in the care burden for the staff - Perception that change is not necessary as long as the resident functions well - Fear of withdrawal effects. Among the nurses, the most common barriers were: - Fear that the residents' initial problems would come back - Preference for a pharmacological treatment - Conviction that change is not necessary as long as the resident functions well. <u>General attitudes</u> The most common attitudes among both GPs and nurses were: - The longer the resident takes the medication, the more difficult it is to stop. - Old age of a resident makes it difficult and unnecessary to stop. - Help of other care professions, such as a psychologist and a pharmacist, are not really necessary. - Alternative strategies are more time consuming - Rhythm of a nursing home with strict bedtimes also limits possibilities for discontinuation. Nurses agreed and GPs disagreed on the statements that there is little knowledge on alternative strategies to cope with problems
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Section 2

De Souto Barreto, 2015 (13)	France	Quantitative non-randomised controlled trial of implementation of an intervention (not targeted at BZRA)	3973 NHRs from 163 NHs, 2167 included in this substudy	Factors associated with BZRA deprescribing at 18 months	BZRA discontinuation	when stopping BZDs and that there is little scientific information available for stopping. In general, no association for NH and NHR factors BUT living in a particular NH affected BZRA deprescribing In the intervention group, use of an antidepressant was a facilitator and female gender was a barrier In the control group, use of meprobamate and a higher number of medications were both barriers
Evvard, 2020 (43)	Belgium	Quantitative cRCT of an intervention (not targeted at BZRA) implementation	418 NHRs with BZRA at baseline, in 54 NHs	Factors associated with BZRA deprescribing at 15 months	Deprescribing included complete cessation or decreased daily dose and cessation of an "if needed" BZRA prescription in addition to an unchanged chronic dose	Enablers: - Intervention (consisting of education program for HCPs, multidisciplinary work[and medication review]) - Hospitalization in the past 3 months - Parkinson/extrapramidal syndrome - Dementia - Number of beds in the NH Barriers: - Public NH (as compared to private non-profit)
Lambson, 2003 (37)	South Africa	Mixed-methods (qualitative interview and quantitative questionnaire)	Interviews: 44 older adults of a retirement village Questionnaire: 10 GPs, 4 nursing staff	Interview: reasons for initiation and continuation of BZRA, duration and frequency of use, perception of their doctor's attitude and prescribing behaviour, desire and/or efforts to stop taking the tablets, and perceptions of usefulness	Not reported	Patient interviews: - Reasons to continue taking the medication related to fear of not sleeping without them - 47% of subjects felt that their doctors were quite happy for them to continue taking the benzodiazepine - 26% reported that they would like to stop taking BZRA GP questionnaire: - 66% believed that it was acceptable to allow an elderly patient to continue a benzodiazepine indefinitely, and 78% felt that a regular sleeping tablet was a good idea. - 44.4% did not mind renewing prescriptions for benzodiazepines, while 33.3% did mind. - 55.5% felt it was easier to renew the prescription than to argue with the patient. - 79% agreed that patients taking sleeping tablets would not be persuaded to give them up.

MacLagen 2020 (53)	Canada	Quantitative, retrospective cohort study	35 169 NHRs from Ontario	Factors associated with BZRA discontinuation (in general and stratified by sex)	≥ 30-day gap in days supplied during the 180- day follow-up period after admission	Questionnaire: BZRA perceptions and concerns - 67% felt they were bothered by endless requests for benzodiazepine prescriptions <u>Nursing staff questionnaire:</u> - 75% felt it was not a problem to continue the sleeping tablet indefinitely - All subjects believed that it was better to tranquillise a restless patient than to allow them to disturb other patients.
Mestres Gonzalvo, 2018 (57)	Netherlands	Quantitative, BZRA deprescribing clinical alert feasibility study, uncontrolled	GPs received 180 alerts about 161 NHRs, in 15 NHs	Reasons for not following a clinical alert related to BZRA deprescribing (as indicated by GPs)	Following the clinical rule meant that the GP started BZRA deprescribing	<u>In general</u> Barriers: - Female gender - Low income - Aggregated Diagnosis group (more comorbidities) Enablers: - Older age - Higher aggressive behaviour scale score <u>Among men</u> Enablers: - Older age - Widowed - Higher aggressive behaviour scale score <u>Among women</u> Barriers: - Low income - Aggregated Diagnosis group (more comorbidities) Enablers: - Older age - Higher aggressive behaviour scale score
				Reasons for not following the clinical rule	27 out of 161 (16.8%) of the alerts actioned were followed	The alert-following group had a shorter median-time of BZRA, compared to the alert non-following group

Section 2

				followers and non-followers		Rate of alert following differed among GPs
Studies conducted in the ambulatory setting						
Allary, 2020 (49)	Canada	Quantitative, RCT of gradual withdrawal program with or without cognitive-behavioural therapy	60 patients of the PASSE-60 study,	Predictors of successful BZRA deprescribing at the patient level in a 16-week RCT, at end of withdrawal, 3 months and 12 months later	Complete BZRA discontinuation	<u>At end of withdrawal:</u> 2 enablers: - o Higher social support satisfaction - o Lower BZRA dose at baseline <u>At 12 months:</u> 4 enablers - o Higher support satisfaction - o Self-perceived competence - o Higher intensity of depressive symptoms - o Poorer quality of sleep
Barter, 1996 (48)	United Kingdom	Qualitative	11 older adults, chronic BZRA users	Interviews about: type of benzodiazepine used; length of use and pattern of taking; social support; reasons for first using these tablets and current reasons; perception of doctor's attitude and prescribing behaviour; wishes and efforts to stop taking the tablets; and general sleep quality	Not reported	<u>Major themes:</u> - Reported efficacy of the prescribing sleeping tablets - Changes in dosage/pattern of use (for current benzodiazepines) - Reasons for use - Patient knowledge and perception of doctor's attitude and prescribing behaviour in relation to benzodiazepine use - Wishes, efforts and past experiences of discontinuing tablets - How people felt about using sleeping tablets
Bell, 2011 (55)	Finland	Quantitative, longitudinal (2 years) observational study	311 patients using BZRA	Factors associated with BZRA deprescribing	No benzodiazepine prescription in the last 6 months	<u>One enabler:</u> - Age over 85 years

Chen, 2010 (47)	Canada	Qualitative	13 HCPs working in a geriatric day hospital 5 patients who had been referred to the pharmacist for BZRA deprescribing	Providers: Interviews and group discussion of perceived and actual role in BZRA deprescribing, barriers and enablers, factors that predispose, enable and reinforce Patients: Barriers and facilitators, factors that predispose, enable and reinforce, role of various providers	Not reported	Providers: - Physicians, nurses and pharmacists were the most involved - Other providers lack of guidance Patients, main themes: - Experiences with BZRA - Willingness to taper - Tolerance of tapering
Chen, 2014 (46)	USA	Quantitative, quasi experimental comparative study. Intervention= losing BZRA reimbursement	Intervention: 250 older adults Control: 216 older adults	Factors associated with BZRA cessation after losing coverage, two regression models	BZRA discontinuation (2 regression models used)	In one of the two models used: Barriers: - Older age - Higher comorbidity scores - Higher BZRA exposure - Higher BZRA dosage Enabler: - Gender: woman
Cook, 2007 Study A (42)	USA	Qualitative	50 older adults, chronic BZRA user	Interviews about: the rationale and circumstances for BZRA use; patient's perceptions of family members and physicians' perspectives; knowledge of adverse effects; experience of skipped doses; reliance on	Not reported	Different themes and subthemes: Purpose and importance of benzodiazepines - Means to cope with stress/anxiety and aid sleep - Lifeline or life-transforming properties - Lack of awareness, underestimation, or disregard for adverse effects Attitudes towards tapering/discontinuation - Negativity or resistance to tapering/discontinuation - Rejection of psychological interventions Power and influence of physician-patient relationship

Section 2

					benzodiazepines; thoughts about discontinuation; interest in finding alternatives				
Cook, 2007 Study B (54)	USA	Quantitative, questionnaire	46 older adults taking BZRA for at least 3 months	Factors associated with willingness to taper/discontinue BZRA	Tapering or discontinuation	2 barriers identified in multivariate analysis: - More frequent benzodiazepine intake - Higher Anxiety Sensitivity Index			
Cook, 2007 Study C (44)	USA	Qualitative	33 GPs	Interviews about: -role of BZRA and management of anxiety, insomnia, and depression in older adults -BZRA prescribing and renewing process -Problems with BZRA use and strategies, including psychotherapy use	Not reported	Different themes and subthemes: Physician minimisation of the problem: - No addiction seen in this population - Little recognition of adverse effects other than addiction - Continuation is compassionate, discontinuation is harsh - Low priority relative to medical problems Justification of short-term and long-term BZRA use: - Effectiveness for anxiety and sleep problems - Belief that stable dosage is safe and effective - Attempt to discontinue will fail - Anticipated resistance from patient - Cost-benefit: Question patient gain and highlight suffering involved in tapering or discontinuation Broad organizational factors and system constraints: - Limited physician time - Poor reimbursement for mental health care - Older patients limited acceptance and access to mental health services			

Iliffe, 2004 (41)	United Kingdom	Qualitative	192 patients, long-term (>6 months) BZRA users	Interviews about: -BZRA prescribing patterns -Reasons for initial and current prescription -Belief in BZRA efficacy -Concerns about BZRA - Previous discontinuation attempts - Perceived advantages and disadvantages of deprescribing Evaluate differences between continuers and withdrawers	Withdrawers= patients who wished to participate in a withdrawal program	Reason for prescription: No difference between continuers and withdrawers in reason for initial or current prescription Beliefs of efficacy: - Continuers reported BZRA as more helpful than withdrawers - More continuers reported that they never had sleeping problems while taking BZRA, while withdrawers reported having problems very often Concerns about BZRA: - In both groups the majority of patients reported that no one ever suggested their BZRA may be harmful - Only few patients had worried about long-term use adverse effects, but more withdrawers than continuers said they had worried Perceived advantages and disadvantages of BZRA deprescribing: - No difference between continuers and withdrawers regarding disadvantages (mainly not sleeping and not being able to manage) - Withdrawers were more likely to mention specific benefits, including 'clearer thinking', 'better memory', 'being more in control', 'more natural sleep', 'having to take less tablets', 'feeling less sleepy', 'feeling proud of myself' Intention: Withdrawers were more willing than continuers to stop BZRA.	Prevalence of beliefs about BZRA deprescribing advantages and disadvantages: - Increased demand on the GP: 48% - Anticipated difficulty in persuading older adults: 51% - Problems anticipated - o Upset or anxious patients: 34% - o Patient insomnia: 24% - o Unmasked depression: 21% - Expected benefits - o Fewer falls: 57% - o Better sleep: 25% - o Better quality of life: 18% - o Increased independence and unmasking of depression: 11% - Better clinical practice: 65% - Reduced prescription costs: 34% - Addressing a "significant public health issue": 22%
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Section 2

Joester, 2010 (56)	Australia	Quantitative, retrospective, cross-sectional study	42 BZRA users, over 65, attending a fall clinic	Factors influencing recommendations for BZRA deprescribing Factors associated with compliance	Successful dose reduction or discontinuation	In addition, respondents were concerned about "how patient would react to being encouraged to withdraw from 'harmful' drugs which had been prescribed by their own GP" Recommendation to deprescribe BZRA in 31/42 patients Enablers of BZRA deprescribing recommendation: - Assessment by a geriatrician (compared to a rehabilitation specialist) - Patients using BZRA as needed or less than three times per week Compliance with recommendation in 21/28 patients Enabler of recommendation compliance - Advise to cease BZRA completely (compared with advice to reduce dose or gradually reduce dose with the aim of cessation)
Kuntz, 2018 (40)	USA	Qualitative study, parallel to a direct-to-patient educational intervention	10 older adults, Z-drug users	Interview about: - Past and current Z-drug use - Prior education about sedative needs - Educational needs - Reactions to the intervention material	Not reported	3 major themes: - Insomnia-related factors (Importance of sleep, treatments alternatives) - Structural and health care delivery system related factor (identification to brochure, individual care, no discussion about it with GP) - Patient experiences and concerns (BZRA taking experience, side-effects)
			7 GPs	Interview about: - Approaches to providing care to older adults with insomnia - Sedative medication prescribing - Reaction to the intervention materials - Factors that hinder or support deprescribing of sedative		3 major themes - Institutional structure (Lack of resources, level of priority) - Patient characteristics and attitudes (patient dependence, communication) - Clinician characteristics and attitudes (care burden, alternatives)

Lasserre, 2010 (36)	France	Quantitative : Cross sectional survey by questionnaire	350 GPs	Questionnaire on: - Knowledge - Opinions about prescriptions - Ways to reduce anxiolytics/hypnotics in older adults - Barriers	Not reported	82% of GPs knew at least one of the 6 national guidelines on management of people with insomnia and/or anxiety 97.1% of GPs previously felt pressure to renew anxiolytics/hypnotics 90.5% declared that it was possible to reduce or stop treatment for their patients High level of patient physical and psychological dependence reported Agreement on ways to reduce anxiolytics/hypnotics: - Campaign to inform general population: 84% - Increased access to psychiatrist: 81% - Reinforcement of physician education: 81% - Increased access to psychotherapy: 60% Agreement with identified barriers: - Patient does not want to stop the treatment: 79% - Psychotherapy is not refunded: 79% - Psychotherapy is not accessible: 73% - No alternative therapy to propose: 70% - Drug withdrawal more dangerous than benefits of stopping: 58% - Relatives of the patient refuse drug withdrawal: 38% - Unaware of drug withdrawal procedure: 8%
Martin, 2017 (38)	Canada	Mixed methods: Quantitative study of factors associated with outcome in the EMPOWER study (educational brochure)	261 adults over 65, receiving at least 5 medicines and chronic BZRA prescription	Evaluation of the three mechanisms of increasing motivation, capacity and opportunity links with outcome	BZRA cessation Individuals who achieved a dose reduction were classified as intent to deprescribe with failed discontinuation Barriers: - Higher perceived necessity score - Poor health Enablers: - Improved knowledge - Increased concern - Higher risk perception about BZRA - Higher self-efficacy to discontinue	Contexts associated with negative outcome (barriers): - Previous discouragement from physician - Poor health status - Unquestioning belief in their physician - Lack of perception of personal risk

Section 2

			and chronic BZRA prescription	- Reasons underlying the decision to taper - Experience with the tapering process - Personal interactions with HCPs		- Reliance on medication for coping/everyday function - Quality of life focus during end of life - Discouragement from a physician - Intolerance to recurrence of symptoms/withdrawal effects - Loss of confidence to complete the tapering process (post intervention) Contexts associated with positive outcome (enablers): - Previous support from physician/positive attitude towards discontinuation - Stable health status - Certainty and confidence about tapering (post intervention) - Positive outlook on ageing - Perception of increased risk - Lack of psychological attachment - Tapering tool provides support - Supportive HCP
Williams, 2016 (50)	Australia	Qualitative	17 older adults with at least 2 nocturnal BZRA prescriptions in the last 6 months	Interviews on: -BZRA initiation -Perception of doctors' attitudes -Thoughts on stopping BZRA -Awareness of alternative treatments	Not reported	3 major themes explored: - Commencement and continuation of nocturnal BZRA (reasons for use, benefits perceived, previous deprescribing attempts) - Participants' knowledge of BZRA and alternative options available (knowledge of adverse effects, treatment alternatives) - Attitudes to BZRA use and cessation (perceived GP opinion, willingness to deprescribe)
Studies conducted in the hospital setting						
Yokoi, 2014 (52)	USA	Quantitative, retrospective chart review	75 patients on standing BZRA, admitted for at least 14 days	Differences at admission between continuers and withdrawers Factors potentially associated with deprescribing	No BZRA at discharge	Withdrawers were less anxious at admission than continuers Continuers had a better mean orientation score than withdrawers 2 potential enablers for BZRA discontinuation: - Older age - Higher antidepressant dose
Legend: BZRA= benzodiazepine receptor agonist, cRCT= cluster randomised control trial, GP= general practitioner, HCP= health care provider, NH= Nursing home, NHR= nursing home resident, TDF= Theoretical domains framework						

Identified barriers and enablers

We identified barriers and enablers across 14 different domains: 7 TDF domains identified as most relevant (beliefs about capabilities; beliefs about consequences; environmental context and resources; intention; goals; social influences; memory, attention and decision process), five other TDF domains, and two domains outside the TDF. The number of domains addressed by the studies ranged from 1 to 11. A summary of the domains identified as barriers and/or enablers per setting and per stakeholder is shown in Fig. 2. We identified mostly barriers. Several domains contained only barriers, whereas others contained barriers and enablers. No domain contained only enablers. Perceived barriers and enablers within domains differed across settings and across stakeholders. As an example, for the domain 'beliefs about consequences', residents in a NH setting reported only barriers, whereas patients in the ambulatory setting and GPs in both settings identified both barriers and enablers. Details of the barriers and enablers identified within each domain per included study are presented in Table 2.

Section 2

Analysis domains	Nursing home setting			Ambulatory setting		
	GPs	NHRs	Nurses	GPs	Patients	
Beliefs about capabilities	Orange	Orange	Orange	Orange	Blue	
Beliefs about consequences	Blue	Orange	Blue	Blue	Blue	
Environmental context and resources	Blue	Blue	Orange	Blue	Blue	
Intention	Orange	Orange	Orange	Orange	Blue	
Goals	Orange			Orange	Blue	
Social influences	Orange	Orange	Orange	Blue	Blue	
Memory, attention and decision process			Orange	Orange	Orange	
Knowledge			Orange		Orange	
Skills			Orange	Orange		
Social, professional role and identity			Orange	Orange		
Reinforcement	Orange	Orange	Orange	Orange	Orange	
Emotion				Orange	Blue	
Patients' characteristics		Blue			Blue	
BZRA prescribing patterns		Blue			Blue	

Fig. 2: Reported relevant analysis domain, identified as barrier and/or enabler per setting and per stakeholders.

Legend: **Orange**=Barrier, **Blue**=Enabler, **BZRA**=Benzodiazepine Receptor Agonists, **GPs**=General Practitioners, **NHRs**=Nursing home residents

Table 2 : TDF domains and subthemes identified as barriers and/or enablers in each included study																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																															
Qualitative analysis themes	Studies conducted in the NH setting		Anthierens, 2009 (45)		Bourgeois, 2014 – Study A (51)		Bourgeois, 2014 – Study B (39)		De Souto Barreto, 2015 (13)		Evrard, 2020 (43)		Lambson, 2003 (37)		MacLagen, 2020 (53)		Mestres Gonzalvo, 2018 (57)		Studies conducted in ambulatory setting		Allary, 2020 (49)		Barter, 1996 (48)		Bell, 2011 (55)		Chen, 2010 (47)		Chen, 2014 (46)		Cook, 2007 – study A (42)		Cook, 2007 – study B (54)		Cook, 2007 – study C (44)		Iliffe, 2004 (41)		Joester, 2010 (56)		Kuntz, 2018 (40)		Lasserre, 2010 (36)		Martin, 2017 (38)		Williams, 2016 (50)		Study conducted in hospital setting		Yokoi, 2014 (52)																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																												
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Section 2

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Knowledge																			
<i>What stakeholders know on BZRA deprescribing</i>																			
Nurses' lack of knowledge	B																		
Patients' lack of knowledge																			
Skills																			
<i>What stakeholders know about how they should perform BZRA deprescribing</i>																			
GPs' lack of systematic strategy																			
Nurses' lack of skills regarding non-pharmacological approaches	B																		
Social, professional role and identity																			
<i>Perception of who stakeholders are (as healthcare professionals)</i>																			
Nurses perceived ideal role	B;																		
Scarce and difficult multidisciplinary work	B																		
Perceived expectation of prescribing																			
Reinforcement																			
<i>Influence of stakeholders' past experiences with BZRA deprescribing</i>																			
Previous attempts and failure																			
Emotion																			
<i>How stakeholders feel about BZRA deprescribing</i>																			
Various patient emotions																			
GP frustration																			
Patient characteristics																			
Older age																			
Woman																			
Depression																			
Anxiety																			
Psychiatric history																			
Dementia																			
Aggressive behaviour																			
Low orientation score																			
Parkinson or extrapyramidal symptoms																			
Comorbidities																			

Section 2

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Below, we present the data relative to the **TDF domains most relevant** for BZRA deprescribing.

Beliefs about capabilities

Beliefs about capabilities represent the perceived capability of stakeholder to perform the behaviour and the problems they face. Twelve studies reported on this domain, mainly as a barrier for BZRA deprescribing; two studies reported that patients' perceived self-efficacy was an enabler of BZRA deprescribing.

"Individuals who decided to deprescribe exhibited higher capacity for tapering, with enhanced self-efficacy compared with those in whom the intervention did not trigger motivation (risk difference, 56.90% (95% CI 45.41% to 65.77%))" Ambulatory setting [38].

GPs and nurses viewed deprescribing, including motivating patients, as challenging.

"Nurses considered a stop possible in 21% of the chronic BZD users." NH setting [39]

"It can be a tough sell to get patients off of these meds." GP interview, ambulatory setting [40].

Additionally, perceived BZRA efficacy and lack of efficacy were respectively a barrier and an enabler for deprescribing. Studies mainly reported that healthcare providers (HCPs) perceived BZRA as effective, while patients had conflicting views.

"More withdrawers reported that their medication was 'a little helpful' and more continuers reported that their sleeping tablets were 'very helpful' for a good night's sleep, a significant difference." Ambulatory setting [41].

Beliefs about consequences

Beliefs about consequences, which represent what stakeholders think could happen from performing the behaviour, were reported in 13 of the studies, mainly as a barrier. In 11 studies, stakeholders did not perceive any adverse effects of BZRA and therefore did not believe stopping them would have any benefit. As patients aged, healthcare providers and patients themselves believed that BZRA deprescribing would not be beneficial.

"I've been on these for so many years and nothing has ever happened so I don't wanna." Older adult interview, ambulatory setting [42].

Furthermore, some HCPs and patients identified several negative potential consequences of BZRA deprescribing: the return of insomnia or anxiety, withdrawal symptoms and an increase in care burden.

Section 2

“Without this medication, I know that my life would be plagued by anxiety, of this I am certain”. (woman, no intent to taper), ambulatory setting [38].

“I know that I’m creating a nightmare with follow-up.” GP interview, ambulatory setting [40]

However, perception of adverse effects of long-term BZRA, and therefore potential positive effects of deprescribing, was a reported enabler in eight reports.

Answers of a panel of GPs about expected benefits: *“fewer falls (n=47, 57%) better sleep (n=21) better quality of life (n=15, 18%) increased independence and unmasking depression (n=9, 11%) Benefice for the practice itself: ‘better clinical practice’ (n=47, 65%), reduced prescription costs (n=28, 34%)”* Ambulatory setting [41].

Environmental context and resources

Environmental context and resources represent how the environment influence stakeholders’ behaviour. This appeared to be an important domain, reported in 13 of the studies, with barriers and enablers identified at micro (individual and HCP) and macro (system) levels.

At the **micro level**, the implementation of strategies (including multidisciplinary review and education) was reported to be effective in enhancing BZRA deprescribing [38, 43]. Some tools were perceived as helpful, while others sometimes did not reach the GPs or patients or were perceived as inadequate.

“In the past I tried to stop the pill all at once. But using the tapering tool, I understood that it need to be a gradual and not a drastic process”. (man, successful taper, ambulatory setting) [38]

“Guidelines were criticized as out of touch with real-world problems” Ambulatory setting [44].

The environmental context at a patient level may also play an important role, with 5 studies reporting favourable or unfavourable moments in life that may encourage or discourage BZRA deprescribing. These moments might influence the person’s perception of consequences and ability to deprescribe.

“Perhaps when I retire, and it is not so important that I go back to sleep, maybe I would consider it then. But right now it seems to serve a purpose.” Older adult interview, ambulatory setting [40]

At the **macro level**, studies reported a lack of resources, highlighted by GPs. This is particularly important in a context where GPs and other HCPs have a heavy workload.

“Here is the thing: We have infinite resources to prescribe pills. We have very finite and limited resources to actually educate and inform patients about the things they need to know to wean themselves off these medicines.” GP interview, ambulatory setting [40]

“We do not have enough time for us to follow[-up] these people. We don’t even have time to see our regular patients”. GP interview, ambulatory setting [40].

Alternative strategies for treating insomnia and anxiety were few, not available, or not reimbursed. Providing these alternatives was also seen as time consuming and tedious.

“Medicare... will not reimburse any Internist for a psychiatric diagnosis. Reimbursement is very low... I think if it was something that we did get reimbursed on I think you would see physicians’ attitudes a lot different. You’d be more willing to spend time.” GP interview, ambulatory setting [44].

“The GPs and nurses perceived that alternative strategies are more time consuming (median 5 vs. 3, NS)” NH setting [39].

In one study, GPs felt that they have inherited the problem from other (older) physicians and a previous prescribing culture.

“The problem is, quite frankly, that we don’t start [prescribing] the medication. Most people come in on them. They were given them by their psychiatrist ten years ago and were continued on these medicines, and we are just left with a panel that has a high prevalence [of use] through nothing that I did” GP interview, ambulatory setting [40].

In two studies, BZRA deprescribing was reported to be not prioritised by the healthcare system.

“Nobody cares how many patients I have tapered off medication.” GP interview, ambulatory setting [40].

Regarding NHs, three studies reported requirements of the specific setting as a barrier. Additionally, being in a specific NH [13] and some NH characteristics (such as private ownership or higher number of beds) [43] were associated with BZRA deprescribing.

Section 2

“The need to have all the residents in bed before the night shift starts and to have the medication round completed enhances BZD use.” Nurse interview, NH setting [45].

“All subjects believed that it was better to tranquillise a restless patient than to allow them to disturb other patients”. Study on nurses [37].

Finally, BZRA-associated expenses seem to have a very small role in BZRA deprescribing: only one study highlighted a small association between BZRA cessation and BZRA costs [46].

Intention

The intention domain refers to how inclined someone is to perform a specific behaviour. Twelve studies reported various levels of intention for BZRA deprescribing. The overall willingness of patients and HCPs was low.

“When asked if they would like to stop taking the benzodiazepine, only 26% (of older adults) felt that they would” NH setting [37].

Reported intention to recommend or use alternatives, including non-pharmacological approaches, was also low.

“I just don’t want to. I’m not one of those people who can sit around and talk about my problems with strangers [i.e. cognitive behavioural therapy]”. Older adult interview, ambulatory setting [42].

Goals

This domain evaluates the importance of the behaviour for stakeholders. We found conflicting results regarding perceived priority of BZRA deprescribing. In five studies, BZRA deprescribing was not reported to be a priority. Indeed, other competing goals were cited by the different stakeholders. Among these, preserving quality of life was more important (five studies). In particular, for older patients, BZRA deprescribing was perceived mainly as impacting one’s well-being near end of life. Treating competing medical issues (three studies) and preserving the patient-doctor relationship (one study) were other goals reported by GPs.

“If we have full schedules and only 20 minutes and people have 8 or 9 different problems, and sedative medications is one of them, it is usually not my top priority” GP interview, ambulatory setting [40].

“For heaven’s sakes! I’m going to be 91 years old. What difference does it make if you give me something that . . . will hurt me in the future?” Older adult interview, ambulatory setting [47].

Nine studies reported strong patient attachment to BZRA, which may reduce the perceived importance of BZRA deprescribing.

“Once they find the medication that works, they are very happy and very irritated by any attempts not to prescribe this medication any longer.” GP interview, ambulatory setting [40].

Two studies reported the importance of a good night of sleep as a barrier perceived by nurses and patients. However, we also found conflicting results, as two other studies reported that sleep became less important with age [38].

“People need to have a good night. It is no use that they lay awake all night and that they are tired the next day and stay in bed all day. Yes I totally agree, sleep is very important in nursing homes, I think even more important than at home. People can be disturbing when they do not sleep...” Nurses focus group, NH setting [45].

Nevertheless, we found one enabler in this domain: two studies reported that some patients did not like being on BZRA and wanted to decrease their sleeping pills and have a more natural sleep.

“I don’t like being on them, I don’t want to be a slave to something.” Older adult interview, ambulatory setting [48].

Social influences

Social influence represents how others influence stakeholders’ behaviour. Social support in general [49] and the influence of each possible stakeholder were important determinants of BZRA deprescribing, addressed in 13 of the studies. In particular, studies reported a strong reciprocal influence between GP and patient. Eight studies reported that GPs were afraid of patient resistance or lack of motivation and two studies reported that GPs felt under pressure to renew prescriptions.

“Of all eight resident-specific barriers, most common among the GPs were the fear of resistance from the resident (median 9 on 10 points Likert scale)” NH setting [39].

Section 2

“Pressure by patients to initiate or renew prescription of anxiolytics/hypnotics had previously been felt by 97.1% of GPs (67.4% often, 29.7% sometimes, 2.9% never).” Ambulatory setting [36].

In several studies, patients viewed prescription by the GP as a guarantee that the BZRAs were harmless. Moreover, patients reported that their GP did not inquire about BZRA use and they took this silence as an approval to continue the drugs.

“I don’t think (the doctor) is against it ... (the doctor) has never queried it.”
Older adult interview, ambulatory setting [48].

This finding is reinforced by the great trust patients have in their GP and confidence in their advice that was reported in four studies. As a consequence, studies reported that patients may rely on the GP’s opinion regarding the deprescribing process, which could both be a barrier or an enabler.

“I have complete faith in Dr. _____. I mean we go back a lot of years. Whatever he says, goes.” Older adult interview, ambulatory setting [42].

To a lesser extent, other forms of social influence were identified: in NHs, nurses reported pressure from colleagues not to attempt any change [45].

Memory, attention and decision process

This domain, focusing on habits factors and decision process regarding the studied behaviour, was reported in eight studies, with only barriers for BZRA deprescribing. Two studies reported that GPs perceive BZRA prescribing or continuous prescribing as the easiest solution.

“It’s just so much easier to just prescribe something and just walk away.”
GP interview, ambulatory setting [44].

Seven studies reported a routine approach regarding BZRA use and prescribing for both patients and HCPs: once a BZRA is started, there is a lack of treatment reevaluation.

“We do not think enough about sleep medication. People have been taking their sleeping tablets for years. There is no evaluation of whether it is still necessary or not”. Nurse interview, NH setting [45].
“It is just like putting a comb through your hair, it is just a thing that you are used to”. Older adult interview, ambulatory setting [48].

In one study, stakeholder preference for keeping a status quo and reluctance to change was a reported barrier.

“The conviction that change is not necessary as long as the resident functions well”. Study on GPs and nurses, NH setting [39].

Conflicting attitudes were reported concerning the decision process by patients. On the one hand, they are reported to feel as “critical consumers who weighed the pros and cons of continuing to take nonbenzodiazepines.” [40]. On the other hand, many of them reported not being able to “recall having consulted their doctor with regards to taking a sleeping table” [37] or not considering “how long they would be taking them.” [50].

Additional TDF domains

Some relevant barriers and enablers for BZRA deprescribing were also found in **other TDF domains**. For all the subthemes mapped into TDF domains, more citations are available in Additional file 5.

Knowledge. Studies that investigated HCP knowledge about BZRA deprescribing mainly interrogated GPs and nurses in the NH setting. In that context, GPs were generally aware of BZRA deprescribing recommendations, that BZRA should not be renewed indefinitely, and of the withdrawal procedure [36]. NH nurses acknowledged a lack of knowledge both on benzodiazepines and their adverse effects, and on sleep hygiene and non-pharmacological approaches for anxiety or insomnia management. Among patients, six studies reported very limited knowledge about BZRA adverse effects or alternative therapies. Moreover, an improvement in patient knowledge was associated with BZRA deprescribing [38].

Skills. One study [44] reported that physicians reported a lack of a systematic strategy to address patient’s concerns regarding deprescribing. For NH nurses, one study reported a lack of skills regarding implementation of non-pharmacological approaches.

Social, professional role & identity. One study reported that the nurses’ perceived role includes reporting on patients’ sleep habits and looking for solutions [45]. Consequently, they would be helpful in a multidisciplinary process. Yet, this multidisciplinary approach is currently reported as too scarce and nurses often feel they are not listened to by GPs. For GPs, two studies reported that they felt they were expected to give something to help the patient [40, 44].

Section 2

Reinforcement. In nine studies, patients and GPs indicated that they had attempted to deprescribe BZRA and failed, which was a barrier to future attempts. However, the link between these previous attempts and future attempts was not observed in all studies [39, 51].

Emotion. Only four studies reported on stakeholders' emotions. Although some patients felt fear or anxiety regarding BZRA deprescribing [42], it could also be seen as an unimportant event [47]. For GPs, the process of BZRA deprescribing was reported as frustrating, because of the level of challenge and effort required [40, 44].

Finally, we identified **two other themes** that did not fit into the TDF, as they are not behaviour related. These themes were "patient characteristics" and "BZRA prescribing patterns".

Patient characteristics. Many studies identified diverse patient characteristics associated with an increased likelihood of BZRA deprescribing: depression [49], Parkinson's or extrapyramidal syndrome [43], dementia [43], poorer orientation score [52], aggressive behaviour [53], poorer quality of sleep [49], hospitalisation in the past 3 months [43], antidepressant use [13, 52] and widowed men [53]. Other patient characteristics were associated with a decreased likelihood of BZRA deprescribing: anxiety [54], low income [53], psychiatric history [51], higher comorbidities [46, 53], higher number of medications [13] and medical cause of sleeplessness [51]. For other characteristics, the influence on BZRA deprescribing was inconsistent across studies. Older age was associated with increased [53, 55] and decreased [39, 46] BZRA deprescribing. Some studies reported that deprescribing was higher among women than men [46], but conflicting results were also found [13, 53].

BZRA prescribing patterns. A few factors were reported as being positively associated with BZRA deprescribing: a lower BZRA dose [46, 49], a lower frequency of BZRA intake [54, 56] and a shorter duration of treatment [57]. BZRA not used for sleeping issues was however reported as a barrier for deprescribing [51].

DISCUSSION

In this systematic review of barriers and enablers for BZRA deprescribing in older adults, we included 23 studies and identified determinants in and out of TDF domains. Compared to another recent systematic review on this topic, which only included qualitative evidence [25], our approach enabled us to include more data and gain a deeper understanding of BZRA deprescribing. Consequently, we were able to report

additional barriers and enablers. The use of the TDF is also valuable with regard to the implementation of future strategies.

Identified barriers and enablers

The most relevant domains were Beliefs about capabilities, Beliefs about consequences, Environmental context and resources, Intention, Goals, Social influences, and Memory, Attention and Decision Process. Most domains were relevant to the ambulatory and NH settings, but there were some specificities to the NH setting (environmental context, role of nurses).

One may wonder whether these results are specific to BZRA deprescribing, or common to deprescribing in general, as it is known that some barriers and enablers might be medication-specific [58]. As an example, BZRA are known to cause physical and psychological dependence, which may impact deprescribing. A systematic review of patient barriers and enablers for deprescribing [59] found the following barriers and enablers that can be linked to our sub-theme analysis: disagreement or agreement with appropriateness of cessation (patients' lack of knowledge, beliefs about consequences), absence or presence of a process for cessation (tool implementation), negative or positive influences to cease medication (social influences, reinforcement), fear of cessation (beliefs about consequences, emotion) and dislike of medication (attachment to the medicine). Consequently, our results show that these general barriers and enablers also apply to BZRA deprescribing. However, we found additional barriers not reported for general medications, such as the lack of intention to use a non-pharmacological approach, or seeing BZRA as an easy solution.

Moving forward to implementation

There is a reported need to translate known barriers and enablers into strategies and tool implementation [58]. Using the TDF enables the identified relevant domains to be linked to behavioural change techniques (BCT) [60]. A recent scoping review identified the BCTs implemented in deprescribing strategies conducted in primary health care [61]. They reported a wide range of BCTs, often used in combination. BCTs were mainly mapped into functions of “environmental restructuring”, “enablement”, and “persuasion”, which also seem appropriate for some of the barriers and enablers we report. A next step would be to choose from among these BCTs those that are best suited for BZRA deprescribing, based on the results of our systematic review. As an example, the barriers of “no perceived benefit” and “competing goals” could respectively be targeted by the BCTs of salience of consequences and goal setting. Combining these BCTs to create a complex strategy is more likely to be effective. As an example, the EMPOWER study used a patients' brochure combining different BCTs, information about health consequences and instructions on how to perform a

Section 2

behaviour. The simple use of this brochure led to a 27% reduction in BZRA use [62]. The determinants of BZRA prescribing patterns and patient characteristics could help choose priority groups for future interventions.

One may also wonder whether past strategies have targeted the TDF domains and barriers and enablers that we reported in this systematic review. Some reviews of strategies targeting BZRA deprescribing in older adults [21, 63] or in adults in primary care [20] have reported on the effects of education, gradual dose reduction, use of alternatives, non-pharmacological approaches, tool implementation and medication review. All these strategies are individual-level (micro) strategies and target the following identified barriers: patient lack of knowledge, no perceived benefit, GP lack of systematic strategy, no intention to use non-pharmacological alternatives, difficulty of alternatives and tool implementation. Although some individual barriers and enablers have been targeted, some major behavioural determinants, such as memory, attention and decision processes or social influences domains, still need to be addressed. Moreover, our systematic review also highlighted barriers and enablers that need to be addressed at the healthcare system-level (macro), such as lack of resources. We found one systematic review of the effects of strategies targeting this macro level [64]. These strategies included making BZRA harder to prescribe, withdrawing the driving license, promoting alternatives through campaigns, increasing the financial burden of BZRA or giving financial incentives to physicians. These policies address barriers that we identified: lack of patient knowledge, BZRA being an easy solution, competing goals and BZRA deprescribing not prioritised by healthcare systems. Nevertheless, further macro-level initiatives are needed.

In the future, implementing a BCT targeting each of the most relevant domains identified in the present review should enhance the probability of success. If possible, strategies should be developed at different levels of the healthcare system to enhance BZRA deprescribing, including the organisational (macro) level. Importantly, as barriers and enablers differ depending on stakeholders and setting, components of the strategies need to be flexible and adapted to account for this and developed in close collaboration with stakeholders.

Recommendations for future research

Among the 23 included studies, the point of view of some stakeholders was under-evaluated and deserves further exploration. Data specific to deprescribing among older adults with cognitive impairment require further investigation. Moreover, no study included informal caregivers or relatives, although such persons are particularly important in dementia patients, for example. Only one study interviewed pharmacists [47], although pharmacists are often involved in deprescribing strategies. The points of

view of psychologists or psychiatrists were also not reported. As these specialists may play an important role in the implementation of non-pharmacological management of insomnia and anxiety, this is a major research gap. Additionally, the hospital setting was under-evaluated in our review, yet it may be an appropriate setting to initiate a deprescribing process.

Strengths and limitations

This review has several strengths. Firstly, including both qualitative and quantitative evidences enabled a deeper comprehension of the complex BZRA deprescribing phenomenon. Indeed, we were able to include various studies addressing this specific topic from different points of view. Secondly, using the TDF as an analysis guide is valuable for the theoretically informed development of future strategies. Thirdly, we used both deductive and inductive coding. By doing so, we were able to include barriers and enablers that did not fit the TDF and therefore develop a more complete understanding of their determinants.

This review also has several limitations. Firstly, none of the included studies used the TDF. Consequently, we had to code based on inference from the text. The use of the TDF itself was also challenging, as some items potentially fit into several domains. However, we were able to reach agreement between researchers, and asked for help from a specialised researcher when needed, which strengthens the validity of findings. Secondly, we did not include non-English literature. Thirdly, because of the qualitative approach of our analysis, we were not able to evaluate the specific effect of each barrier and enabler. Finally, the included studies were conducted in only nine countries. Therefore, it is likely that some of our results are not transferable to other countries, in particular the barriers and enablers identified in the environmental context and resource domain.

CONCLUSION

By systematically reviewing barriers and enablers for BZRA deprescribing, we were able to identify the most relevant TDF domains and other determinants. While similar barriers and enablers were reported across different settings of care, there are also singular barriers at the environmental context level which need to be taken into account. Future investigation should focus on the identified barriers and enablers at macro- and micro-levels, as well as addressing research gaps.

Section 2

Supplementary material

Supplementary material can be accessed online and comprises:

- Additional file 1: PRISMA 2020 Checklist
- Additional file 2: Research equations
- Additional file 3: Data extraction form
- Additional file 4: Quality of studies included in the review
- Additional file 5: TDF domains, analysis subthemes and matching citations. (Contains additional citations for each analysis subtheme).

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Chapter 3. Adaptation and validation of the revised Patients' Attitudes towards Deprescribing (rPATD) questionnaire for benzodiazepine receptor agonists

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Article published in *Research in Social and Administrative Pharmacy* (2023)

DOI: <https://doi.org/10.1016/j.sapharm.2023.05.010>

Section 2

AUTHORS' CONTRIBUTIONS

CP: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing – Original Draft, Visualization, Writing – Review & editing, Project administration. **AS:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision, Project administration. **M-LL:** Conceptualization, Resources, Investigation, Writing – review & editing, Project administration. **AN:** Conceptualization, Resources, Investigation, Writing – review & editing, Project administration. **SH:** Conceptualization, Methodology, Software, Validation, Formal analysis, Visualization, Writing – Review & editing, Supervision, Project administration.

ACKNOWLEDGEMENTS

We would like to thank Dr. Emily Reeve, for permitting us to adapt her questionnaire and for having provided feedback on our results. We are also grateful to Prof. Gaëtane Caesens (UCLouvain) and the *Support en Methodologie et Calcul Statistique* (SMCS) team for providing expertise and assistance during the data analysis. We thank Mrs. Laura Jones for having proofread the manuscript for English. We also thank all healthcare providers and NH that helped in recruiting participants for this study, which required extra effort in the COVID-19 pandemic context. Finally, we thank warmly all older adults that participated in our study.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

DECLARATION OF INTEREST

None.

ABSTRACT

BACKGROUND: The revised Patients' Attitudes Towards Deprescribing (rPATD) questionnaire explores older adults' views on deprescribing in general. Those views may differ, however, when the target is a specific drug such as benzodiazepine receptor agonists (BZRA).

OBJECTIVE: This study aimed to adapt the 22-item French rPATD questionnaire to create a BZRA-specific instrument and to assess the psychometric properties of this new tool.

METHODS: The adaptation of the questionnaire comprised 3 steps: 1) item transformation during group discussions with 8 healthcare providers and 8 BZRA users (aged ≥ 65 years), 2) pre-test of the questionnaire with 12 other older adults to ensure items understanding, 3) evaluation of the psychometric properties of the new questionnaire with 221 older BZRA users recruited in Belgium, France, and Switzerland. Construct validity was assessed using exploratory factor analysis (EFA), internal consistency with Cronbach's alpha, and test-retest reliability with intraclass correlation coefficient (ICC).

RESULTS: After the pre-test, the questionnaire had 24 items (19 adapted from the French rPATD, 3 removed, and 5 added). The EFA, however, found that several items performed poorly. Eleven items were consequently removed, based on statistical performance and clinical relevance. Three factors were extracted from the EFA performed on the 11 retained items and were named "Concerns about stopping BZRA", "BZRA inappropriateness", and "Dependence on BZRA". The questionnaire also includes two global questions about willingness to reduce BZRA dosage and willingness to discontinue BZRA. All factors showed acceptable internal consistency ($0.68 \leq \text{Cronbach's alpha} \leq 0.74$). Two factors showed acceptable test-retest reliability. The "Concerns about stopping BZRA" factor was found to vary over time (ICC [95%CI]: $0.35[-0.02; 0.64]$).

CONCLUSIONS: We developed and validated a 13-item questionnaire to evaluate the attitudes of older people towards BZRA deprescribing. Despite some limitations, this questionnaire appears to be a useful tool for facilitating shared decision-making on BZRA deprescribing.

Section 2

INTRODUCTION

Deprescribing is defined by Farrell *et al* as “the planned and supervised process of dose reduction or stopping medication(s) that may be causing harm or are no longer providing benefits” [1]. It aims to reduce polypharmacy and drug-related adverse effects, enhance medication safety, and align treatment with patients’ preferences regarding care goals [1-3]. Benzodiazepine receptor agonists (BZRA), which are prescribed to treat insomnia and anxiety, are among the medications with the highest priority for deprescribing [4]. In older adults, these medications have a poor risk-benefit balance and have been associated with a higher risk of falls and hip fractures and, if used long-term, with a risk of dependence, tolerance, and a decrease in cognitive functions [5-8]. Guidelines therefore recommend avoiding or stopping BZRA use after 4 weeks in older people [9, 10]. Despite those recommendations, older adults frequently take BZRA, often for a long time [11]. Although a trend towards decreased use has been observed in Europe and Canada, prevalence remains quite high, with around 15 – 20% of older adults in the general population taking a BZRA [12-15]. This suggests that various barriers to BZRA deprescribing exist.

A key component of deprescribing is shared decision-making involving both physicians and their patients [16]. To explore patients’ perspectives on deprescribing, Reeve *et al* developed the revised Patient Attitudes Towards Deprescribing questionnaire (rPATD) in 2016 [17]. A French-language cross-cultural version was validated in 2020 (French rPATD) [18]. Although the questionnaires provide useful information about patients’ attitudes toward deprescribing in general, they do not make it possible to assess attitudes towards the deprescribing of a specific medication class. Previous literature has suggested, however, that a patient’s willingness to stop a specific medication could be influenced by the nature of the treatment [19, 20]. To our knowledge, no validated tool exists that specifically assesses older adults’ attitudes towards BZRA deprescribing. The aim of this study was, therefore, 1) to adapt the French rPATD questionnaire to create a version that would be specific to BZRA and 2) to validate this questionnaire in older people aged ≥ 65 who had been taking at least one BZRA for at least four weeks in primary care (PC) and nursing home (NH) settings in Belgium, France, and Switzerland.

METHODS

The adaptation of the rPATD to BZRA comprised 3 steps, which are summarized in Figure 1: 1) item transformation, 2) a pre-test of the questionnaire, and 3) validation of the questionnaire. Older adults corresponding to the inclusion and exclusion criteria

stipulated below and healthcare professionals (HCP) were involved. The two first steps were conducted in Belgium only.

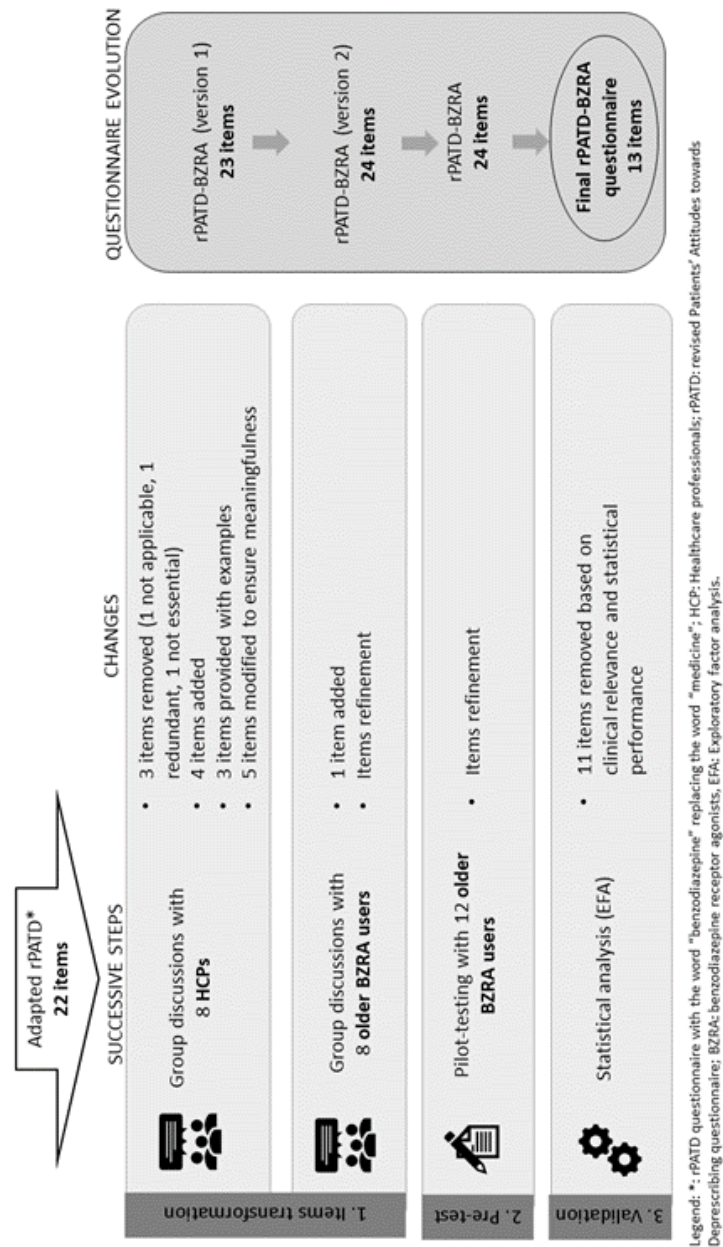


Figure 1. Summary of the adaptation process

Section 2

Patients met the inclusion criteria if they were aged 65 or over and having been taking at least one BZRA (ATC codes N05BA, N05CD, N05CF, or N03AE01) for at least 4 weeks. Clomethiazole (N05CM02) was added for Switzerland only, as it has a pharmacological profile similar to BZRA and is used there for the same indications [21].

Exclusion criteria comprised suffering from psychiatric troubles or alcoholism (present or past), being unable to complete the questionnaire due to functional or cognitive decline, being unable to give consent, and not understanding or speaking French.

1. Item transformation of the French rPATD questionnaire

The item-transformation phase included a first round with a panel of HCPs and a second round with a panel of older adults. This phase enabled the evaluation of face and content validity. As in the original rPATD study, we used the Lawshe technique and calculated a content-validity ratio (CVR) for each item, using the written feedback described below [22].

a. Round with healthcare professionals

After the French rPATD questionnaire had been transformed by replacing the word “medicine” with “benzodiazepines”, 8 healthcare experts (2 geriatricians, 2 pharmacists, 2 general practitioners (GP), and 2 nurses) were each asked to provide written feedback on the transformed items. For each transformed item, they were asked to rate: 1) its relevance in assessing attitudes towards BZRA deprescribing and 2) its necessity in such a questionnaire. HCPs were also encouraged to add ideas or comments in designated blank spaces. The results were discussed collectively during 3 group sessions (each HCP attended only one) in order to reach agreement on which items to keep, delete, add, or transform. The results were then discussed with the research team, which led to the first draft of the questionnaire.

b. Round with older adults

Eight participants were recruited through a university for seniors and a geriatric rehabilitation hospital. They were each asked to provide written feedback on the first draft of the questionnaire and they discussed the results collectively during 2 group

sessions (each older adult attending only one). This resulted in a second version of the questionnaire.

2. Pre-test of the questionnaire

To assess both the clarity of the items after transformation and the overall acceptability of the questionnaire, a convenience sample of 12 older adults was recruited. The participants were asked to complete the questionnaire, and the time taken to complete it was recorded. The participants were encouraged to “think aloud” and offer suggestions relating to the wording of the items or difficulties in understanding them. The results were then discussed with the research team, and further changes were made to some items.

3. Validation of the rPATD-BZRA questionnaire

a. Sample size estimation and recruitment

Construct validity, test-retest reliability, and internal consistency required a larger sample of older adults. The recruitment of at least 200 participants was planned, the minimum sample size required to perform an exploratory factor analysis (EFA) [23]. A 20% non-response rate was anticipated, based on the rPATD and French rPATD studies [17, 18], so the sample size was increased to 240 participants. To ensure proper representation of NH residents, among whom BZRA use is particularly high [24], the sample was split into 160 participants from the PC setting and 80 from the NH setting. Participants were recruited in Belgium, France, and Switzerland, depending on the recruitment opportunities of the research teams involved. Participants in the PC setting were recruited through community pharmacies and general practitioners. They provided eligible patients with an envelope containing the information form, the consent form, and the questionnaire, as well as a stamped envelope in which to return the questionnaire and the signed consent form. For NH residents, a convenience sample of NHs was contacted regarding participation. A researcher or an NH staff member informed eligible residents, asked them to sign the consent form, and helped them to complete the questionnaire if required. Recruitment started in July 2020 and ended in November 2021. To improve the recruitment rate, in view of difficulties caused by the COVID-19 epidemic, an online questionnaire was also made available in January 2021 and distributed through older adults’ associations and personal and professional networks in Belgium and Switzerland.

From the main sample, we selected 20 older adults for test-retest analysis. For practical reasons, only Belgian participants were selected. To ensure that the selection of participants was random, we selected one in every 5 participants in each setting until we had 6 NH residents and 14 PC patients. Those participants were contacted by

Section 2

phone (or, in the case of some NH residents, visited again) and asked to complete the questionnaire a second time, one to two weeks after the completion of the first questionnaire.

Paper questionnaires were encoded using REDCap as an electronic case report form [25]. Online questionnaires were hosted and distributed via Qualtrics software, Version 01/2021 (Qualtrics, Copyright © 2021. Provo, UT, USA. Available at <https://www.qualtrics.com>; accessed on January 2021). Databases from both platforms were merged before analysis.

b. Data collection

The first part of the questionnaire collected socio-demographic data and medication-related information. In the second part of the questionnaire, the adapted items were rated on a Likert scale ranging from 1 “strongly disagree” to 5 “strongly agree”. At the end of the questionnaire, patients were asked if they had needed help answering it.

c. Descriptive analysis of participants

A descriptive analysis of participants was performed. Categorical variables were expressed as numbers and percentages and continuous variables as mean $\pm$ standard deviation or median [P₂₅–P₇₅] depending on the normality assessment.

d. Evaluation of the psychometric properties of the questionnaire

An exploratory factor analysis (EFA) was performed to assess construct validity. As with the rPATD and French rPATD questionnaires, global questions were excluded from the analysis [17, 18]. The appropriateness of the data for factor analysis was assessed using the Kaiser-Meyer-Olkin test and Bartlett’s test of sphericity [26]. Factors were extracted using the principal axis factoring method and an oblique rotation (Promax) to consider correlations between factors. The number of factors was determined using the Kaiser-Guttman criterion (eigenvalue >1), the scree test, and parallel analysis. Loadings over 0.3 were considered significant. Items loading lower than 0.3 were removed from the analysis.

The internal consistency of each factor was estimated using Cronbach’s alpha. A value over 0.7 was taken to indicate good internal consistency.[27] Corrected item-total correlations were calculated at the item level, a value >0.30 being considered satisfactory [28].

Test-retest reliability was assessed using linear-weighted Cohen’s Kappa and percent agreement at the item level, and the intraclass correlation coefficient (ICC) at the

factor level. Following Landis and Koch's guidance for Cohen's Kappa interpretation, we considered values ≤ 0 to be poor agreement, 1 – 20 to be slight agreement, 21 – 40 to be fair agreement, 41 – 60 to be moderate agreement, 61 – 80 to be substantial agreement, and ≥ 81 to be almost perfect agreement [29]. ICC values > 0.50 were considered acceptable [30].

The analyses were performed using R software version 4.0.5 and the following packages: *irr*, *psych*, and *GPArotation*. [31-34] This study was approved by the Ethics Committees of CHU UCL Namur (Belgium) (NUB: B039201940824) and Limoges CHU (CE:335-2019-101). No authorization from an ethics committee was required for Switzerland, where all data were gathered anonymously.

RESULTS

The consecutive changes to the French rPATD at each step are summarized in Figure 1.

1. Item transformation of the French rPATD to BZRA
 - a. *Healthcare professional panel*

Every participating HCP provided individual written feedback. All but one attended a group session. The HCP that could not participate was interviewed by phone.

Three items were removed from the original questionnaire: "Taking my benzodiazepine every day is very inconvenient" was considered not applicable to benzodiazepines. "I feel that I am taking a large number of benzodiazepines" was judged redundant and replaced with "Sometimes I think that I take too many benzodiazepines". Finally, "I like to know as much as possible about my benzodiazepine" was judged not essential to the questionnaire.

Four items were added: "I am aware of the potential side effects of my benzodiazepine", "I know non-pharmaceutical methods of improving my symptoms", "I feel dependent on my benzodiazepine", and "If the doctor told me it was possible, I would be willing to reduce the dose of my benzodiazepine". The latter item was added to complete the global questions and allow the evaluation of "intermediary" willingness to accept BZRA deprescribing. For three items, examples were provided to make the questions easier to understand, for example: "I feel that my benzodiazepine is a burden to me (e.g., I need to plan to have it at home/on me, I need to plan my prescriptions, I am afraid of not having it if I am hospitalized, etc.)". Five items were modified to make the wording relevant to the context of BZRA use. For example, "If my benzodiazepine was stopped, I would be worried about missing out on future benefits"

Section 2

was changed to “If my benzodiazepine was stopped, I would be worried about my health or well-being”. Finally, the HCPs hesitated about the removal of three items: “I spend a lot of money on my benzodiazepine”, “I am taking one or more benzodiazepines that I may no longer need”, and “If I have questions about my benzodiazepine, I ask a healthcare professional”. They agreed to keep them in the first draft of the questionnaire, letting the older adults decide whether to keep them or not.

b. Older adults’ panel

Eight older adults aged 67 to 95 participated in the panel. Six older adults said they needed help with providing individual written feedback. A phone or face-to-face interview was then organized, resulting in a “think aloud” discussion, which provided the research team with valuable input. Of those 8 older adults, 5 participated in the group sessions. During this step, no items were removed. Several items were further revised for clarification. Participants stressed that they felt they had “no choice but to take benzodiazepines to feel or sleep well”. Item 5 was added to include this new dimension.

2. Pre-test of the questionnaire

Twelve older adults aged between 65 and 92 years tested the questionnaire. The median time taken to complete the questionnaire was 20 minutes (interquartile range (IQR): 15 – 29). The wording of some items was further modified to improve clarity. For example, the wording of the item “If I have questions about my benzodiazepine, I ask a healthcare professional” was given a low score by older adults who used other reliable information sources, leading to a misleadingly low involvement score. The item was modified as follows: “If I have questions about my benzodiazepine, I ask a healthcare professional or I consult other reliable sources of information”.

3. Psychometric evaluation of the rPATD-BZRA

a. Study participants

A total of 221 older adults were recruited in 3 countries: Belgium (n= 153), France (n= 48), and Switzerland (n=20), of whom 208 completed a paper questionnaire and 13 the online version. The recruitment was stopped when the 200th complete questionnaire was received, as that was the minimal sample size required to perform statistical analysis.

Table 1 presents the main characteristics of the participants. One hundred and fifty-seven participants were recruited in the PC setting (71.0%) and 64 (29.0%) in the NH setting. The median age of the participants was 78.5 years; 71.9% were women. Fifty-

five percent had completed at least higher secondary education. A sizeable majority (80.5%) of the participants used only one BZRA daily. For 84.2% of the participants, the initial prescriber of the BZRA was a general practitioner; for 43.9%, the BZRA was prescribed at the patient's request.

Table 1: Description of the participants and their BZRA use (N=221)			
Variable	Total (N=221) n (%) or median [P25; P75]	Primary care setting (N= 157) n (%) or median [P25; P75]	Nursing home setting (N= 64) n (%) or median [P25; P75]
Age, in years ^a	78.5 [72.0; 87.0]	76.0 [71.0; 82.0]	89.0 [84.0; 93.0]
65-74 years	76 (34.4)	67 (42.7)	9 (14.1)
75-84 years	68 (30.8)	59 (37.6)	9 (14.1)
≥85 years	76 (34.4)	30 (19.1)	46 (71.9)
Female ^a	159 (71.9)	113 (72.0)	46 (73.0)
Country			
Belgium	153 (69.2)	117 (74.5)	36 (56.2)
France	48 (21.7)	22 (14.0)	26 (40.6)
Switzerland	20 (9.0)	18 (11.5)	2 (3.1)
Education			
Primary or no education	38 (17.2)	16 (10.2)	22 (34.4)
Lower secondary	60 (27.1)	37 (23.6)	23 (35.9)
Higher secondary	69 (31.2)	57 (36.3)	12 (18.8)
Higher	54 (24.4)	47 (29.9)	7 (10.9)
Number of medications taken daily	5.5 [4.0; 8.0]	5.0 [3.0; 7.3]	7.0 [5.0; 9.3]
1-4	65 (29.4)	55 (35.0)	10 (15.6)
5-9	90 (40.7)	64 (40.8)	26 (40.6)
(polypharmacy)			
≥10 (severe polypharmacy)	29 (13.1)	17 (10.8)	12 (18.8)
Missing values	37 (16.7)	21 (13.4)	16 (25.0)
Number of BRZA taken ^b			
1	178 (80.5)	132 (84.1)	46 (71.9)
≥2	32 (14.5)	23 (14.6)	9 (14.1)
Does not know	9 (4.1)	2 (1.3)	7 (10.9)
Type of BZRA use ^b			
Benzodiazepines	129 (58.4)	89 (56.7)	40 (62.5)
Z-drugs	64 (29.0)	54 (34.4)	10 (15.6)

Section 2

Both benzodiazepines and z-drugs	17 (7.7)	12 (7.6)	5 (7.8)
Clomethiazole	0 (0.0)	0 (0.0)	0 (0.0)
Does not know	9 (4.1)	2 (1.3)	7 (15.6)
Top 3 of most used molecules (n=247)			
Zolpidem	61 (24.7)	56 (35.7)	5 (7.8)
Alprazolam	43 (17.4)	31 (19.7)	12 (18.8)
Lormetazepam	37 (15.0)	21 (13.4)	16 (25.0)
Duration of BZRA use ^b			
Between 3 months and 1 year	9 (4.1)	8 (5.1)	1 (1.6)
More than 1 year	192 (86.9)	138 (87.9)	54 (84.4)
Does not remember	18 (8.1)	11 (7.0)	7 (10.9)
Frequency of BZRA intake during the last 7 days ^d			
Not at all	2 (0.9)	2 (1.3)	0 (0.0)
Less than daily	12 (5.4)	9 (5.7)	3 (4.7)
Once a day	150 (67.9)	112 (71.3)	38 (59.4)
Several times a day	53 (24.0)	33 (21.0)	20 (31.2)
Missing values	4 (1.8)	1 (0.6)	3 (4.7)
Reason(s) for BZRA use ^c			
Insomnia/sleep problems	128 (57.9)	91 (58.0)	37 (57.8)
Anxiety/stress	34 (15.4)	23 (14.6)	11 (17.2)
Both insomnia and anxiety	46 (20.8)	35 (22.3)	11 (17.2)
Other	2 (0.9)	2 (1.3)	0 (0.0)
Insomnia & other	5 (2.3)	4 (2.5)	1 (1.6)
Does not know	3 (1.4)	1 (0.6)	2 (3.1)
Initial prescriber of BZRA ^e			
GP	186 (84.2)	130 (82.8)	56 (87.5)
Specialist	18 (8.1)	15 (9.6)	3 (4.7)
Both GP and specialist	7 (3.2)	5 (3.2)	2 (3.1)
Other	3 (1.4)	3 (1.9)	0 (0.0)
Does not remember	4 (1.8)	3 (1.9)	1 (1.6)

BZRA initially prescribed on personal request ^d			
Yes	97 (43.9)	73 (46.5)	24 (37.5)
No	101 (45.7)	70 (44.6)	31 (48.4)
Does not remember	19 (8.6)	12 (7.6)	7 (10.9)
BZRA initially prescribed during a hospitalization ^e			
Yes	21 (9.5)	14 (8.9)	7 (10.9)
No	184 (83.3)	137 (87.3)	47 (73.4)
Does not remember	11 (5.0)	5 (3.2)	6 (9.4)
BZRA: Benzodiazepine receptor agonists; GP: General practitioner ^a 1 missing value (0.5%); ^b 2 missing values (0.9%); ^c 3 missing values (1.4%); ^d 4 missing values (1.8%); ^e 5 missing values (2.3%)			

Overall, 42.5% of the participants reported that they needed assistance with completing the questionnaire. There were, however, considerable differences between settings: 85.9% of NH residents needed help, compared to only 24.8% of PC participants.

b. Construct validity

An EFA was carried out on the data of the participants who answered all the items ($n=200$). Overall, no item was systematically not answered and there were few missing data. Many items showed a floor or ceiling effect $>30\%$ (see Supplementary Table 1). The data showed average adequacy for factor analysis (Kaiser-Meyer-Olkin test: 0.75; Bartlett's test of sphericity $p<0.001$). The scree test, Kaiser-Guttman criteria, and parallel analysis indicated an inconsistent number of factors to extract, from 2 to 7. Of all the potential solutions, none was statistically acceptable (low loadings or cross-loadings for several items, low percentage of explained variance, and/or low internal consistency of identified factors). The statistical performance and clinical relevance of each item were discussed by the research team members. Eleven items were removed on the basis of those two criteria (Supplementary Table 2). A new EFA was carried out on the data of the participants who answered all the retained items ($n=209$). The data showed improved adequacy for factor analysis compared to the initial analysis (Kaiser-Meyer-Olkin test: 0.79; Bartlett's test of sphericity $p<0.001$). The scree test, Kaiser-Guttman criteria, and parallel analysis indicated 2 to 3 factors to extract. Three factors were extracted. Loadings were significant for all items and, this time, no cross-loadings were observed. The final model includes 11 items and 2 global questions (see Table 2) and explains 47% of the variance. The factors were named "Concerns about stopping

Section 2

BZRA”, “BZRA inappropriateness”, and “Dependence on BZRA”. The 2 global questions assess willingness to reduce the BZRA dose (item 23) and willingness to stop the BZRA (item 24). The final questionnaire in French and the English translation are available in Table 3.

Table 2: Psychometric assessment of the included items				
	Exploratory factor analysis (N=209)	Internal consistency (N=209)	Test-retest reliability (N=20)	
	Factor loading	Cronbach's alpha (95%CI) Item-total correlation	ICC (95%CI) Linear-weighted Cohen's kappa	Percent agreement tolerance =1 (%)
Concerns about stopping BZRA		0.74 (0.69; 0.80)	0.35 (-0.02; 0.64)	
Item 11 (reluctant)	0.34	0.44	0.20	60
Item 12 (worry)	0.70	0.65	0.35	75
Item 13 (stress)	0.66	0.49	0.27	65
Item 14 (abandonment)	0.65	0.60	0.23	60
BZRA inappropriateness		0.74 (0.68; 0.79)	0.71 (0.47; 0.86)	
Item 9 (help reduction)	0.76	0.69	0.27	85
Item 10 (try stopping)	0.75	0.67	0.48	70
Item 7 (experience side effects)	0.44	0.48	0.49	95
Item 22 (satisfaction (R))	0.59	0.32	0.54	95
Dependence on BZRA		0.68 (0.61; 0.76)	0.59 (0.28; 0.79)	
Item 15 (bad experience)	0.40	0.42	0.33	75
Item 3 (dependent)	0.57	0.48	0.56	90
Item 5 (no choice)	0.88	0.59	0.17	65
Global questions				

Item 23 (willing to reduce BZRA)	NA	NA	0.35	70
Item 24 (willing to stop BZRA)	NA	NA	0.50	80
CI: confidence interval; ICC: intraclass correlation coefficient; BZRA: Benzodiazepine receptor agonists; R: reversed item (the scoring of this item was reversed so that greater satisfaction with the benzodiazepine currently being taken meant less perceived BZRA inappropriateness)				

c. Internal consistency

Two factors, “Concerns about stopping BZRA” and “BZRA inappropriateness” showed Cronbach’s alpha values of 0.74, whereas the Cronbach’s alpha for the “Dependence on BZRA” factor was slightly below the threshold of 0.70 (0.68, 95% confidence interval (CI): (0.61; 0.76)). Item-total correlations were all above 0.30, which shows that there was a satisfactory correlation between each item and its factor.

d. Test-retest reliability

Of the 20 participants who completed the questionnaire both times, 16 were women (80%). The median age was 76 (IQR: 70.8 – 85). Half of the respondents had completed at least higher secondary education.

Table 2 presents the results for test-retest reliability. The results from the linear-weighted Cohen’s kappa showed that 6 items had fair concordance and 5 items had moderate concordance. Two items were found to have only slight concordance. At the factor level, the “BZRA inappropriateness” and “Dependence on BZRA” factors were found to have acceptable test-retest reliability, whereas the “Concerns about stopping BZRA” factor had an ICC of less than 0.50, demonstrating the variability of the participant’s responses over time.

Table 3: Final questionnaire in French (+ English translation)

Préoccupations par rapport à l’arrêt des BZRA

Je serais hésitant(e) à l’idée d’arrêter ma benzodiazépine. (item 11)

Si ma benzodiazépine était arrêtée, je serais inquiet(e) pour ma santé ou mon bien-être. (item 12)

Si ma benzodiazépine était changée (exemple, changement de dose, de molécule, de marque), je serais inquiet(e) et/stressé(e). (item 13)

Section 2

Si mon médecin me recommandait d'arrêter ma benzodiazépine, j'aurais le sentiment qu'il ne tient pas ou plus compte de mes symptômes. (item 14)

Caractère inapproprié des BZRA

J'aimerais que mon médecin m'aide à réduire la dose de ma benzodiazépine. (item 9)

Avec l'aide de mon médecin, j'aimerais essayer d'arrêter ma benzodiazépine pour voir comment je me sentrais sans celle-ci. (item 10)

Je crois que ma benzodiazépine me donne des effets secondaires. (item 7)

Globalement, je suis satisfait(e) de ma benzodiazépine actuelle. (R) (item 22)

Dépendance aux BZRA

Je sens que je suis dépendant(e) de ma benzodiazépine. (item 3 *)

J'ai le sentiment de ne pas avoir d'autre choix que de prendre ma benzodiazépine pour me sentir bien ou bien dormir. (item 5*)

J'ai déjà eu une mauvaise expérience quand on a essayé d'arrêter ma benzodiazépine. (item 15)

Questions globales

Si mon médecin me le recommandait, je serais prêt(e) à diminuer la dose de ma benzodiazépine. (item 23 *)

Si mon médecin me le recommandait, je serais prêt(e) à arrêter ma benzodiazépine. (item 24)

English translation**

Concerns about stopping BZRA

I would be reluctant to stop taking my benzodiazepine. (item 11)

If my benzodiazepine was stopped, I would be worried about my health or well-being. (item 12)

If my benzodiazepine was changed [e.g.: change of dose, composition, brand name] I would get stressed. (item 13)

If my doctor recommended stopping my benzodiazepine, I would feel that he was not (or was no longer) taking my symptoms into account. (item 14)

BZRA inappropriateness

I would like my doctor to help me reduce my benzodiazepine dose. (item 9)

With my doctor's help, I would like to try stopping my benzodiazepine to see how I would feel without it. (item 10)

I believe that my benzodiazepine is giving me side effects. (item 7)

Overall, I am satisfied with my current benzodiazepine. (R) (item 22)
Dependence on BZRA I feel dependent on my benzodiazepine. (item 3*) I feel like I have no choice but to take my benzodiazepine to feel okay or sleep well. (item 5*) I had a bad experience when my benzodiazepine was stopped before. (item 15)
Global questions If my doctor recommended it, I would be willing to reduce the dose of my benzodiazepine. (item 23*) If my doctor recommended it, I would be willing to stop taking my benzodiazepine. (item 24)
* New item compared to items adapted from French rPATD ** Only the French questionnaire was validated. R: reversed item (the scoring of this item was reversed so that greater satisfaction with the benzodiazepine currently being taken meant less perceived BZRA inappropriateness)

DISCUSSION

We adapted the French rPATD to the context of BZRA. Our final questionnaire contains 13 items, of which 11 are distributed between 3 factors and 2 are global questions. Two of the factors derive from the rPATD (“Concerns about stopping BZRA” and “BZRA inappropriateness”) and one is new (“Dependence on BZRA”).

To our knowledge, few studies have adapted rPATD items to a specific medication class. Eldeman *et al.* partially adapted the rPATD, changing the word “medicine” to “alpha-blockers” in the “appropriateness” and “concerns about stopping” factors,[35] and Crutzen *et al* did the same for cardiometabolic medications [36]. However, no validation of the changed questions was undertaken. This was the first study to fully adapt the rPATD questionnaire to a specific medication class and assess the psychometric properties of the adapted questionnaire.

Making the rPATD questionnaire specific to a medication class strongly impacted its structure. Two rPATD factors (“Burden” and “Involvement”) were removed, mainly due to the poor statistical performance of the adapted items. This suggests that factors that are important to measure when considering deprescribing in general may no longer be relevant when considering a specific medication. The “Burden” factor might be less relevant to BZRA deprescribing for 2 reasons: 1) it concerns a medication that is taken

Section 2

once a day by most patients and 2) BZRA are perceived as relieving uncomfortable symptoms, which could make their use feel less burdensome. Different results might have been found if we had focused on a drug that was being taken several times a day, one requiring close monitoring, and/or one that was not perceived as providing symptom relief. In our study, items adapted from the “Involvement” factor showed a significant ceiling effect, as did many other items that were also found to have a floor or a ceiling effect. In the French rPATD, Roux *et al.* also found that factors had either a ceiling or a floor effect [18], showing that some polarization already existed when exploring attitudes toward deprescribing in general. Specifying a medication class may have strengthened this polarization and limited the variance of these items and, therefore, their statistical power and relevance in the questionnaire. This may have been particularly true for BZRA, to which patients are strongly attached [37].

Global questions in rPATD-BZRA assess not only willingness to stop the medication but also willingness to reduce the dose of the medication. Both dimensions of deprescribing, as defined by Farrell *et al.*, are therefore considered [4]. Assessing willingness to reduce the dose is particularly important for BZRA; a dose reduction represents a reduction in the risk of adverse effects. Furthermore, this is also an important item for use in questionnaires in future research aimed at encouraging BZRA dose reduction and BZRA cessation, as explored in previous studies [24, 38].

The rPATD-BZRA questionnaire has some statistical limitations. First, poor test-retest reliability was found for the “Concerns about stopping BZRA” factor. Literature has shown, however, that health behaviour, self-efficacy, and risk assessment are mood sensitive [39]. Levels of concern could therefore vary depending on the patient’s mood, or how well they slept the night before. Furthermore, participants responding a second time to the questionnaire were interviewed by phone (for those living in the PC setting), whereas the first completion of the questionnaire occurred alone, at home. Social desirability induced by the phone interview may have influenced how and whether concerns were expressed and altered test-retest reliability. Secondly, the “Dependence on BZRA” factor showed below-standard internal consistency (Cronbach’s alpha <0.70). For both the original and French rPATD, however, lower values of Cronbach’s alpha were tolerated for one factor [17, 18]. Moreover, this low value could be explained by the small number of items evaluating dependence on BZRA: only 3 items are grouped in this factor and Cronbach’s alpha is known to increase with the number of items [27]. Finally, 47% of the variance was explained by the items, suggesting that other dimensions might be missing. Beliefs about capabilities were highlighted as a major domain in a recent systematic review on barriers and enablers of BZRA deprescribing using the Theoretical Domains Framework[37]. In addition, as theorized in the COM-B model, it is capability that (along

with opportunity and motivation) induces behaviour[40]. Capability is defined as “the individual’s psychological and physical capacity to engage in the activity concerned” (p. 4)[40]. So, as none of the items in the rPATD-BZRA assess self-perceived capability for BZRA deprescribing, we hypothesize that this could be one of the missing dimensions.

Although it is not statistically perfect, the rPATD-BZRA questionnaire is still a useful tool for BZRA deprescribing in clinical practice. Fear of patients’ resistance is a major barrier to physicians discussing BZRA deprescribing with older patients; this leads to clinical inertia [41]. Physicians, however, have an important role to play in BZRA deprescribing, especially GPs, who were the initial prescribers of BZRA for the vast majority of our respondents. A recent qualitative study has found that trust in physicians was essential for patients to consider and follow their recommendation to deprescribe BZRA [42]. This trust was strongly related to a clinical relationship based on shared decision-making, understanding, and open discussion [42]. Moreover, the first steps in the deprescribing process involve exploring patients’ views and attitudes to deprescribing [43, 44]. The rPATD-BZRA could help to initiate a patient-physician dialogue regarding BZRA deprescribing. Moreover, this new questionnaire is quite short compared to rPATD, which would enhance its acceptability and ease of use in busy clinical practice. Moreover, the rPATD-BZRA could also be helpful in targeting older adults who are more receptive to a BZRA deprescribing intervention, or in allowing more effective allocation of resources. Future work is needed to assess the predictive value of the rPATD-BZRA and ascertain the extent to which attitudes towards BZRA deprescribing predict actual BZRA deprescribing.

This study has several strengths and limitations. The first limitation is the long recruitment period due to the COVID-19 pandemic, which strongly hindered data collection. The COVID-19 crisis also increased anxiety and insomnia, which are indications for BZRA prescription [45]. In a national health interview survey carried out in December 2020 in Belgium, 23% of older adults declared that they had increased their sedative use compared to their use before the pandemic (including none)[46]. A significant majority of the respondents had used BZRA for more than one year, but the pandemic may have affected their answers. Another limitation is that participants were selected by pharmacists, GPs, and NH staff members, who may have asked older adults whom they perceived to be more open and willing to participate. The possibility of selection bias cannot, therefore, be excluded. Finally, due to recruitment difficulties, statistical power was narrowly achieved. Despite these limitations, this study has several strengths. More vulnerable older adults (i.e. less educated participants or those aged ≥ 85 years) are represented fairly. Moreover, data were collected in 3

Section 2

European countries in both NH and PC settings, which strengthened the results and their generalizability.

CONCLUSION

Adapting the French rPATD to BZRA revealed major differences between assessing attitudes towards deprescribing in general and assessing attitudes towards a particular medication class. Psychometric assessment of a questionnaire adapted to other medication classes is therefore essential to ensuring validity.

This 13-item questionnaire thus appears to be a useful tool, in both clinical practice and research, for assessing older adults' attitudes toward BZRA deprescribing. The rPATD-BZRA could facilitate the initiation of a conversation about BZRA deprescribing with older adults and their engagement in a shared decision-making process. It could be used in BZRA deprescribing interventions to help target more receptive participants or to identify specific barriers to address.

Supplementary materials

Supplementary materials are available online and comprise:

- Supplementary table 1. Assessment of floor and ceiling effect
- Supplementary table 2. Items removed from analysis and reason for removal

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Section 2

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Additional data: Attitudes of older adults towards benzodiazepine receptor agonists deprescribing

OBJECTIVE

This part aims to describe older adults' attitudes towards BZRA deprescribing using the data collected to validate the rPTAD-BZRA questionnaire.

METHODS

We computed descriptive statistics on items that were retained in the final version of the rPATD-BZRA questionnaire. Results were stratified according to the setting (community or nursing home setting) to assess similarities or differences between settings.

RESULTS

Table 1 describes attitudes towards BZRA deprescribing (n=221). Overall, most participants reported negative attitudes towards BZRA deprescribing. For example, 69% of them would be reluctant to stop taking their benzodiazepine (agree + strongly agree) and 61% would be worried about their health or well-being if their benzodiazepine was stopped (agree + strongly agree). Only 13% of the participants agree or strongly agree that their benzodiazepine is giving them side effects and 88% declare to be satisfied with their current benzodiazepine (agree + strongly agree). Three-quarters of the participants indicated feeling dependent on their BZRA and 77% indicated feeling having no other choice but to take their BZRA to sleep or feel well (agree + strongly agree). Results were mixed regarding the impact on the doctor-patient relationship: on one side 48% of older patients would feel that their doctor is not or no longer taking their symptoms into account if their doctor recommended stopping their BZRA (agree + strongly agree), on the other side, 39% would disagree or strongly disagree with that statement. Overall, intention towards BZRA deprescribing was low, with 32% that would be willing to stop their BZRA if the doctor recommended it. However, 52% would be willing to reduce the dose of their BZRA if the doctor recommended it.

Section 2

Table 1. Attitudes of older adults towards BZRA deprescribing (N=221)					
	Strongly disagree N(%)	Disagree N(%)	Unsure N(%)	Agree N(%)	Strongly agree N(%)
Concerns about stopping BZRA factor					
I would be reluctant to stop taking my benzodiazepine. ^a					
Total	27 (12.2)	27 (12.2)	11 (5.0)	70 (31.7)	83 (37.6)
CS (157)	13 (8.3)	23 (14.6)	9 (5.7)	60 (38.2)	50 (31.8)
NH (64)	14 (21.9)	4 (6.2)	2 (3.1)	10 (15.6)	33 (51.6)
If my benzodiazepine was stopped, I would be worried about my health or well-being. ^b					
Total	32 (14.5)	37 (16.7)	15 (6.8)	58 (26.2)	77 (34.8)
CS (157)	23 (14.6)	30 (19.1)	11 (7.0)	47 (29.9)	44 (28.0)
NH (64)	9 (14.1)	7 (10.9)	4 (6.2)	11 (17.2)	33 (51.6)
If my benzodiazepine was changed [e.g.: change of dose, composition, brand name] I would get stressed. ^c					
Total	54 (24.4)	54 (24.4)	21 (14.0)	50 (22.6)	31 (14.0)
CS (157)	38 (24.2)	45 (28.7)	23 (14.6)	35 (22.3)	16 (10.2)
NH (64)	16 (25.0)	9 (14.1)	8 (12.5)	15 (23.4)	15 (23.4)
If my doctor recommended stopping my benzodiazepine, I would feel that he was not (or was no longer) taking my symptoms into account. ^b					
Total	41 (18.6)	46 (20.8)	27 (12.2)	47 (21.3)	58 (26.2)
CS (157)	27 (17.2)	35 (22.3)	22 (14.0)	42 (26.8)	30 (19.1)
NH (64)	14 (21.9)	11 (17.2)	5 (7.8)	5 (7.8)	28 (43.8)
BZRA inappropriateness factor					
I would like my doctor to help me reduce my benzodiazepine dose. ^d					
Total	87 (39.4)	35 (15.8)	40 (18.1)	29 (13.1)	25 (11.3)
CS (157)	47 (29.9)	32 (20.4)	31 (19.7)	23 (14.6)	20 (12.7)
NH (64)	40 (62.5)	3 (4.7)	9 (14.1)	6 (9.4)	5 (7.8)
With my doctor's help, I would like to try stopping my benzodiazepine to see how I would feel without it. ^a					
Total	83 (37.6)	53 (24.0)	19 (8.6)	34 (15.4)	29 (13.1)
CS (157)	44 (58.0)	45 (28.7)	16 (10.2)	29 (18.5)	21 (13.4)
NH (64)	39 (60.9)	8 (12.5)	3 (4.7)	5 (7.8)	8 (12.5)
I believe that my benzodiazepine is giving me side effects. ^b					
Total	124 (56.1)	54 (24.4)	13 (5.9)	24 (10.9)	4 (1.8)
CS (157)	86 (54.8)	43 (27.4)	8 (5.1)	15 (9.6)	3 (1.9)
NH (64)	38 (59.4)	11 (17.2)	5 (7.8)	9 (14.1)	1 (1.6)
Overall, I am satisfied with my current benzodiazepine (R). ^c					
Total	4 (1.8)	15 (6.8)	6 (2.7)	55 (24.9)	140 (63.3)
CS (157)	2 (1.3)	10 (6.4)	4 (2.5)	44 (28.0)	96 (61.1)

NH (64)	2 (3.1)	5 (7.8)	2 (3.1)	11 (17.2)	44 (68.8)
Dependence on BZRA					
I feel dependent on my benzodiazepine. ^b					
Total	21 (9.5)	24 (10.9)	8 (3.6)	82 (37.1)	84 (38.0)
CS (157)	14 (8.9)	17 (10.8)	5 (3.2)	71 (45.2)	49 (31.5)
NH (64)	7 (10.9)	7 (10.9)	3 (4.7)	11 (17.2)	35 (54.7)
I feel like I have no choice but to take my benzodiazepine to feel okay or sleep well. ^a					
Total	12 (5.4)	25 (11.3)	10 (4.5)	64 (29.0)	107 (48.5)
CS (157)	5 (3.2)	18 (11.5)	8 (5.1)	54 (34.4)	69 (43.9)
NH (64)	7 (10.9)	7 (10.9)	2 (3.1)	10 (15.6)	38 (59.4)
I had a bad experience when my benzodiazepine was stopped before. ^c					
Total	40 (18.1)	20 (9.0)	98 (44.3)	20 (9.0)	42 (19.0)
CS (157)	27 (17.2)	12 (7.6)	70 (44.6)	17 (10.8)	31 (19.7)
NH (64)	13 (20.3)	8 (12.5)	28 (43.8)	3 (4.7)	11 (17.2)
Global questions					
If my doctor recommended it, I would be willing to reduce the dose of my benzodiazepine. ^e					
Total	46 (20.8)	39 (17.6)	17 (7.7)	61 (27.6)	54 (24.4)
CS (157)	19 (12.1)	29 (18.5)	14 (8.9)	51 (32.5)	40 (25.5)
NH (64)	27 (42.2)	10 (15.6)	3 (4.7)	10 (15.6)	14 (21.9)
If my doctor recommended it, I would be willing to stop taking my benzodiazepine. ^e					
Total	70 (31.7)	54 (24.4)	23 (10.4)	36 (16.3)	34 (15.4)
CS (157)	36 (22.9)	42 (26.8)	22 (14.0)	31 (19.7)	24 (15.3)
NH (64)	34 (53.1)	12 (18.8)	1 (1.6)	5 (7.8)	10 (15.6)
^a 3 missing values (1.4%); ^b 2 missing values (0.9%); ^c 1 missing value (0.5%); ^d 5 missing values (2.3%); ^e 4 missing values (1.8%) Legend: BZRA : Benzodiazepine receptor agonists; CS : Community setting; NH : Nursing home setting; R : the scoring of this item should be reversed so that greater satisfaction with the benzodiazepine currently being taken meant less perceived BZRA inappropriateness					

Differences were observed between the settings, with nursing home residents tending to score more often at the extremes and expressing more negative views than older adults living in the community. For example, compared to the community-dwelling older adults (n=164), a higher proportion of nursing home residents (n=57) strongly disagreed or disagreed with statements evaluating the willingness to reduce or stop their BZRA if the doctor said it was possible. Similarly, if older adults living in the community more often disagreed or strongly disagreed with the statement “If my benzodiazepine was changed [e.g.: change of dose, composition, brand name] I would

Section 2

get stressed”, nursing home residents more often agreed or strongly agreed with that statement.

DISCUSSION

Our data suggests that most older adults would be reluctant to consider BZRA deprescribing. This low level of intention matches the results of our systematic review regarding barriers and enablers towards BZRA deprescribing which highlighted low intention as a major barrier [1]. These results contrast however with the attitude of older adults towards deprescribing in general. The systematic review and meta-analysis conducted by Weir *et al.* in 2021, which included 36 studies using the rPATD or its previous version (PATD), showed that 84% (95%CI: 81%-88%) of older adults would be willing to stop one of their medications if the doctor said it was possible [2]. It supports the idea, previously suggested in the literature [3, 4], that attitudes of older adults differ from one medication to another and that specific challenges may arise depending on the medication. Even though intentions to consider BZRA deprescribing are low, still one-third of patients would be willing to consider stopping their BZRA, which given the high prevalence of BZRA use, represents a large number of older adults.

A very low percentage of older adults think their BZRA is giving them side effects. However, a study exploring older adults' awareness of potential risks of BZRA use, showed that if older adults were in general quite well aware of the risks of dependence, dizziness, and interaction with alcohol, a minority of them were aware of the risks of falls, memory and psychomotor problems and muscle weakness [5]. This lack of knowledge may prevent older adults from recognizing these symptoms as BZRA side effects. Improving older adults' knowledge about potential BZRA risks, through patient education interventions or awareness campaigns seems therefore crucial.

In 2022, the systematic review of Oktora *et al* examined differences in attitudes towards deprescribing according to context factors and found no difference between healthcare settings [6]. Our results may suggest otherwise regarding BZRA deprescribing, as discrepancies regarding willingness to stop BZRA and reduce BZRA were found between settings, with nursing home residents tending to have a more negative view than older adults living in the community. Indeed, a qualitative study among nursing home residents showed that most of them were unwilling to consider BZRA deprescribing and felt that they needed their BZRA to sleep well [7]. Besides, if the causes of insomnia are multifactorial, nursing home residents face specific environmental difficulties such as noise, lights being turned on or left on during the night, and bedtime schedule constraints by the staff availability for dependent patients

[8, 9]. We hypothesize that these specific difficulties might play a role in worsening their attitudes towards BZRA deprescribing.

While around 40 % of our participants would disagree (or strongly disagree) with the statement “If my doctor recommended stopping my benzodiazepine, I would feel that he was not (or was no longer) taking my symptoms into account”, almost half of them agree or strongly agree, showing a potential negative impact of a BZRA deprescribing proposal on the doctor-patient relationship. This contrasts with the results of a qualitative study led in the Swiss primary care which interviewed older adults who chose to refuse a deprescribing proposal made by their GP (all medications) [10]. In this study, almost every patient reported feeling no less valued by their GP making deprescribing recommendations [10]. One explanation for our results might be the limited alternative pharmacological options available, which might lead to patients feeling abandoned if not prescribed BZRA. This highlights the importance of GP’s support during BZRA deprescribing.

Given the low percentage of participants with a positive attitude toward stopping their BZRA, the higher percentage of participants willing to consider reducing the dose of their BZRA is good news, as it might be a first step toward complete cessation. In the context of smoking cessation, which, like BZRA use, involves problems of dependence, it has been shown that smokers who reduce their consumption, are more likely to succeed in giving up smoking [11]. As was hypothesized for smoking cessation [11], successfully reducing BZRA use might increase self-perceived efficacy and lead to stopping BZRA.

As stated in the discussion of the main article, participants were recruited by healthcare professionals who may have selected older adults perceived to be more open to participate. Therefore, these results must be taken with caution as they may not fully reflect the attitudes of all older BZRA users. Taking this limit into account, this is, however, the first study to assess attitudes towards BZRA deprescribing using a validated questionnaire that allowed us to highlight some clear messages about the barriers to target in future interventions.

CONCLUSION

Interventions aiming at BZRA deprescribing should anticipate a low motivation of older adults towards BZRA deprescribing, especially in nursing home residents. Future deprescribing interventions should target concerns about stopping and low perception of side effects. Leaning on a strategy focused on BZRA reduction might enhance older adults’ willingness to consider BZRA deprescribing.

Section 2

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Chapter 4. Deprescribing benzodiazepine receptor agonists in older adults: a mixed-methods study to adapt the Canadian D-PRESCRIBE intervention to the Belgian community setting

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Article published in *BMJ Open* (2024)

DOI: 10.1136/bmjopen-2024-085396

Section 2

AUTHORS' CONTRIBUTIONS

The protocol of this study was designed and written by CP, AS, and SH and then reviewed by MdM, ND, and ED. CP performed the interviews and group discussions, transcribed them, and summarized the results. Results were discussed during meetings gathering all authors (CP, ND, MdM, ED, AS and SH), that took main final decisions on how to adapt the components of D-PRESCRIBE. CP wrote the first draft of the manuscript, which was then revised and amended by all authors (CP, ND, MdM, ED, AS and SH). All authors read and approved the final manuscript.

During the preparation of this work the authors used Deepl AI in order to provide assistance in the language editing of the manuscript draft. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

ACKNOWLEDGEMENTS

The authors would like to thank Professor Cara Tannenbaum for providing her authorization for adapting the components of the D-PRESCRIBE intervention. We also thank Dr Sandrine Roussel (UCLouvain) for having provided her feedback on our results and given advice and expertise regarding the adaptation of the tools. Finally, we thank the older adults, pharmacists, and GPs who participated in this study.

FUNDING

The final layout of the adapted brochure and pharmaceutical proposal were produced by a professional graphic designer funded partly by a grant from EBPracticenet, and partly by a grant (Crédit de Recherche) from the Fonds de la Recherche Scientifique (n°40013898). This research received no other external funding.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the ethics committee of CHU UCL Namur on the 26th of April 2022 (NUB: B0392022000037). All participants in the interviews and group discussions signed a consent form before participation. General practitioners and pharmacists participating in the survey about the pharmaceutical proposal had to confirm their approval for participation by ticking a box before answering the questions.

DECLARATION OF INTEREST

None

ABSTRACT

OBJECTIVE: Guidelines recommend deprescribing benzodiazepine receptor agonists (BZRA) in older adults, yet implementation in clinical practice remains limited. Adapting effective, evidence-based interventions to a new context is a resource-saving strategy. In Canada, the D-PRESCRIBE intervention comprised a patient educational brochure and a pharmaceutical opinion inviting physicians to revise BZRA prescribing and consider safer alternatives. Due to its effectiveness on BZRA deprescribing among Canadian older adults, we aimed to adapt the D-PRESCRIBE intervention to the Belgian community setting.

DESIGN: Recommendations from the ADAPT guidance, that provides a systematic approach for adapting interventions to new contexts, were followed. We conducted a mixed-methods study that comprised (1) group discussions and cognitive interviews to assess the acceptability and need for adaptation of the intervention's components and (2) a survey on the adapted pharmaceutical opinion. A research committee involving stakeholders' representatives decided on the adaptations, respecting the core functions of both tools. Changes in intervention components were reported following the Model for Adaptation Design and Impact (MADI) framework.

SETTING: Belgian French-speaking community setting

PARTICIPANTS: Six older adults (≥ 65 years), 6 general practitioners (GP), and 7 pharmacists participated in the group discussions or interviews. Forty-six GPs and 91 pharmacists responded to the survey.

RESULTS: Participants welcomed the brochure positively. Still, some changes in the vocabulary, wording, photos, and icons were made for several purposes including making the patient feel concerned by the brochure and softening the use of fear. The pharmaceutical opinion aroused mixed perceptions. Its name, layout, and content were adapted to enhance its acceptability and fit with our healthcare system, practices, and national guidelines. The survey highlighted several enablers and barriers to its use from the GP and pharmacist perspectives.

CONCLUSIONS: The Canadian D-PRESCRIBE intervention was adapted to the Belgian setting following a thorough and transparent process. Its feasibility will be tested in a future pilot study. (NCT: 05929417)

Section 2

Overview of theoretical frameworks used in this chapter and purpose for their use		
Framework	Reference	Purpose
ADAPT guidance	Moore <i>et al</i> , BMJ, 2021	Provided steps to guide the adaptation process. Highlighted the need to contact intervention developers, set up a steering committee with stakeholders' representatives, explore in detail differences between contexts, and describe the programme theory of the intervention, as a preliminary work before undertaking the adaptations. Provided additional resources to explore context (CICI framework) and to report adaptations (MADI framework).
Medical Research Council (MRC) framework	Skivington <i>et al</i> , BMJ, 2021	Provided additional justification for the rationale of adapting an intervention rather than creating one from scratch. Supported the need for stakeholders' involvement in the process and helped identify them. Supported the importance of context exploration and identification of the programme theory.
COM-B model	Michie <i>et al</i> , Implement Sci, 2011	Provided additional justification for choosing the D-PRESCRIBE intervention for adaptation. According to this model, 3 dimensions are needed for behavior change: capability, opportunity, and motivation. The D-PRESCRIBE intervention addresses them all, making this intervention particularly relevant to adapt.
Context and Implementation of Complex Interventions (CICI) framework	Pfadenhauer <i>et al</i> , Implement Sci, 2017	As suggested by the ADAPT guidance, was used "to structure the thinking about context", making sure we considered all relevant dimensions of context.
Theoretical Framework of Acceptability (TFA)	Sekhon <i>et al</i> , BMC Health Serv Res, 2017	Helped design the interview guides regarding the acceptability of the intervention components making sure we addressed all dimensions of acceptability.

Model for Adaptation Design and Impact (MADI) framework	Kirk <i>et al</i> , Implement Sci, 2020	Was used to report the adaptations that were done to the original intervention, along with their goal and the anticipated obstacles they aimed to overcome or a justification.
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Section 2

BACKGROUND

Benzodiazepine receptor agonists (BZRA) are often prescribed to treat insomnia or anxiety. In older adults (≥ 65 years), current guidelines recommend avoiding or limiting their use to the management of acute situations [1] and for a period not exceeding two to four weeks [2]. BZRA have well-known potential adverse effects encompassing higher risks of falls, hip fractures, car accidents, and death [3-6]. Therefore, BZRA deprescribing is strongly recommended especially when they are taken for insomnia [7]. However, despite the evidence and recommendations, between 15 and 20 % of older adults in Western countries use a BZRA [8-11]. In Belgium, a limited reduction in BZRA use in older adults was observed over the past years but its prevalence remains high with around 18% of older adults (≥ 65 years) using a BZRA [12].

Numerous barriers to BZRA deprescribing have been highlighted from older patients' and prescribers' perspectives, e.g.: the patients' and prescribers' belief in BZRA efficacy, the perceived absence of benefits of BZRA deprescribing, the belief of patients that prescription renewal means the safety of BZRA use, the fear of withdrawal symptoms or return of the condition, the prescriber's expected resistance of patients toward BZRA deprescribing or perceived pressure for continuous prescribing [13]. A recent qualitative study explored Belgian patients', pharmacists', and GPs' perspectives on factors participating in BZRA long-term use [14]. The results revealed additional barriers to BZRA deprescribing, such as patients' belief that BZRA use is harmless, the social acceptance of the "medicalization of psychosomatic problems", and the existing stigma around BZRA long-term use that impedes open discussion around potential deprescribing. The study also showed that BZRA use was preferred over non-pharmacological alternatives because more financially and practically accessible. Besides, the authors highlighted a "wait-and-see attitude" from prescribers and pharmacists, and poor interprofessional collaboration whereas they pinpointed it as a key element.

In Belgium, federal awareness campaigns have been organized since 2002 to reduce BZRA use, producing educational materials for both patients and healthcare providers [15]. However, these campaigns target the general population and may not effectively reach older adults. The 2018 campaign promoted alternative treatments [15], although research indicates older adults prefer warnings about BZRA side effects [16]. The 2023 campaign emphasizes interprofessional collaboration but lacks practical communication tools [17]. The continued high use of BZRAs among Belgian older adults highlights the need for alternative interventions.

The Canadian D-PRESCRIBE intervention combined a patient educational brochure (EMPOWER) with a communication tool between the pharmacist and the prescriber,

called pharmaceutical opinion, aiming to promote BZRA deprescribing (among 3 other medication classes) [18]. The EMPOWER brochure invites older patients to test their knowledge of the risks of BZRA use. It also provides information on these risks and possible non-pharmacological alternatives, along with a testimonial from an older adult who successfully stopped their BZRA and a BZRA tapering scheme. Throughout the brochure, patients are encouraged to discuss BZRA deprescribing with their healthcare provider. In Quebec, the sending of this brochure by the pharmacist to community-dwelling older adults resulted in 27% of the intervention group ceasing their BZRA at six months (vs. 5% in the control group) [19]. The pharmaceutical opinion is *“a document sent from the pharmacist to the prescriber detailing a problem with a patient’s pharmacotherapy and recommending a management strategy to address the drug-related problem”* (p.134) [20]. For the D-PRESCRIBE trial, an evidence-based pharmaceutical opinion about BZRA was elaborated and made available for pharmacists [20]. The D-PRESCRIBE intervention has shown substantial effectiveness with a BZRA deprescribing rate of 43% at six months in the intervention group compared to 9% in the control group [18], supporting the importance of interprofessional collaboration to potentiate the effects of the EMPOWER brochure.

If other interventions were found to be effective in reducing BZRA use among older adults, such as pharmacological substitution combined or not with psychological support or tapering programs combined with psychological support, these interventions require a lot of resources [21].

The D-PRESCRIBE intervention seemed most appropriate to test in our country for several reasons: 1) it has demonstrated efficacy and cost-effectiveness in Canada [22]; 2) it addresses important barriers to BZRA deprescribing that were highlighted previously; 3) as other educational interventions, it might be easy to implement in real-life practice [21]; 4) it addresses the three dimensions needed for behavior change described by the COM-B model (capability, opportunity, and motivation) [23].

If implementing an effective intervention could spare considerable resources by avoiding “reinventing the wheel”, its adaptation to a new context or country is often required to ensure fit with a different healthcare system and culture [24]. For instance, the pharmaceutical opinion currently does not exist in Belgium, contrary to Quebec.

The ADAPT guidance provides recommendations and a systematic approach for adapting interventions in new contexts [25]. The purpose of this study was to adapt both components of the D-PRESCRIBE intervention for the Belgian community setting following this guidance, and recommendations from the new Medical Research Council (MRC) framework on developing and evaluating complex interventions [26]. The guidance for reporting intervention development studies in health research

Section 2

(GUIDED) was used to report this study [27]. The GUIDED checklist is available in Supplementary file 1.

METHODS

The ADAPT guidance recommends four steps: 1. *assess the rationale for the intervention and consider the intervention-context fit*, 2. *plan and undertake the adaptations*, 3. *plan and undertake piloting and evaluation*, and 4. *implement and maintain the adapted intervention and scale* [25]. The current study reports the process and results for the two first steps.

Step 1: Assess the rationale for the intervention and consider the intervention-context fit

This first step aimed to have a clear idea of:

- 1) the “core functions and forms” of the intervention [28]. A core function relates to “*the underlying mechanisms of change that make an intervention effective*” and forms relate to activities that are performed to achieve core functions [28]. The identification of the core functions is essential to preserve the integrity of the original intervention: core functions must remain unchanged while forms are adaptable [28].
- 2) similarities and differences between Quebec’s and Belgian contexts (defined as “*any feature of the circumstances in which an intervention is implemented that might interact with the intervention to produce variation in outcomes*” (p.2)[25]).

For these purposes, published data on the D-PRESCRIBE intervention was reviewed. Core functions and forms are similar in their definition to programme theory which describes how each component of the intervention is supposed to work to achieve the desired outcomes in a specific context [29]. We searched, therefore, for any element related to core functions or programme theory. In addition, the intervention developers were contacted. We asked them for permission to adapt the D-PRESCRIBE intervention and to validate the core functions and forms that we had highlighted as a result of the literature review. In addition, Quebec’s and Belgian contexts were compared using the Context and Implementation of Complex Interventions (CICI) framework [30]. This framework defines context with 7 major domains: geographical, epidemiological, socio-cultural, socio-economic, ethical, legal, and political context [30]. We limited the comparison to domains and aspects relevant to our project. First, related to the epidemiological context, published literature on BZRA use prevalence between Quebec and Belgium was reviewed to compare rates of BZRA use in both contexts.

Second, related to the socio-cultural, socio-economic, ethical, and legal contexts, we compared the pharmacist's role and remuneration system in both countries. Indeed, as the D-PRESCRIBE intervention was pharmacist-led, we anticipated that these two aspects could influence the uptake of the intervention. This comparison of contexts was also submitted to the intervention developers to ascertain that all important elements had been considered.

Step 2: Plan and undertake the adaptations

Steering committee

Three categories of key stakeholders were identified based on the MRC framework definition: patients (intervention recipients), community pharmacists (intervention deliverers), and general practitioners (GP), who will support or not the deprescribing process after receiving the pharmaceutical opinion. As a starting point, a steering committee was set up to manage this project and included one representative of each category of key stakeholders and members of the research team. The stakeholders' representatives brought their specific points of view during the research meetings. All participants in the steering committee read and revised the research protocol and related documents, gave feedback and advice regarding the results, and finally, helped in making decisions regarding the adaptation of the intervention components.

Interviews and group discussions with stakeholders

To explore in detail the need for adaptation and acceptability of both the EMPOWER brochure and the pharmaceutical opinion, group discussions and interviews were conducted with additional stakeholders. We aimed to recruit at least four community pharmacists, three to four GPs, and three to five patients to participate. General practitioners and pharmacists were recruited through advertising professional organizations, university alumni (community pharmacists who attended a pharmaceutical care certificate program), and professional networks. Patients were recruited through participating GPs and pharmacists. The patient's inclusion criteria comprised being aged 65 years and older, using a BZRA for at least four weeks, and living at home. Exclusion criteria included cognitive impairment, current alcohol withdrawal, major mental health issues (e.g.: schizophrenia, major depression), and incapacity to understand French. All participants were asked to sign an informed consent form before participation.

Group discussions gathering community pharmacists and GPs were organized in a meeting room at the research team office with the possibility to attend online. Some of them were interviewed individually in case they could not join a group discussion. For practical reasons and for avoiding power issues during group discussion with

Section 2

healthcare professionals (HCPs), patients were only interviewed individually. Interviews took place at the participant's home, workplace, or online. The cognitive interview technique was used, including "think aloud" interviewing, and probing. These techniques were originally developed for improving questionnaires and surveys [31] but have also been used in the cultural adaptation of interventions and decision aids [32-34]. Practically, both the EMPOWER brochure and the pharmaceutical opinion were discussed, asking participants to express feelings and comments while reading each page. Probes included open questions such as "What do you understand of what is presented here?", "Does anything on this page bother you?", "Are you feeling comfortable with the content/layout of the page?", "What would you formulate/present differently?". In addition to the content of the intervention, its delivery mode was also discussed with participants. At the end of the detailed review, the general acceptability of both materials and intervention as a whole was also explored based on the theoretical constructs of acceptability described by Sekhon et al. [35]. These authors described 7 constructs *"that reflect the extent to which people delivering or receiving a healthcare intervention consider it to be appropriate based on anticipated or experiential cognitive and emotional responses to the intervention"* (e.g.: affective attitude, opportunity cost) (p. 93) [35]. Questions about each of these constructs were included in our interview guides (available in Supplementary file 2 and 3 (in French)).

Each group discussion or interview was audio-recorded and a summary of comments and suggestions for change was transcribed. Synthesized results of these group discussions and interviews were discussed with the steering committee to make decisions on how to adapt the brochure and the pharmaceutical opinion. The guiding principles for the adaptations were that the intervention components should be best suited for the Belgian context, acceptable to the 3 categories of stakeholders, and feasible to implement in routine practice. The Model for Adaptation Design and Impact (MADI) framework was used to report all adaptations made during the process [36].

Survey to assess the adapted pharmaceutical opinion

An online survey was performed to allow a larger panel of pharmacists and GPs to give feedback on the first version of the adapted pharmaceutical opinion (Supplementary file 4). As already stated, pharmaceutical opinions are fully innovative in Belgium, hence the need to explore its acceptability on a broader scale. The questionnaire was based on the study of Martin and Tannenbaum about the development of their evidence-based pharmaceutical opinion and comprised questions to be rated on a Likert scale, multiple-choice, and open-ended questions [20]. The results helped refining the pharmaceutical opinion.

The online survey was published online on 11 October 2022 and closed on 5 December 2022. The survey was hosted on Qualtrics software, version 10/2022 (Qualtrics, copyright © 2022. Provo, UT, USA. Available at <https://www.qualtrics.com>, accessed on 11 October 2022), and disseminated through professional organizations and social networks. To enhance the GP participation rate, a paper version of this survey was distributed to GPs attending a professional meeting in December 2022. These questionnaires were then encoded into Qualtrics.

Patient and public involvement

This study included the involvement of a patient representative (ED) in the steering committee. For recruiting this person, the Belgian association of healthcare service users (*Ligue des Usagers des Soins de Santé*) was contacted before the beginning of this study and one of its members accepted to participate. The role of steering committee members was described above.

RESULTS

Step 1: Assess the rationale for the intervention and consider the intervention-context fit

Identification of the core functions of the D-PRESCRIBE intervention

The core functions and forms of the D-PRESCRIBE intervention or its programme theory were not described as such by the authors. However, their main elements are presented in the D-PRESCRIBE study protocol [37] and research article [18]. Besides, the programme theory of the EMPOWER brochure was described in a realist evaluation [38]. Briefly, the EMPOWER brochure triggers 2 main mechanisms or core functions: 1) motivation by increasing knowledge and concerns about BZRA long-term use, and 2) capacity to initiate BZRA deprescribing by enhancing patients' self-efficacy [38]. The importance of the prescriber's support in deprescribing led the intervention developers to combine the EMPOWER brochure with the sending of a pharmaceutical opinion from the pharmacist to the prescriber in the later D-PRESCRIBE trial [37]. One objective of the pharmaceutical opinion is to increase knowledge and skills among pharmacists and physicians about pharmacological recommendations so that they are better equipped to support patients in deprescribing [37]. The intervention also tackled clinical inertia by increasing "*accountability for adhering to evidence-based recommendations*" (p.1895)[18] made possible by a communication strategy involving the triad patient-physician-pharmacist [18, 37].

In light of this information and validation by intervention developers, the core functions of the D-PRESCRIBE intervention are:

Section 2

- 1) To increase patients' knowledge and concerns about BZRA use
- 2) To empower patients by increasing their self-efficacy
- 3) To increase physicians' and pharmacists' knowledge about current guidelines regarding BZRA use in older adults
- 4) To provide tripartite communication about BZRA deprescribing and therefore limiting clinical inertia.

Kirk recommends mapping core functions to forms by asking “*Does this particular form activate the core function?*”(p. 328) [28]. The EMPOWER brochure activates core functions 1 and 2, and the pharmaceutical opinion activates core functions 3 and 4.

Quebec and Belgian context comparison

a. Epidemiological context

BZRA use in older adults is decreasing both in Quebec and Belgium but remains high with respectively 24.8% in 2016 and 18% in 2013 taking at least one BZRA [12, 39]. The percentage in Quebec does not include z-drugs use [39]. However, authors defined BZRA use as “one drug claim in the year” while the Belgian study is based on medications taken during the last 24 hours, making accurate comparisons difficult. However, some similarities can be found between the two populations: first, the higher BZRA use prevalence in women compared to men [12, 39]. Second, the relationship between BZRA use and multimorbidity, in Quebec, 30% of multimorbid older adults (≥ 2 chronic conditions) were BZRA users, and in Belgium, 69.1% of BZRA users reported suffering from 2 or more chronic conditions [12, 39]. If the results of these studies cannot be directly compared, both demonstrate a link between BZRA use and multimorbidity in these countries. Differences in most used molecules are to be noted, with lorazepam, oxazepam, and clonazepam being the top three most used BZRA in Quebec while lormetazepam, lorazepam, and alprazolam were the most used in Belgium [12, 39]. Besides, in Belgium, most long-term BZRA prescriptions in 2019 were for older adults (55%) [40]. If we found no recent data on the long-term BZRA use prevalence in Quebec, the systematic review of Kurko et al, estimated that it concerned 47% percent of older BZRA users [41]. Despite the lack of more detailed information on prescribing patterns, the data clearly highlight opportunities for BZRA deprescribing in both countries.

b. Socio-cultural, socio-economic, ethical, and legal context

In Belgium, people are covered by a mandatory health insurance scheme, which intervenes in healthcare expenses such as medical consultations or the purchase of medications, either by reimbursing part or all the costs or by paying the provider directly [42]. This health insurance is financed jointly and severally by social contributions deducted from citizens' income [42]. In Quebec, however, people must individually

subscribe to a medication insurance either private (mostly through their employer) or public (if not eligible for private insurance) [43]. Older adults may choose between private or public insurance [43]. If benzodiazepines (but not z-drugs) are covered by Quebec's public insurance [44], no BZRA are covered in Belgium.

Major differences exist between both healthcare systems in terms of pharmacists' role and remuneration system. In Quebec, the pharmacist's role encompasses medication dispensing while ensuring that they are safe and appropriate, and, since 2020, medication prescription (in collaborative practice setting/agreement, for minor health conditions, for tobacco cessation, or in an emergency), therapeutic substitution, dosage, formulation or regimen adjustment of specific medications, prescription renewal or extension for continuity of care, and vaccination [45, 46]. The clinical role is emphasized through the remuneration system based on professional dispensing and pharmaceutical care fees [47] that are included in the total price of the medication [48]. Until April 2024, pharmaceutical opinions were part of the remunerated pharmaceutical care services, but from April 2024, only pharmaceutical opinions sent in the frame of medication initiation will be funded [49]. Indeed, pharmaceutical opinions have been less used since 2020 because of the extension of pharmacists' prescribing privileges. In Belgium, the role of the pharmacist in pharmaceutical care comprises the analysis and validation of the prescription, medication dispensing, and provision of information to ensure safe and efficient use [50]. The scope of pharmaceutical care practice is less extensive than in Quebec, with medication prescription (except for COVID-19 and influenza vaccination [51]) and dosage adjustment being an exclusive medical prerogative. The remuneration system emphasizes the pharmacist dispensing role as it is essentially based on the profit margin and a fixed dispensing fee due per medication box (for reimbursed medications) [52]. To date, four specific pharmaceutical care activities are remunerated [52], which is much less than the 30 or so pharmaceutical services listed in Quebec [49]. Besides, contrary to Quebec where pharmaceutical opinions are a formal way to communicate between pharmacists and prescribers, no formal communication system exists in Belgium, the communication taking place mostly by telephone [53].

We assume that these differences shape patients' expectations about pharmacists' services as well as physician's expectations in terms of collaboration and professional role.

The uptake of the intervention by patients, pharmacists, and general practitioners might be influenced by these differences. However, there is a growing interest for pharmacists to take a more clinical role in Belgium, as demonstrated by recent studies

Section 2

assessing the implementation of medication reviews led by the community pharmacist [54-56].

Step 2: Plan and undertake the adaptations

Participants

Between May and June 2022, two group discussions gathered pharmacists and GPs to discuss the EMPOWER brochure and one to discuss the pharmaceutical opinion. In total, seven pharmacists and six GPs participated either in a group discussion or an interview. All healthcare providers (HCPs) discussed both topics (i.e., the EMPOWER brochure and the pharmaceutical opinion). All pharmacists were women, and four of six GPs were men. The age of the pharmacists ranged from 29 years to 52 years and GPs from 26 years to 64 years. Five pharmacists worked as independent pharmacists and two worked in a chain group pharmacy. Three pharmacists but no GP worked in a rural setting. All GPs worked in a group practice. Four pharmacists and five GPs declared having sometimes or regularly deprescribed or collaborated with BZRA deprescribing.

Six patients were interviewed, two online and four at home. Four of the six patients were women. Their median age was 76.5 years [range: 62-92 years]. One patient was slightly younger than the inclusion criteria (62 years). As the patient was in a BZRA-reducing process and therefore had meaningful feedback to provide on the D-PRESCRIBE tools, the research committee agreed on the inclusion.

Adaptations

Overall, the EMPOWER brochure was positively perceived by both patients and HCPs, who acknowledged that it was well-structured and documented. HCPs more than patients disliked the main message “You are at risk” which was considered too aggressive. However, the brochure was deemed simple, corresponding to professional values, and able to engage patients in a deprescribing attempt. Many minor changes were suggested by participants and arbitrated with the research team. The structure of the brochure remained unchanged. However, colors, most of the photos, and some icons were replaced. Minor changes were made to the wording and content of the brochure. Five main goals underpinned these changes: soften the message, make the patient feel concerned, provide important information, provide practical information, and maintain the relationship with the patient.

The pharmaceutical opinion aroused mixed perceptions. Interviewed HCPs found that it was a good idea but acknowledged that some colleagues could be less open. Two patients found the document interesting but four had negative reactions, doubting that

it was the role of the pharmacist to proactively communicate with the physician. Again, five main goals underpinned the adaptations made to the document: preserve a good pharmacist-GP relationship, enhance document clarity, refer to national clinical guidelines, adapt the document to the Belgian healthcare system, and provide important information. The final document holds in one double-sided page and is designed for a quick and efficient use. The research team decided to name the document “pharmaceutical proposal” as suggested by an interviewed pharmacist, with “proposal” being perceived as less blaming or moralizing than “opinion”.

Tables 1 and 2 present examples of changes to the brochure and pharmaceutical opinion along with their goal of adaptation and justification. The full list of adaptations may be found in Supplementary file 5. We estimate that none of these adaptations changed the core functions of the D-PRESCRIBE intervention.

Section 2

Table 1. Examples of adaptations made to the EMPOWER brochure		
Goals for adaptation	Nature of adaptation	Anticipated obstacle/Justification
Soften the message	The title of the brochure was changed to "You may be at risk".	"You are at risk" was considered too aggressive.
	The photo on page 4 was replaced.	The facial expression of the man in the original photo was perceived too negatively.
Make the patient feel concerned	Logos on page 1 were replaced by logos of Belgian scientific societies that agreed to support this brochure.	Belgian logos can be recognized by the patient and be perceived as proof of the quality of the brochure.
	On page 8, the message "Get exercise during the day" was replaced by "Stay active during the day"	"Get exercise" was assimilated to "Do some sport" which was perceived as inapplicable for most older adults.
	On page 10, the name of the lady who provides a testimony was replaced.	The original family name "Robinson" is not a common Belgian family name.
	On page 3 (quiz), the order of the questions was changed. The wording of the questions was modified to be more specific (e.g., using "insomnia and/or anxiety" instead of "symptoms") or to shorten the sentences.	Rearranging the order of the questions was felt necessary to allow a more logical flow. Shortening a bit the questions allowed better understanding, especially for patients with lower literacy.
Provide important information	On page 7, a question about the tolerance phenomena was added.	Stressing somehow tolerance and dependence related to BZRA use was judged important.
	On page 5, the wording "these medications are not the best long-term treatment" was changed to "these medications are no longer the best long-term treatment".	The original affirmation was perceived as too aggressive for patients and too blaming for the healthcare providers.
Maintain the relationship with the patient	On page 5, The answer "TRUE" was changed to "TRUE...temporarily".	Adding some message of empathy and encouragement was judged necessary to avoid being perceived as too moralizing.
	Some words about the potential difficulty of BZRA deprescribing were added.	
Provide practical information	On page 9, a word about the availability of activities adapted for seniors was added. A message about whom to ask for more information about these activities was also added.	Some patients and HCPs perceived that the original message could be disregarded because yoga or tai-chi was perceived as too difficult for older adults. It was found that providing more practical and concrete information could help older adults to engage in these activities.
Legend: BZRA : Benzodiazepine receptor agonists; HCP : Health care provider		

Table 2. Examples of adaptations made to the pharmaceutical opinion		
Goals for adaptation	Nature of adaptation	Anticipated obstacle/Justification
Preserve a good pharmacist-GP relationship	The name of the document was changed to “pharmaceutical proposal” instead of “pharmaceutical opinion”. The wording “Your patient” was replaced with “Our patient”.	Participants feared the document to be perceived as blaming or moralizing by the GP.
Enhance document clarity	Proposals were added for the pharmacist to tick specific risk factors observed with the patient.	As all older adults share the same risks of falls, fractures, etc. due to BZRA use, pharmacists did not know what to write in the blank space to specify risks.
Provide important information	The proposal presents 2 tapering options: 1. The EMPOWER tapering program with a mention that this tapering scheme is an example (to use with some freedom depending on the patient). A sentence was added to emphasize that the pharmacist could help if the pill is difficult to cut. 2. Three stepwise (5, 7, or 10 steps) tapering programs using capsules containing a decreasing percentage of the compound, prepared by the pharmacist. Reimbursement opportunities regarding these preparations were mentioned.	In February 2023, a national pilot program aiming for BZRA deprescribing through stepwise reduction using capsules compounded by the pharmacist was launched. These stepwise programs were added to fit with this new opportunity.
Adapt to the Belgian Healthcare system	The sentence indicating a replacement by another molecule as well as the box for certifying this document stands for a new prescription were removed.	As pharmaceutical opinions are not used in Belgium, this document does not comply with Belgian requirements for a prescription, which is mostly electronic.
Refer to national clinical guidelines	The original reference to Beers criteria was replaced by STOPP criteria and Belgian references.	Beers criteria are not well-known in Belgium contrary to STOPP criteria. A national pharmaceutical platform (CBIP) provides Belgian recommendations in terms of prescribing. It is widely used in Belgium and known by both pharmacists and GPs.
Legend: BZRA : Benzodiazepine receptor agonists; GP : General Practitioner; CBIP : Centre Belge d'Information Pharmacothérapeutique (Belgian Center for Pharmacotherapeutic Information); STOPP : Screening Tool of Older Person's Prescriptions		

Section 2

Regarding the delivery mode of the intervention, pharmacists unanimously thought that the brochure should be given hand-to-hand to patients, which would allow a small conversation about its content with them. Sending the brochure by postal mail – one of the mechanisms used in D-PRESCRIBE - seemed inappropriate for the participants. Patients stated that they would welcome this brochure from their pharmacist, especially if given directly. The pharmaceutical proposal cannot be sent by fax as it was done during the D-PRESCRIBE as no Belgian pharmacy or GP uses commonly this communication tool nowadays. No consensus on a unique mode was identified by stakeholders, therefore a question of the online survey investigated the best communication channel for smooth communication between HCPs.

Survey on the first version of the pharmaceutical proposal.

A total of 91 pharmacists and 46 GPs participated. Table 3 presents the main characteristics of respondents. Forty-three percent of GPs were aged from 25 to 34 years. Most participants were women (60.9%) and worked in a group practice (80.4%). Community pharmacists were also mainly women (60.4%) and self-employed for 80.2% of them.

Table 3. Characteristics of the participants in the survey about the first version of the pharmaceutical proposal		
Variables n(%)	General practitioners (n=46)	Community pharmacists (n=91)
Age		
<35 years	21 (45.7)	30 (33.0)
35-44 years	7 (15.2)	18 (19.8)
45-54 years	5 (10.9)	26 (28.6)
≥55 years	13 (28.3)	17 (18.7)
Gender		
Female	28 (60.9)	55 (60.4)
Professional experience		
Less than 5 years	15 (32.6)	19 (20.9)
5-14 years	12 (26.1)	21 (23.1)
15-24 years	4 (8.7)	21 (23.1)
25-34 years	7 (15.2)	24 (26.4)
≥35 years	8 (17.4)	6 (6.6)
Professional environment		
Urban	30 (65.2)	35 (61.5)
Rural	16 (34.8)	56 (38.5)
Type of practice		
• GP		
Group practice	37 (80.4)	

Solo practice	9 (19.6)	
• <u>Pharmacists</u>		
Collaborative practice		18 (19.8)
Independent practice		73 (80.2)
Frequency of BZRA deprescribing (GP) or contribution to BZRA deprescribing (pharmacists)		
Never	2 (4.3)	28 (30.8)
Sometimes	29 (63.0)	52 (57.1)
Regularly	15 (32.6)	11 (12.1)
Legend: GP: general practitioner; BZRA: benzodiazepine receptor agonists		

Table 4 presents the results of the survey. Overall, the first version of the pharmaceutical proposal was judged clear and understandable. However, 30 participants (22%) left a comment asking for a simpler and clearer document. The layout of the document was therefore revised. Most of the HCPs agreed with the proposed alternatives to BZRA and judged the content of the pharmaceutical proposal solid scientifically (Table 4). Some comments asked for adding pharmaceutical alternatives such as melatonin and valerian to the proposed alternatives. As there is currently no evidence of their efficacy, the Belgian current guidelines do not recommend them [57]. Therefore, we added them to a new paragraph entitled “non-recommended alternatives”.

Table 4. General practitioners' and pharmacists' assessment of the first version of the pharmaceutical proposal		
General assessment	GP (N=46) Agree/strongly agree (%)	Pharmacists (N=91) Agree/strongly agree (%)
<i>Filling in the document</i>		
The document is clear and well-presented.	33 (71.7)	76 (83.5)
I understand easily what I would have to complete as a pharmacist/doctor.	38 (82.6)	83 (91.2)
Time for reading and completing the document is acceptable.	30 (65.2)	65 (71.4)
<i>Content of the document</i>		
I agree with the alternatives to benzodiazepines proposed in the document.	34 (73.9)	60 (65.9)
The information provided by the document is scientifically solid.	40 (87.0)	75 (82.4)

Section 2

Some information provided by the document was new to me.	11 (23.9)	14 (15.4)
Acceptability of the pharmaceutical proposal: Pharmacists' perspective		Pharmacists (N=91) Agree/strongly agree (%)
<i>Relationship with the prescriber</i>		
I would be willing to send this document to a prescribing doctor I know.		73 (80.2)
I would be willing to send this document to a prescribing doctor I know little or do not know.		51 (56.0)
Communicating with the doctor through this document seems an interesting idea to me.		56 (61.5)
I would be afraid of damaging the relationship with the doctor if I sent him this document.		20 (22.0)
I think that sending this document to the prescribing doctor would help to promote benzodiazepine deprescribing in older adults.		55 (60.4)
I think it is necessary to contact the prescribing doctor personally before sending this document.		55 (60.4)
Communication with the prescribing doctor in the context of benzodiazepine deprescribing corresponds to my professional values.		78 (85.7)
<i>Relationship with the patient</i>		
I would be willing to propose to a patient I know well to communicate with his prescribing doctor through this document.		73 (80.2)
I would be willing to propose to a patient I do not know well to communicate with his prescribing doctor through this document.		29 (31.9)
I think this could strengthen the therapeutic bond I have with the patient.		69 (75.8)
As a pharmacist, it is my role on behalf of the patient to be proactive with the doctor concerning benzodiazepine deprescribing in older adults.		72 (79.1)
Acceptability of the pharmaceutical proposal: General practitioners' perspective		GP (N=46) Agree/strongly agree (%)
<i>Relationship with the pharmacist</i>		
I would receive this document positively from a pharmacist I know.		39 (84.8)

I would receive this document positively from a pharmacist I know little or do not know.	28 (60.9)
I would prefer to be contacted personally by the pharmacist (by email or telephone) before receiving this document.	28 (60.9)
I think it is the pharmacist's role to ask me about potential benzodiazepine deprescribing for my patients.	25 (54.3)
Collaborating with the pharmacist on benzodiazepine deprescribing in older adults is in line with my professional values.	39 (84.8)
I would be happy to respond to the pharmacist if I received such a document.	38 (82.6)
Communicating with the pharmacist through this document seems an interesting idea to me.	32 (69.6)
<i>Relationship with the patient</i>	
Receiving this document would give me a good opportunity to start a discussion with my patient about benzodiazepine deprescribing.	38 (82.6)
I am concerned about losing the patient's trust if the pharmacist asks me about a potential benzodiazepine deprescribing for my elderly patient.	8 (17.4)
Legend: GP : General practitioner	

Most of the pharmacists (80.2%) would accept sending the proposal to a doctor they know, and most GPs (84.8%) would welcome this document positively from a pharmacist they know. Lower acceptance was observed if the pharmacist and GP do not know each other. While the great majority of pharmacists (79.1%) do believe it is their role on behalf of the patient to proactively ask about a potential BZRA deprescribing to the prescriber, only 54.3% of the GPs agree with that statement. However, 84.8% of the GPs agree that collaborating with the pharmacist on BZRA deprescribing corresponds to their professional values. Twenty-two percent of the pharmacists would be afraid of damaging their relationship with the GP by sending the document, and 17.4% of the GPs would be afraid of losing the patient's trust over the pharmacist's questioning. However, a large majority of the GPs (82.6%) agree that receiving this document would give them a good opportunity to discuss BZRA deprescribing with their patients. Finally, some comments underlined that the Canadian EMPOWER deprescribing scheme would be too complex for some patients. Indeed, this deprescribing scheme involves taking different dosages every day (e.g., half a tablet on two days of the week, whole tablet on the other days). The final pharmaceutical proposal presents two tapering options: the EMPOWER tapering scheme and three stepwise tapering schemes, using capsules containing a decreasing percentage of the compound, prepared by the pharmacist. This latter option was made

Section 2

possible by the launch, in February 2023, of a pilot program funded by the Belgian National Institute of Health and Disability Insurance (NIHDI) to promote BZRA deprescribing in the adult population (≥ 18 years)[58]. Under certain conditions, including the signature of a contract between the pharmacist, the GP, and the patient, the patient can benefit from a tapering program using capsules compounded by the pharmacist [58]. The fees for the making of the capsules and two consultations with the pharmacist are financed by the NIHDI [58]. Except for the cost of the BZRA itself, this pilot program is free for the patient [58]. We decided to include that option in the pharmaceutical proposal.

Regarding the delivery mode of the pharmaceutical opinion, no consensus was obtained. Using emails was excluded due to privacy concerns. Handing the document through the patient moved the intervention away from direct contact between professionals. It was decided to propose several channels: postal mail and an application or an electronic mailbox both secured and specific to healthcare providers.

The adapted EMPOWER brochure and pharmaceutical proposal are available in Supplementary files 6 and 7.

DISCUSSION

We adapted the D-PRESCRIBE intervention to the Belgian community setting using the ADAPT guidance and recommendations of the new MRC framework [25, 26]. To our knowledge, this study is one of the first to use the recent ADAPT guidance to conduct the adaptation process.

The EMPOWER brochure has already been used in different contexts, with or without adaptations. For example, the original brochure was used in the hospital setting in Canada [59, 60]. For its use in the Australian hospital setting, adaptation consisted of changing the names of the available benzodiazepines [61]. Other researchers adapted it for older American veterans, with more extensive changes such as the replacement of photos, the removal of the tapering program, or the addition of a section dedicated to a specific website offering cognitive and behavioral therapy online [62, 63]. Our adaptations remain minor but essential to fit with the Belgian context and optimize its uptake. Changes comprised a change in color, the replacement of most photos, and minor changes to the content (e.g., the adaptation of some sentences or the addition of extra information related to the Belgian context).

However, the pharmaceutical opinion, renamed “pharmaceutical proposal”, undertook more significant changes to enhance its acceptability as a new tool in the Belgian context. Despite these adaptations, some uncertainties remain regarding the implementation of the pharmaceutical proposal in our country. These uncertainties

are mainly related to the change in pharmacists' role that the document would entail. If most interviewed HCPs were open to this new tool, most patients expressed reluctance or skepticism. Even if the provision of clinical services is slowly expanding in our country, patients do not expect such initiative from their pharmacist and can feel trapped in a conflict of loyalty to their doctor. A focus-group study was conducted in the Canadian province of Alberta in 2012 and 2013, five years after policies widened pharmacy services largely (up to prescribing) [64]. The authors stressed the importance of pharmacists' communication about this new role to inform patients about what they can expect [64]. Their results also showed that personalizing the professional relationship with patients helped them to recognize the expertise and clinical role of the pharmacist [64]. Therefore, we anticipate that pharmacists' attitudes and communication skills will be essential for the uptake of this new tool by patients. Besides, our results showed that only a third of the pharmacists would use the pharmaceutical proposal with a patient they know little or do not know. If patients are free to go to any pharmacy to obtain medicines in Belgium, we believe that this initiative is more likely to be adopted by both patients and pharmacists if it comes from a reference or regular pharmacist. As healthcare professional support is a key element in the success of BZRA deprescribing [38], it is even more important. In Belgium, a patient with chronic polypharmacy can sign a contract with a community pharmacist who is appointed as the reference pharmacist. The role of the reference pharmacist is to keep an updated list of medicines and make it available to the patient's HCPs [65]. This status could help the pharmacist to take a more proactive role on behalf of the patient.

The survey also highlighted other barriers to the pharmaceutical proposal from the perspective of HCPs. Unsurprisingly, not knowing the other side reduced the acceptability of the pharmaceutical proposal for both pharmacists and GPs. The paucity of professional relationships has indeed been described as an obstacle to GP and pharmacist collaboration [66]. Previous literature also underlined that GP-pharmacist collaboration could be hindered by role boundaries issues and power imbalance [66, 67]. Our results showed that the sending of the pharmaceutical proposal, even adapted, could also raise these issues (e.g.: more than one out of five pharmacists would be afraid of damaging the relationship with the prescriber over the sending of the document). Most pharmacists and GPs agree on the necessity of a contact before the sending of this document. In practice, this contact could increase pharmacists' workload by adding an extra task. However, taking the time to present and explain this innovation may be unavoidable during the period needed to change habits. Medical-Pharmaceutical Concertations (MPC) could also help in this matter. MPC are meetings between GPs and pharmacists, funded by the NIHDI, organized at

Section 2

the local level on a voluntary basis, and designed to improve interprofessional collaboration [68]. Despite these challenges, a change in the pharmacist's role from dispensing to providing more pharmaceutical care seems feasible, as demonstrated by other results of the survey (e.g., 80% of the pharmacists thought it was their role on behalf of the patient to be proactive with the doctor concerning benzodiazepine deprescribing). The example of Alberta, where that shift has already occurred is also encouraging [64]. The Belgian context is moving further in that direction. BZRA deprescribing might not be the simplest clinical situation to begin implementing pharmaceutical proposals as others could draw less resistance from patients, pharmacists, and physicians. However, tools must evolve with the scope of practice. As such, implementing pharmaceutical proposals in Belgium might meet an unaddressed need for a more formal communication between the pharmacist and the GP, and help pharmacists to take a more clinical role. The launch of the NIHDI BZRA tapering pilot program that fosters interprofessional collaboration could be particularly timely and facilitate pharmaceutical proposal implementation.

This study has several strengths and limitations. A first strength is the use of the ADAPT guidance that allowed a rigorous and transparent adaptation process of the D-PRESCRIBE intervention. The second strength of this study is the implication of stakeholders, including older adults, throughout the whole process, as recommended by both ADAPT and MRC recommendations [25, 26]. In the context of clinical trials, involving patients in the development of information tools has been found to enhance their readability and appropriateness [69]. Similarly, we believe that their participation increased the relevance of adaptations that were made to the D-PRESCRIBE intervention. Finally, using both qualitative and quantitative data allowed a reliable adaptation of the pharmaceutical opinion. One limitation is that participating HCPs and patients were recruited voluntarily. We cannot exclude that they might have been more positive than the general population of HCPs and patients. Besides, young GPs and GPs working in group practice were overrepresented in our survey. Literature has shown that experienced GPs collaborate less with pharmacists [47]. Therefore, the barriers that we have highlighted regarding the pharmaceutical proposal may be more important than shown by our results. In addition, the adaptation of this tool was limited to the French-speaking part of our country. Apart from a different language, cultural differences exist between the Flemish and French-speaking parts of Belgium, making a similar work necessary before using them in Flanders.

The adaptation process of the D-PRESCRIBE intervention is still in progress. We will next test the adapted D-PRESCRIBE intervention in a feasibility study (NCT: 05929417) (step 3 of the ADAPT guidance) [25]. Concerning the remaining uncertainties about the

pharmaceutical proposal, the coming feasibility study is crucial to assess the level of uptake of this new tool by patients, pharmacists, and GPs.

CONCLUSIONS

The D-PRESCRIBE intervention was adapted following a transparent and rigorous process with the help of the ADAPT guidance. Of its two components, one (the EMPOWER brochure) undertook minor changes and was well accepted by both patients and healthcare providers. Some uncertainties remain about the uptake of the second component (the pharmaceutical proposal) in our country, mainly because of the changes that this document would imply regarding the role of pharmacists. An ongoing feasibility study will allow us to test the adapted intervention in real practice and evaluate if further adaptations are needed.

Supplementary files

Supplementary file 1.(.docx) GUIDED checklist

Supplementary file 2. (.docx) Interview guide regarding the EMPOWER brochure (in French)

Supplementary file 3. (.docx) Interview guide regarding the pharmaceutical opinion (in French)

Supplementary file 4. (.docx) Pharmacists and general practitioners survey on the first version of the pharmaceutical proposal

Supplementary file 5. (.docx) Changes to the D-PRESCRIBE intervention according to the Model for Adaptation Design and Impact framework

Supplementary file 6 (.pdf) Adapted EMPOWER brochure

Supplementary file 7. (.pdf) Pharmaceutical proposal

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Section 2

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Section 2

Supplementary file 1. GUIDED checklist		
Item description	Page in manuscript where item is located	Other*
1. Report the context for which the intervention was developed.	Background Results	
2. Report the purpose of the intervention development process.	Background	
3. Report the target population for the intervention development process.	Background	
4. Report how any published intervention development approach contributed to the development process.	Background	
5. Report how evidence from different sources informed the intervention development process.	Background Methods	
6. Report how/if published theory informed the intervention development process.	Methods	
7. Report any use of components from an existing intervention in the current intervention development process.	Background Methods	
8. Report any guiding principles, people or factors that were prioritized when making decisions during the intervention development process	Methods	
9. Report how stakeholders contributed to the intervention development process	Methods Results	
10. Report how the intervention changed in content and format from the start of the intervention development process	Results+ table 1, 2 (examples) + supplementary table 2 (complete)	
11. Report any changes to interventions required or likely to be required for subgroups	No changes are likely to be required for subgroups.	
12. Report important uncertainties at the end of the intervention development process.	Discussion	
13. Follow TIDieR guidance when describing the developed intervention	Items 1 to 6 of the TIDieR checklist are reported in this article.	
14. Report the intervention development process in an open access format.		
*e.g. if item is reported elsewhere, then the location of this information can be stated here.		
Legend: GUIDED : Guidance for reporting intervention development studies in health research; TIDieR : Template for Intervention Description and Replication)		

Supplementary file 2. Interview guide regarding the EMPOWER brochure

Groupe de discussion n°1 : Quelle est l'acceptabilité de la brochure éducative EMPOWER (jointe à ce courrier) et quelle seraient les adaptations à y apporter ?

Bonjour et merci pour votre participation à ce premier groupe de discussion. Pour ce 1^{er} groupe de discussion, nous allons évaluer l'acceptabilité et le besoin d'adaptation de la brochure EMPOWER, développée par l'équipe du Pr Cara Tannenbaum au Canada.

Comme vous allez le voir, il s'agit d'une brochure éducative destinée, entre autres, à apporter de l'information au patient par rapport à sa prise de benzodiazépine. Dans l'intervention canadienne, elle est donnée en main propre par le pharmacien au patient ou envoyée par courrier.

L'objectif de ce groupe de discussion est de lister les éléments qui seraient à modifier dans cette brochure pour qu'elle corresponde au mieux au contexte belge. Nous noterons la raison de ce besoin de modification et les propositions de changement qui seront suggérées. Il n'y a pas de « bons » ou « mauvais » commentaires ou suggestions de changement. L'objectif n'est pas d'atteindre un consensus sur une « bonne » façon d'adapter cette brochure. Chaque avis et ressenti compte et enrichit la discussion.

Voici comment nous allons procéder :

Nous allons regarder ensemble chaque page de la brochure. Pour chacune d'entre elle, je vais vous demander de partager le ressenti et les commentaires qu'elle vous inspire de façon tout à fait libre. Ci-dessous voici quelques questions qui pourraient être posées pour lancer ou relancer les échanges :

- Que comprenez-vous de ce qui est présenté ici ?
- Y a-t-il quelque chose qui vous dérange sur cette page ?
- Vous sentez-vous confortable avec le contenu de ce qui est présenté ? avec la mise en page ?
- Que formuleriez-vous ou présenteriez-vous autrement ?

Après la revue page par page de la brochure, nous en discuterons de façon plus générale. Le point de vue de chaque partie impliquée dans l'intervention sera exploré. Voici les questions qui seront abordées:

- Dans quelle mesure serait-il facile ou difficile :
 - de donner cette brochure à un patient ? (pharmacien)
 - de recevoir cette brochure ? (patient)
 - de soutenir le contenu de cette brochure ? (médecin)
 - si des difficultés sont soulevées, quelles modifications faudrait-il apporter à cette brochure pour y remédier ?

Section 2

- Dans quelle mesure cette brochure correspond à vos valeurs entre tant que pharmacien, médecin, patient ?
- Dans votre compréhension de l'outil, comment la brochure est sensée «fonctionner » pour atteindre son but (c'est-à-dire favoriser la déprescription des benzodiazépines chez les personnes âgées) ?
- A votre avis, dans quelle mesure est-il probable que la brochure permette à des personnes âgées d'arrêter ou de réduire leur benzodiazépine ?
- Pratiquement, de quelle façon préféreriez-vous recevoir cette brochure (patient) ? En main propre, par courrier?
- Pratiquement, de quelle façon préféreriez-vous donner cette brochure (pharmacien) ? En main propre, par courrier ?

Pour finir, je vous demanderai de partager si vous le souhaitez tous les commentaires et autres suggestions que vous n'auriez pas encore eu l'occasion d'exprimer lors de la discussion.

Supplementary file 3: Interview guide regarding the pharmaceutical opinion

Groupe de discussion : Quelle est l'acceptabilité de l'opinion pharmaceutique (jointe à ce courrier) et quelle seraient les adaptations à y apporter ?

Bonjour et merci pour votre participation à ce groupe de discussion !

Comme vous le savez, l'objectif de notre étude est d'adapter, pour les soins de santé primaires belges, l'intervention D-PRESCRIBE, développée au Canada par l'équipe du Pr Tannenbaum. L'intervention comprend 2 volets, une brochure éducative donnée par le pharmacien au patient et l'envoi par le pharmacien au médecin prescripteur d'une opinion pharmaceutique (voir ci-joint). C'est de ce deuxième volet dont nous allons discuter ensemble le 31 mai, pour en évaluer l'acceptabilité et le besoin d'adaptation.

L'opinion pharmaceutique est un document que le pharmacien envoie au médecin prescripteur pour attirer son attention sur le fait que son patient prend un médicament qui serait potentiellement inapproprié selon les données probantes actuelles. Le médecin peut alors répondre au pharmacien en indiquant sa décision par rapport à cette opinion pharmaceutique. Il s'agit d'une pratique standard au Québec.

L'objectif de ce groupe de discussion est de lister les éléments qui seraient à modifier dans cette opinion pharmaceutique pour qu'elle corresponde au mieux au contexte belge. Nous noterons la raison de ce besoin de modification et les propositions de changement qui seront suggérées. Il n'y a pas de « bons » ou « mauvais » commentaires ou suggestions de changement. L'objectif n'est pas d'atteindre un consensus sur une « bonne » façon d'adapter cette opinion pharmaceutique. Chaque avis et ressenti compte et enrichit la discussion.

Voici comment nous allons procéder :

Nous commencerons par discuter du document en tant que tel, partie par partie. Je vous demanderai de partager votre ressenti par rapport à celui-ci et les commentaires qu'il vous inspire de façon tout à fait libre. Vous serez également invité.e à partager toutes les idées de modifications que vous trouveriez nécessaires. Ci-dessous voici quelques questions qui pourraient être posées pour lancer ou relancer les échanges :

- Dans cette partie du document, dans quelle mesure êtes-vous confortable avec le contenu/la forme ?
- Que formuleriez-vous ou présenteriez-vous différemment ?

Ensuite, nous discuterons de façon plus générale de l'opinion pharmaceutique. Le point de vue de chaque partie impliquée dans l'intervention sera exploré. Voici les questions qui seront abordées :

- Dans quelle mesure serait-il facile ou difficile :

Section 2

- D'envoyer cette opinion pharmaceutique au médecin prescripteur? (pharmacien)
 - De recevoir cette opinion pharmaceutique ? (médecin)
 - D'envoyer un retour au pharmacien? (médecin)
 - De recevoir le retour du médecin (pharmacien)
 - Si des difficultés sont soulevées, quelles modifications faudrait-il apporter à ce mode de communication pour y remédier ?
- Dans quelle mesure cette opinion correspond-elle à vos valeurs entre tant que pharmacien, médecin ?
- Dans votre compréhension de l'outil, comment cette opinion pharmaceutique est sensée «fonctionner» pour atteindre son but (c'est-à-dire favoriser la déprescription des benzodiazépines chez les personnes âgées) ?
- A votre avis, dans quelle mesure est-il probable que l'opinion pharmaceutique permette à des personnes âgées d'arrêter ou de réduire leur benzodiazépine ?
- Dans quelle mesure pensez-vous que vous pourriez saisir l'occasion de recevoir cette opinion pharmaceutique pour discuter avec votre patient de déprescrire sa benzodiazépine ? (médecin)
- Pratiquement et avec les ressources actuellement à votre disposition, de quelle façon préféreriez-vous délivrer cette opinion pharmaceutique. (pharmacien)
- Pratiquement et avec les ressources actuellement à votre disposition, de quelle façon préféreriez-vous recevoir cette opinion pharmaceutique. (médecin)

Pour finir, je vous demanderai de partager si vous le souhaitez tous les commentaires et autres suggestions que vous n'auriez pas encore eu l'occasion d'exprimer lors de la discussion.

Supplementary file 4: Pharmacists and general practitioners survey on the first version of the pharmaceutical proposal

Le groupe de recherche en Pharmacie Clinique de l'UCLouvain souhaite adapter au contexte des soins primaires belges une intervention canadienne favorisant la **déprescription des benzodiazépines chez les personnes âgées**. Cette intervention, menée par le pharmacien, a montré une grande efficacité en termes de déprescription chez les personnes âgées au Canada (Etude D-PRESCRIBE, Martin et al. JAMA, 2018).

L'intervention comprend 2 volets :

1) La remise au patient par le pharmacien d'une **brochure éducative**. Cette brochure a pour but d'attirer son attention sur les risques potentiels liés à la prise de sa benzodiazépine. Elle vise également à augmenter le sentiment d'auto-efficacité du patient pour arrêter ce médicament.

2) L'envoi par le pharmacien au médecin prescripteur d'une **proposition pharmaceutique**. Ce document, basé sur les guidances cliniques actuelles, invite le médecin à réévaluer la prescription de benzodiazépines chez son patient. Le médecin peut ensuite informer le pharmacien de la décision qu'il a prise à ce sujet (continuer, arrêter progressivement, changer vers une autre molécule, ...) en lui renvoyant le document.

L'objet de cette enquête est la proposition pharmaceutique. Si cette pratique est courante au Canada, elle ne l'est pas en Belgique. Après avoir interviewé des patients, des médecins généralistes et des pharmaciens belges, nous souhaitons récolter l'avis d'un plus large panel de professionnels de la santé (**médecins généralistes et pharmaciens**) à propos d'une première version du document canadien que nous avons adapté suite à ces interviews. Ce document tient en 3 pages.

Vous êtes invité(e) à donner votre avis en répondant de façon anonyme aux questions de cette enquête. Votre participation nous permettra d'affiner l'outil et d'en évaluer l'acceptabilité.

Répondre à l'enquête prend environ 10 minutes. A la fin du questionnaire, vous disposerez d'un espace pour indiquer tous les commentaires que vous souhaiteriez.

Si vous répondez à cette enquête en format papier, veuillez rendre le questionnaire avant de repartir.

En cas de questions, n'hésitez pas à nous contacter: Catherine Pétein (catherine.petein@uclouvain.be)

Section 2

Merci pour votre participation!

En cochant la case ci-dessous, vous déclarez avoir lu et compris les informations ci-dessus et accepter de participer à l'étude visant à adapter les outils canadiens de l'intervention D-PRESCRIBE au contexte belge.

☐ J'accepte de participer

A. Caractéristiques socio-démographiques et professionnelles

1. A quel genre vous identifiez-vous?

☐ Femme

☐ Homme

☐ Autre

2. Quel âge avez-vous?

☐ Entre 25 et 34 ans

☐ Entre 35 et 44 ans

☐ Entre 45 et 54 ans

☐ Entre 55 et 64 ans

☐ 65 ans ou plus

3. Quelle profession exercez-vous ?

☐ Médecin généraliste

☐ Pharmacien

Si profession = pharmacien :

4. Depuis combien de temps exercez-vous votre profession (assistantat compris)?

- ☐ Moins de 5 ans
- ☐ Entre 5 et 14 ans
- ☐ Entre 15 et 24 ans
- ☐ Entre 25 et 34 ans
- ☐ Plus de 35 ans

Si profession = médecin généraliste

4. Depuis combien de temps exercez-vous votre profession (assistantat compris)?
- ☐ Moins de 5 ans
 - ☐ Entre 5 et 14 ans
 - ☐ Entre 15 et 24 ans
 - ☐ Entre 25 et 34 ans
 - ☐ Plus de 35 ans
5. Où exercez-vous votre profession?
- ☐ En milieu urbain
 - ☐ En milieu rural

Si profession = pharmacien

6. Exercez-vous...?
- ☐ Au sein d'une pharmacie indépendante
 - ☐ Au sein d'une pharmacie « de chaîne »

Si profession = médecin généraliste:

6. Exercez-vous...?
- ☐ En pratique indépendante

Section 2

☐ En pratique groupée

Si profession = pharmacien

7. A quelle fréquence vous arrive-t-il de contribuer à déprescrire des benzodiazépines chez les personnes âgées?

☐ Jamais

☐ Parfois

☐ Régulièrement

Si profession = médecin généraliste

7. A quelle fréquence vous arrive-t-il de déprescrire des benzodiazépines chez les personnes âgées?

☐ Jamais

☐ Parfois

☐ Régulièrement

B. Votre avis sur la 1ère version de la proposition pharmaceutique:

Vous trouverez à la page suivante le document sur lequel nous souhaitons avoir votre opinion

Proposition pharmaceutique basée sur les guidelines actuelles

Benzodiazépines et z-drugs

La collaboration médecin-pharmacien-patient est une approche efficace pour favoriser la déprescription des benzodiazépines chez les personnes âgées¹. Cette proposition pharmaceutique s'inscrit dans cette démarche collaborative.

Date (jj/mm/aaaa): _____

A l'attention du Dr

Adresse : _____
Tél : _____
Email : _____

Nom du pharmacien : _____
Adresse : _____
Tél : _____
Email : _____

Notre patient, _____
né le ____/____/____ (DDN (jj/mm/aaaa)),
prend actuellement la benzodiazépine/z-drug suivant : _____
(posologie : _____) pour traiter son anxiété et/ou son insomnie. Etant donné son âge,
d'autres solutions plus sûres existent pour minimiser le risque de chutes, de fractures et de troubles de la mémoire.

Une démarche de déprescription pourrait être envisagée car notre patient présente les facteurs de risque suivants:

(à cocher par le pharmacien):

- | | |
|---|---|
| ☐ Utilisation prolongée ≥4 semaines | ☐ Utilisation concomitante avec des opioïdes |
| ☐ Utilisation de ≥3 médicaments du système nerveux central | ☐ Utilisation au-delà de la dose recommandée |
| | ☐ Autre (à préciser): _____ |

Les guidelines actuelles (voir verso) recommandent les alternatives listées dans le cadre ci-dessous.

- Envisager la thérapie cognitivo-comportementale dont l'efficacité a été démontrée pour traiter tant l'insomnie que l'anxiété et pour aider le patient à cesser les benzodiazépines et z-drugs (voir brochure : « **Comment obtenir une bonne nuit de sommeil sans médicaments** », disponible sur le site : <https://www.reseaudeprescription.ca/ressources>).
- Encourager l'adoption de changements de comportement pour traiter l'insomnie et l'anxiété comme la relaxation, la gestion des habitudes alimentaires, etc.
- Dans le traitement des troubles anxieux généralisés, envisager la possibilité de prescrire un SSRI, si nécessaire. *Note : Ces médicaments sont également associés au risque de chutes chez les personnes âgées, mais leur profil de risque est moindre. Attention, il n'est pas recommandé de substituer une benzodiazépine par trazodone ou tout autre médicament de classe z.**
- Débuter et suivre un programme de sevrage. Un exemple de programme est disponible page 3.

Cadre à remplir par le pharmacien

Actions entreprises par le pharmacien

- ☐ Une brochure éducative sur les risques à l'utilisation des benzodiazépines et les alternatives possibles a été distribuée au patient. Cette brochure comprend également le schéma de sevrage présenté en page 3.
- ☐ Autre (précisez) : _____

Avis du pharmacien (facultatif): Après discussion avec le patient, je proposerais (indiquer ici d'éventuelles propositions en termes de molécule, galénique, plan de sevrage,...): _____

Cadre à remplir par le médecin (svp, cochez toutes les cases qui s'appliquent au patient et retournez ce document au pharmacien)

Décision du médecin: Après discussion avec le patient, il a été décidé de :

- | | |
|---|----------------------|
| ☐ Modifier la prescription actuelle (voir prescription électronique) | Date: _____ |
| ☐ Débuter un programme de sevrage (voir prescription électronique) | Nom: _____ |
| ☐ Aucun changement à la prescription jusqu'à la prochaine réévaluation prévue le _____ | Numéro INAMI : _____ |

1/3

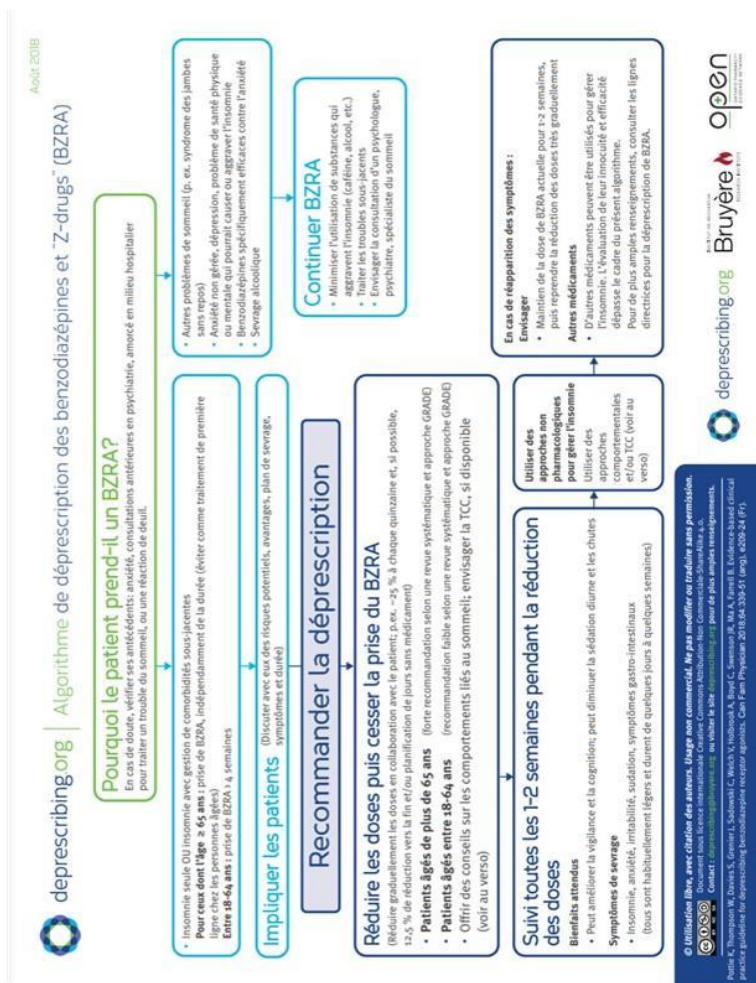
Section 2

Fondements et directives cliniques sur lesquels est basée la proposition :

Le formulaire de soins aux personnes âgées de Farmaka - CBIP ne recommande pas l'emploi des benzodiazépines et z-drugs dans le traitement de l'insomnie et de l'anxiété (sauf situation aiguë, pour un traitement très limité dans le temps).*

L'usage de benzodiazépines entraîne un risque 2 fois plus élevé de chutes et de fracture, 5 fois plus élevé de troubles cognitifs ou de la mémoire et 2 fois plus élevé d'accidents de voiture.²⁻⁴ La déprescription progressive est recommandée en cas de traitement chronique (critères STOPP).⁵

Algorithme de déprescription des benzodiazépines et z-drugs du réseau canadien deprescribing.org :



*Références :

*Formulaire de soins aux personnes âgées, Farmaka CBIP-BCFI, disponible sur le site : <https://farmaka.cbip.be/fr/formulaire-p-a>, consulté le 11/09/2022.

¹ Martin P *et al.* JAMA 2018;320:1889-1898. ² Hansen RN *et al.* Am J Public Health 2015;105(8):e64-69. ³ Glass J *et al.* BMJ 2005;331(7526):1169. ⁴ Donnelly K *et al.* PLoS One 2017;12(4):e0174730. ⁵ O'Mahony D *et al.* Age Ageing 2015;44:213-218. 2/3

PROGRAMME DE SEVRAGE

Voici un exemple de programme de sevrage. Il est issu de la brochure EMPOWER développée par le Réseau canadien pour l'usage approprié des médicaments et la déprescription. (<https://www.reseaudeprescription.ca/ressources/>). Certaines personnes ont besoin de moins de temps ou de plus de temps. Il peut être adapté en fonction des besoins du patient. Si le médicament ne se coupe pas facilement, le pharmacien peut aider à trouver une alternative. Dans certains cas, l'emploi d'une préparation magistrale peut être utile. Les honoraires du pharmacien pour la préparation de celle-ci peuvent être remboursés par la mutuelle si elle est prescrite par le médecin traitant.

SEMAINES	PLAN DE SEVRAGE							✓
	LUN	MAR	MER	JEU	VEN	SAM	DIM	
1 et 2								
3 et 4								
5 et 6								
7 et 8								
9 et 10								
11 et 12								
13 et 14								
15 et 16								
17 et 18								

Légende			
	Pleine dose		La moitié de la dose
	Le quart de la dose		Aucune dose

Section 2

B.1. Remplissage du document: Pour chaque affirmation, veuillez indiquer votre degré d'accord avec celle-ci.

	Pas du tout d'accord	Plutôt en désaccord	Ni d'accord, ni en désaccord	Plutôt d'accord	Tout à fait d'accord
Le document est clair et bien présenté.	☐	☐	☐	☐	☐
Je comprends facilement ce que je devrais remplir en tant que pharmacien/médecin.	☐	☐	☐	☐	☐
Le temps pour lire le document et le compléter me semble acceptable.	☐	☐	☐	☐	☐

B.2. Evaluation du contenu du document: pour chaque affirmation ci-dessous, veuillez indiquer votre degré d'accord.

	Pas du tout d'accord	Plutôt en désaccord	Ni d'accord, ni en désaccord	Plutôt d'accord	Tout à fait d'accord
Je suis d'accord avec les alternatives aux benzodiazépines proposées dans le document.	☐	☐	☐	☐	☐
Les informations reprises dans ce document sont solides scientifiquement.	☐	☐	☐	☐	☐
Certaines informations reprises dans le document sont nouvelles pour moi.	☐	☐	☐	☐	☐

Si profession = pharmacien

B.3. Acceptabilité de la démarche: relation avec le médecin. Pour chacune des affirmations suivantes, cochez votre degré d'accord avec celle-ci.

	Pas du tout d'accord	Plutôt en désaccord	Ni d'accord, ni en désaccord	Plutôt d'accord	Tout à fait d'accord
J'accepterais d'adresser ce document à un médecin prescripteur que je connais.	☐	☐	☐		☐
J'accepterais d'adresser ce document à un médecin prescripteur que je ne connais pas ou peu.	☐	☐	☐	☐	☐
Communiquer avec le médecin au travers de ce document me semble être une idée intéressante.	☐	☐	☐	☐	☐
J'aurais peur de détériorer la relation que j'ai avec le médecin si je lui envoie ce document.	☐	☐	☐	☐	☐
Je pense qu'envoyer ce document au médecin prescripteur permettrait de favoriser la déprescription des benzodiazépines chez les personnes âgées.	☐	☐	☐	☐	☐

Section 2

Je pense qu'il est nécessaire de contacter le médecin prescripteur personnellement avant de lui adresser ce document.	☐	☐	☐	☐	☐
La communication avec le médecin prescripteur dans le cadre de la déprescription des benzodiazépines correspond à mes valeurs professionnelles.	☐	☐	☐	☐	☐

B.4. Acceptabilité de la démarche: relation avec le patient. Pour chacune des affirmations suivantes veuillez indiquer votre degré d'accord avec celle-ci.

	Pas du tout d'accord	Plutôt en désaccord	Ni d'accord, ni en désaccord	Plutôt d'accord	Tout à fait d'accord
Je serais à l'aise de proposer à un patient que je connais bien de communiquer avec son médecin prescripteur via ce document.	☐	☐	☐	☐	☐
Je serais à l'aise de proposer à un patient que je ne connais pas ou peu de communiquer avec son médecin prescripteur via ce document.	☐	☐	☐	☐	☐

Je pense que cette démarche pourrait renforcer le lien thérapeutique que j'ai avec le patient.	☐	☐	☐	☐	☐
En tant que pharmacien, c'est mon rôle pour le patient d'être proactif auprès du médecin par rapport à la déprescription des benzodiazépines chez les personnes âgées.	☐	☐	☐	☐	☐

C. Comment vous verriez-vous adresser ce document au médecin prescripteur?

Cochez la solution qui vous semble la meilleure.

Pour information, un e-mail ne peut pas contenir le document de proposition pharmaceutique pour des raisons de protection des données du patient (respect du RGPD), c'est pourquoi il ne fait pas partie des propositions possibles.

- ☐ Envoi par courrier postal
- ☐ Circulation du document via le patient

D. Introduire la démarche auprès du médecin prescripteur sera indispensable. Comment préféreriez-vous le faire ? Classez ces propositions de la meilleure à la moins bien selon vous.

- _____ Au moyen d'un courrier postal (un modèle serait mis à votre disposition)
- _____ En lui envoyant un e-mail (qui ne contient pas la proposition pharmaceutique)
- _____ En lui téléphonant directement

E. A votre avis, comment faudrait-il améliorer ce document?

--

Section 2

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F. Veuillez indiquer ici toutes les remarques ou commentaires que vous souhaiteriez faire à propos de ce document.

--

Merci d'avoir pris le temps de répondre à cette enquête !

Si profession = médecin généraliste

B.3. Acceptabilité de la démarche: relation avec le pharmacien. Pour chacune des affirmations suivantes, cochez votre degré d'accord avec celle-ci.

	Pas du tout d'accord	Plutôt en désaccord	Ni d'accord, ni en désaccord	Plutôt d'accord	Tout à fait d'accord
Je recevrais de façon positive ce document de la part d'un pharmacien que je connais.	☐	☐	☐	☐	☐
Je recevrais de façon positive ce document de la part d'un pharmacien que je ne connais pas ou peu.	☐	☐	☐	☐	☐
Je préférerais être contacté personnellement par le pharmacien (par email ou par téléphone) avant de recevoir ce document.	☐	☐	☐	☐	☐
Je pense qu'il est du rôle du pharmacien de m'interpeller au sujet d'une déprescription potentielle des benzodiazépines pour mes patients.	☐	☐	☐	☐	☐

Section 2

La collaboration avec le pharmacien dans le cadre de la déprescription des benzodiazépines chez les personnes âgées correspond à mes valeurs professionnelles.	☐	☐	☐	☐	☐
Je répondrais volontiers au pharmacien si je recevais un document de ce genre.	☐	☐	☐	☐	☐
Communiquer avec le pharmacien au travers de ce document me semble être une idée intéressante.	☐	☐	☐	☐	☐

B.4. Acceptabilité de la démarche: relation avec le patient. Pour chacune des affirmations suivantes veuillez indiquer votre degré d'accord avec celle-ci.

	Pas du tout d'accord	Plutôt en désaccord	Ni d'accord, ni en désaccord	Plutôt d'accord	Tout à fait d'accord
Recevoir ce document me donnerait une bonne opportunité pour entamer la discussion avec mon patient au sujet de la déprescription des benzodiazépines.	☐	☐	☐	☐	☐

Je crains de perdre la confiance du patient si le pharmacien m'interpelle au sujet d'une déprescription potentielle de benzodiazépines pour mon patient âgé.	☐	☐	☐	☐	☐
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C. Comment vous verriez-vous renvoyer ce document au pharmacien? Cochez le choix qui s'appliquerait.

Pour information, un e-mail ne peut pas contenir le document de proposition pharmaceutique pour des raisons de protection des données du patient (respect du RGPD), c'est pourquoi il ne fait pas partie des propositions possibles.

- ☐ Par courrier postal
- ☐ Via le patient
- ☐ Je ne souhaiterais pas renvoyer ce document au pharmacien.

D. A votre avis, comment faudrait-il améliorer ce document?

E. Veuillez indiquer ici toutes les remarques ou commentaires que vous souhaiteriez faire à propos de ce document.

Merci d'avoir pris le temps de répondre à cette enquête !

Section 2

Supplementary file 5. Changes to the D-PRESCRIBE intervention according to the Model for Adaptation Design and Impact framework			
What is modified: the content of the D-PRESCRIBE tools and the delivery mode of the D-PRESCRIBE intervention (see the table below reporting the nature of adaptations) Who participated in the adaptation decision-making: research team + 1 representative of each key stakeholder (patients, community pharmacists, general practitioner) + 1 expert in health communication. For whom/what is the adaptation made: the adaptation was made so that the intervention was acceptable for the patients (intervention recipients), community pharmacists (intervention deliverers), and general practitioners (intervention supporters). When did adaptation occur: pre-implementation			
A. Nature of the adaptations made in the EMPOWER brochure, goals for adaptation, and anticipated obstacles or justification.			
Page number	Nature of adaptation	Goals for adaptation	Anticipated obstacle/Justification
All pages	The main color was changed.	Soften the message	The orange color of the first page was disliked. The red color for the words FALSE on page 5 was perceived as "infantilizing" (as red is used at school to correct copies). As orange and red are associated with a warning and blue with sleep and benzodiazepine medication boxes, it was decided to replace the orange and red color with blue (throughout the brochure) but to leave key messages in red (title, warning on page 6).
1	The title of the brochure was changed to "You may be at risk".	Soften the message	"You are at risk" was considered too aggressive.
	Logos were replaced by logos of Belgian scientific societies that agreed to support this brochure.	Make the patient feel concerned	Belgian logos can be recognized by the patient and be perceived as proof of the quality of the brochure.
	The photo was replaced.		The original photo represents a lot of pills which seemed too far for patients taking only one BZRA/day (most Belgian patients)
	The wording "sedative-hypnotics" was replaced with "sleeping pills – tranquilizer".		"Sedative-hypnotics" was deemed too complex for patients. "Sleeping pills – tranquilizer" is used by the Belgian Public Health Federal services. We replaced this terminology to keep coherence with it.
	The sentence "You are taking a sleeping pill or a tranquilizer" was put before "You may be at risk".		Putting the sentence "you are taking a sleeping pill or a tranquilizer" before the brochure title was deemed more logical.

2	The photo was replaced.	Make the patient feel concerned	The original photo presented an Asian man who was perceived as too young for being aged 65 or more.
3	The order of the questions was changed. The wording of the questions was modified to be more specific (e.g., using "insomnia and/or anxiety" instead of "symptoms") or to shorten the sentences. The photo was replaced.	Provide important information	Rearranging the order of the questions allowed a more logical flow. Shortening the question allows better understanding, especially for less literate patients.
4	The photo was replaced.	Make the patient feel concerned	In Belgium, medications are packaged in boxes, not tins.
5	The photo was replaced.	Soften the message	The facial expression of the man in the original photo was perceived too negatively.
		Make the patient feel concerned	The original photo presented a man of Asian ethnicity. This ethnicity was perceived as too far from common ethnic communities living in Belgium.
			Keep coherence throughout the document
	Some vocabulary words were replaced (e.g., sedative-hypnotic → sleeping pills-tranquilizer)	Make the patient feel concerned	Use familiar vocabulary consistently throughout the brochure.
	The wording "these medications are not the best long-term treatment" was changed to "these medications are no longer the best long-term treatment".	Soften the message Maintain the relationship with the patient	The original affirmation was perceived as too aggressive for patients and too blaming for the healthcare providers.
	The answer "TRUE" was changed to "TRUE...temporarily". Some words about the potential difficulty of BZRA deprescribing were added.	Maintain the relationship with the patient	Adding some message of empathy and encouragement was judged necessary to avoid being perceived as too moralizing.

Section 2

	The sentence "Your body has probably developed a physical addiction to this medication" was changed to "Your body has probably developed a physical and psychological addiction to this medication".	Provide important information	Adding the psychological dimension of BZRA dependence was deemed necessary.
6	The order of the messages was rearranged.	Provide important information	It was judged necessary to improve the logical flow of the information
	The sentence "Except in special cases, these medications should never be taken" was removed.	Soften the message. Maintain the relationship with the patient	This affirmation was perceived as too aggressive for the patients and too blaming for the healthcare providers.
	Icons were replaced.	Make the patient feel concerned	One icon was judged as not explicit enough and the other as too confusing (the 2 last). The 3 others were kept very similar to the original ones.
7	The term "hangover" was replaced	Make the patient feel concerned	This term was perceived as inappropriate for older adults and not explicit for patients not drinking alcohol (e.g., Muslim people).
	A question about the tolerance phenomena was added.	Provide important information	Stressing somehow tolerance and dependence related to BZRA use was judged important.
	"Around the age of 65" was added to the paragraph "As you age".	Make the patient feel concerned	Some older patients did not feel concerned about aging.
	The wording and structure of the paragraph were slightly changed to improve clarity.	Provide important information	The sentence "Changes related to illnesses you may have had" was deemed confusing.

8	"Get exercise during the day" was replaced by "Stay active during the day".	Make the patient feel concerned	"Get exercise" was assimilated to "Do some sport" which was perceived as inapplicable for most older adults.
	Cola drinks and tea were added to substances to avoid.	Provide important information	Adding these widely used drinks was perceived necessary.
	What kind of information is to be found in the brochure "How to get a good night's sleep without medication" was added.	Provide important information Provide practical information	The list of behavioral tips was perceived as incomplete and too short. This addition was made to give an insight into the "How to get a good night of sleep" brochure's content where exhaustive information is to be found. Some tips such as doing breathing or relaxation exercises appeared too general. Adding the information that techniques are to be found in the brochure can help older adults apply the advice.
	Information about clinics specialized in treating sleeping problems was added.	Provide important information	These clinics are not well-known and might be a helpful resource for patients.
	A message about the possibility of personalized solutions to be found with the healthcare provider was added.	Maintain the relationship with the patient	Providing behavioral tips only was found to be potentially perceived as too discouraging for some patients.
9	The reference to group support was removed.	Make the patient feel concerned	Group support is not very common in Belgium.
	The order of the message was rearranged	Provide important information	Enhance the logical flow of help-seeking, from relaxation techniques to therapist consultation.
	Music therapy was added. A word about the availability of activities adapted for seniors was added. A message about whom to ask for more information about these activities was also added.	Provide important information Provide practical information	Some patients and HCP perceived that the original message could be disregarded because yoga or tai-chi was perceived as too difficult for older adults. It was found that providing more practical and concrete information could help older adults to engage in these activities.
	A word about specialized physicians for treating anxiety troubles was added.	Provide important information	Consulting a therapist or a psychiatrist is perceived as stigmatizing in Belgium. This sentence could help refer the patient to a psychiatrist.

Section 2

10	The photo was replaced. The age mentioned in the testimony was replaced by "75 years".	Make the patient feel concerned	The original photo was perceived as presenting a too-old woman compared to the age of 65 years mentioned in the brochure. The facial expression was perceived as not positive enough.
	Lorazepam was changed into lormetazepam. A well-known brand name was added.	Make the patient feel concerned	Lormetazepam is a molecule frequently used by older adults in Belgium. Patients do not often know the molecule they are taking.
	The name of the lady was replaced	Make the patient feel concerned	The original family name "Robinson" is not a common Belgian family name.
	A sentence about the provided tapering scheme being an example to be adapted according to patients' needs was added. The mention "example of" was added in the title of the tapering scheme.	Make the patient feel concerned Maintain the relationship with the patient.	The tapering scheme was perceived as too complex, too long, or too short for some patients.
11	Information about pharmacists' help with galenic, the possibility of obtaining magistral preparations, and reimbursement opportunities were added.	Provide practical information	This practical information is not well-known by older patients. Reimbursement opportunities are new.
	The third question was replaced with "Are there other solutions to this medication"?	Provide important information	The original sentence was perceived as referring more to a pharmaceutical treatment than to the behavioral treatment explained in this brochure.
12	An icon referring to the pharmacist was added.	Maintain the relationship with the patient	In the original brochure, there is only an icon with a stethoscope (referring to the physician). Visually referring to the pharmacist was perceived as needed.
	The reference to the deprescribing website was removed		

B. Nature of the adaptation made in the pharmaceutical opinion, goals for adaptation, and anticipated obstacles or justification.		
Nature of adaptation	Goals for adaptation	Anticipated obstacle/Justification
Adding a sentence that the process aims at emphasizing the collaboration.	Preserve a good pharmacist-GP relationship	Participants feared the document to be perceived as blaming or moralizing by the GP
Replacing the wording "Your patient" with "Our patient".		
"Replacing the wording "Sedative-hypnotic us is not recommended" with "Safer alternatives exist to minimize risks".		
The name of the document was changed to "pharmaceutical proposal" instead of "pharmaceutical opinion".		
Proposals were added for the pharmacist to tick specific risk factors observed with the patient	Enhance document clarity	As all older adults shared the same risks of falls, fractures, etc. due to BZRA use, pharmacists did not know what to write in the blank space to specify risks.
	Provide important information	GPs felt that pharmacists have a better overview of the patient's treatment (including what is prescribed by other physicians). These propositions could provide important extra information to the GP.
A blank space to specify the dosage was added	Provide important information	Provide extra information to the GP

Section 2

Proposed alternatives to tick by the physician were restructured as information about current guidelines. Two boxes indicating explicitly what is to be filled in by the pharmacist and by the physician were added. The possibility of replacing BZRA with an SNRI was removed.	Enhance document clarity	Neither pharmacists nor GP understood very well who was supposed to complete the alternative box. Besides, the roles regarding these alternatives were unclear.
The sentence indicating a replacement by another molecule as well as the box for certifying this document stands for a new prescription were removed.	Refer to national clinical guidelines	Belgian clinical guidelines do not support SNRI use to replace a BZRA.
In the pharmacist-specific box, a space for indicating the actions undertaken by the pharmacists (including the provision of the EMPOWER brochure) was added. A space to provide proposals in terms of molecules, tapering, and galenic was added.	Adapt to the Belgian Healthcare system	As pharmaceutical opinions are not used in Belgium, this document does not comply with Belgian requirements for a prescription, which is mostly electronic.
In the GP-specific box, only three choices were left to select: modifying the prescription, initiating a tapering scheme (with a reference to the electronic prescription), and no change to the prescription. A blank space to provide a date for the next re-evaluation was added.	Provide important information Preserve a good pharmacist-GP relationship	HCP felt that if the pharmacist's implication in the document was higher, the acceptability of the document might be enhanced. Besides, some GPs were interested in having some extra pharmaceutical advice.
	Adapt to the Belgian Healthcare system Provide important information	This answer is short, practical, and by the Belgian prescribing system. The re-evaluation date was added for the pharmacist to know when it would be appropriate to contact again the GP.

The original reference to American guidelines was replaced by national references.	Refer to national clinical guidelines	Beers' criteria are not well-known in Belgium contrary to STOPP criteria. A local pharmaceutical platform (CBIP) provides local recommendations in terms of prescribing. It is widely used in Belgium and known by both pharmacists and GPs.
A QR code referring to the Canadian deprescribing algorithm was added.	Provide important information	Providing more practical information on how to deprescribe was perceived as necessary. Adding a QR code was perceived to provide this information without overloading the document.
The proposal presents 2 tapering options: 1. The EMPOWER tapering program with a mention that this tapering scheme is an example (to use with some freedom depending on the patient). A sentence was added to emphasize that the pharmacist could help if the pill is difficult to cut. 2. Three stepwise (5, 7, or 10 steps) tapering programs using capsules containing a decreasing percentage of the compound, prepared by the pharmacist. Reimbursement opportunities regarding these preparations were mentioned.	Provide important information	In February 2023, a national pilot program aiming for BZRA deprescribing through stepwise reduction using capsules prepared by the pharmacist was launched. These stepwise programs were added to fit with this new opportunity.
A "non-recommended alternatives" chunk was added.	Provide important information	Some HCP felt that melatonin or plant alternatives such as valerian were lacking. However, these alternatives are not recommended by national guidelines due to a lack of evidence of their efficacy. We decided to group this information with the original information on trazodone and z-drug use as non-recommended alternatives.
Legend: BZRA : Benzodiazepine receptor agonists; CBIP : Centre Belge d'Information Pharmacothérapeutique (Belgian Center for Pharmacotherapeutic Information); D-PRESCRIBE : Developing Pharmacist-Led Research to Educate and Sensitize Community Residents to the Inappropriate Prescriptions Burden in the Elderly; GP : General practitioner; HCP : Healthcare professionals; SNRI : Serotonin-norepinephrine reuptake inhibitor; STOPP : Screening Tool of Older Person's Prescriptions		

Section 2

Supplementary file 6 : Adapted EMPOWER brochure

The adapted brochure is available online: see [Belgian EMPOWER brochure](#) or scan the following QR code.



Supplementary file 7: Pharmaceutical proposal

UCLouvain

PROPOSITION PHARMACEUTIQUE BASÉE SUR LES GUIDELINES ACTUELLES

Déprescription des benzodiazépines et z-drugs chez les personnes âgées

La collaboration médecin-pharmacien-patient est une approche efficace pour favoriser la déprescription des benzodiazépines chez les personnes âgées*. Cette proposition pharmaceutique s'inscrit dans cette démarche collaborative.

Nom du pharmacien : _____
 Adresse : _____
 Tél : _____
 Email : _____

A l'attention du Dr _____
 Adresse : _____

Date : ____/____/____

Notre patient e, _____
 né e le ____/____/____, prend actuellement la/les
 benzodiazépine(s)/z-drug(s) suivante(s) + posologie :

pour traiter son anxiété et/ou son insomnie.
 Une démarche de déprescription pourrait être envisagée
 car notre patient présente les facteurs de risque suivants :

(à cocher par le pharmacien) :

- ☐ Utilisation prolongée ≥ 4 semaines
- ☐ Utilisation de ≥ 3 médicaments du système nerveux central
- ☐ Utilisation concomitante avec des opioïdes
- ☐ Utilisation au-delà de la dose recommandée
- ☐ Autre (à préciser) : _____

D'autres solutions plus sûres existent (voir ci-contre) pour
 minimiser les risques de chutes et de fracture (2x plus
 élevés), de troubles cognitifs (2x plus élevés) et d'accident de
 voiture (5x plus élevés) 2-4.

Fondements et directives cliniques sur lesquels
 est basée la proposition :

Le formulaire de soins aux personnes âgées de
 Famaka - CBIP ne recommande pas l'emploi des
 benzodiazépines et z-drugs dans le traitement de
 l'insomnie et de l'anxiété (sauf situation aigue, pour
 un traitement très limité dans le temps)*.
 La déprescription progressive est recommandée
 en cas de traitement chronique (critères STOPP) 5.

Alternatives recommandées :

- Envisager la thérapie cognitivo-comportementale
 dont l'efficacité a été démontrée pour traiter tant
 l'insomnie que l'anxiété et pour aider le patient
 à cesser les benzodiazépines et z-drugs (voir
 brochure : « Comment obtenir une bonne nuit
 de sommeil sans médicaments », disponible
 sur le site :
<https://www.reseaudaprescription.ca/ressources/>

- Encourager l'adoption de changements de
 comportement pour traiter l'insomnie et l'anxiété
 comme la relaxation, la gestion des habitudes
 alimentaires, etc.

- Dans le traitement des troubles anxieux
 généralisés, envisager la possibilité de prescrire
 un ISRS, si nécessaire. Note : Ces médicaments
 sont également associés au risque de chutes
 chez les personnes âgées, mais leur profil de
 risque est moindre.

- Débuter et suivre un programme de sevrage.
 Un exemple de programme est disponible au
 verso.

Alternatives non recommandées :

Attention, il n'est pas recommandé de substituer
 une benzodiazépine par de la trazodone, d'autre
 antidépresseurs sédatifs à faible dosage ou tout
 autre médicament de classe z.*

L'efficacité de la mélatonine ou de la valériane pour
 les troubles du sommeil n'est pas scientifiquement
 établie, c'est pourquoi le CBIP ne recommande
 pas l'usage de ces deux molécules.*

Cadre à remplir par le pharmacien

Actions entreprises par le pharmacien

- ☐ Une brochure éducative sur les risques à l'utilisation
 des benzodiazépines et les alternatives possibles a
 été distribuée au patient. Cette brochure comprend
 également le schéma de sevrage présenté au verso.
- ☐ Autre (précisez) : _____

Avis du pharmacien (facultatif) : Après discussion

avec le patient, je proposerais (indiquer ici d'éventuelles
 propositions en termes de molécule, galénique, plan de
 sevrage...): _____

Cadre à remplir par le médecin (s.v.p. cochez toutes
 les cases qui s'appliquent au patient et retournez ce
 document au pharmacien)

Décision du médecin : Après discussion avec le patient,
 il a été décidé de :

- ☐ Modifier la prescription actuelle
 (voir prescription électronique)
- ☐ Débuter un programme de sevrage
 (voir prescription électronique)
- ☐ Aucun changement à la prescription jusqu'à la prochaine
 réévaluation prévue le ____/____/____. Nom : _____

Date : ____/____/____

Numéro INAMI : _____

PROGRAMME DE SEVRAGE

Voici un **exemple** de programme de sevrage.

Il est issu de la brochure EMPOWER développée par le Réseau canadien pour l'usage approprié des médicaments et la déprescription. (<https://www.reseaudeprescription.ca/ressources/>). Certaines personnes ont besoin de temps ou de plus de temps. Il peut être adapté en fonction des besoins du patient. Si le médicament ne se coupe pas facilement, le pharmacien peut aider à trouver une alternative.

SEMAINES	EXEMPLE DE PLAN DE SEVRAGE							✓
	LUN	MAR	MER	JEU	VEN	SAM	DIM	
1 et 2								
3 et 4								
5 et 6								
7 et 8								
9 et 10								
11 et 12								
13 et 14								
15 et 16								
17 et 18								
Légende								
Pleine dose								
La moitié de la dose								
Le quart de la dose								
Aucune dose								

Références : "Formulaire de soins aux personnes âgées, Famaka CBJP-BCFI, disponible sur le site : <https://famaka.cbjp.be/fr/formulaire-cs>, consulté le 11/05/2022." Martin P et al. JAMA 2018;320:1898-1899.² Hansen RN et al. Am J Public Health 2015; 105(8):e64-69.³ Glass J et al. BMJ 2005;331(7526):1169-4.⁴ Donnelly K et al. PLoS One 2017; 12(4):e0174730.⁵ O'Mahony D et al. Age Ageing 2015;44:213-218.

Dans certains cas, l'emploi d'une **préparation magistrale** peut être préférable. Le sevrage se fait alors **par paliers**. Chaque palier peut durer 10, 20 ou 30 jours. Plusieurs schémas sont possibles :



A partir du 1/02/2023 et sous certaines conditions, les honoraires du pharmacien pour la préparation des magistres sont pris en charge par la mutuelle.



Besoin de plus d'information sur comment et pour qui déprescrire les benzodiazépines et z-drugs? Utilisez l'algorithme de déprescription développé par le réseau canadien pour la déprescription. Scannez le code Qr.

SECTION 3: Evaluation of an implementation program to BZRA deprescribing

Chapter 5. Feasibility of the adapted D-PRESCRIBE intervention in the Belgian community setting: protocol for a cluster randomized controlled trial (END-IT CS study).

Chapter 6. Feasibility of the adapted D-PRESCRIBE intervention to favor benzodiazepine deprescribing in the Belgian community setting: results from a cluster randomized controlled trial (END-IT CS study).

Chapter 5. Feasibility of the adapted D-PRESCRIBE intervention in the Belgian community setting: protocol for a cluster randomized controlled trial (END-IT CS study)

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Submitted manuscript

Section 3

STUDY SPONSOR

UCLouvain, Belgium

AUTHORS' CONTRIBUTIONS

CP, TC, JA, PE, ST, SH et AS conceived the study and were involved in the writing of this protocol. JA and ST developed the economic part of this protocol specifically. SH and AS equally contributed to this work and share the last authorship.

ACKNOWLEDGEMENTS

The authors would like to thank older adults and pharmacists who contributed to the development of this research protocol. We also thank Prof. Catherine Legrand for providing her statistical expertise regarding the sample size calculation, and Ms. Anne-Gaëlle Peters for providing legal support with the writing of the research conventions.

FUNDINGS

This work is supported by a grant from EBPracticenet (Projet d'implémentation EBPracticenet 2023), by a grant (Crédit de Recherche) from the Fonds National de la Recherche Scientifique (n°40013898), and by an Actions de Recherche Concertées (DI-PRESCRIBE project; 22/27-124). Funders have no role in study design, collection, management, analysis, and interpretation of data.

COMPETING INTERESTS

Neither the principal investigator nor other research team members have any financial or competing interest to declare.

ABSTRACT

INTRODUCTION. Benzodiazepine receptor agonists (BZRA) deprescribing interventions are needed to tackle high BZRA use in the older population. This study aims to assess the feasibility of the D-PRESCRIBE intervention, adapted from Canada to the Belgian community setting. This pharmacist-led intervention comprises a patient educational brochure and a pharmacist-to-prescriber communication tool.

METHODS AND ANALYSIS. We will conduct a feasibility study of a cluster randomized controlled trial involving 8 to 10 community pharmacies (clusters) and aiming to recruit 56 to 80 patients (≥ 65 years). Intervention pharmacies will deliver the adapted D-PRESCRIBE intervention and control pharmacies, usual care. Patients will be blinded to group allocation. Quantitative data will be collected at baseline, three months, and six months through patients' and pharmacists' questionnaires. Implementation outcomes, mechanisms of impact, and contextual factors will be measured and analyzed using descriptive statistics. The feasibility of conducting the study will be assessed through participation rate, completeness of the data, and a satisfaction survey. If data permits, an exploratory cost-effectiveness analysis will be performed. To gain a deeper understanding, interviews will be conducted with intervention patients and pharmacists after the 6-month quantitative data collection. The Theoretical Domains Framework will be used as a deductive framework for analysis.

ETHICS AND DISSEMINATION. This study was approved by the Ethics Committee of CHU UCL Namur (NUB: B0392023000036). Participants will receive a summary of the results. Results will also be disseminated through the organization of a local symposium and a peer-reviewed publication.

TRIAL REGISTRATION. This protocol was registered on the ClinicalTrials.gov website (NCT05929417).

Section 3

INTRODUCTION

Benzodiazepine receptor agonists (BZRA) are medications frequently prescribed in the treatment of insomnia and anxiety. However, they have well-known potential side effects that comprise a higher risk of falls, hip fractures, car accidents, tolerance and dependence, and cognitive decline [1-5]. Older adults are at higher risk of these side effects [6]. For these reasons, current guidelines strongly recommend avoiding their use in older adults or stopping it after four weeks or two weeks if taken for insomnia [7, 8]. Despite these recommendations, BZRA are frequently taken long-term in older adults [9]. In Belgium, 14.7% of older adults aged 65-74 years and 24.6% of older adults aged ≥ 85 years take a BZRA [10]. Deprescribing interventions are therefore needed. Deprescribing is defined by Farrell et al. as *“the planned and supervised process of dose reduction or stopping medication that may be causing harm or are no longer providing benefits”* [11](p.2).

Decreasing BZRA use has been on the Belgian political agenda for many years. Several campaigns were launched aiming to raise awareness about the risks of BZRA use and to promote alternatives, the latest was published in September 2023 [12, 13]. These campaigns, however, were not tailored for older adults particularly, whose needs may be specific compared to the general population. For example, Green et al. showed that older adults had a strong preference for talking about side effects when discussing BZRA deprescribing [14] while the main message of the penultimate campaign focused on non-pharmacological alternatives for sleep and anxiety.

New interventions can be developed from scratch or adapted from interventions proven effective in other contexts [15]. The latter is resource-saving [16]. Therefore, we adapted the Canadian D-PRESCRIBE intervention to the Belgian community setting. This intervention targeted community-dwelling older adults specifically and demonstrated high efficacy in BZRA deprescribing (43% in the intervention group vs. 9% in the control group) in Canada [17]. It was led by the pharmacist and comprised two components: a patient educational brochure (EMPOWER) given by the pharmacist to the patient and a written pharmaceutical opinion sent by the pharmacist to prescribers inviting them to reconsider BZRA prescribing according to currently available guidelines [17]. We adapted this intervention following recommendations from the ADAPT guidance and from the new Medical Research Council (MRC) framework on developing and evaluating complex interventions [15, 18]. At the end of the adaptation process, some uncertainties remained about the uptake of the adapted pharmaceutical opinion by patients, pharmacists, and GPs [19]. These uncertainties were mostly related to the discomfort of pharmacists and GPs with the pharmacists taking a more proactive role than usual in Belgium.

Testing the feasibility of a new or adapted intervention is recommended to identify challenges before undertaking a full effectiveness trial [15, 18]. The novelty of this adapted intervention in Belgium justifies the need for such study.

This article describes the protocol for a feasibility study. Our research objectives are three-fold:

1. To assess the feasibility of conducting the study, especially in terms of recruitment and data collection processes needed for a full trial assessing the effectiveness and cost-effectiveness of the intervention.
2. To assess the feasibility of the adapted D-PRESCRIBE intervention in Belgium.
3. If considered feasible with regards to collected data, to explore the potential cost and effectiveness of the intervention.

Results will allow us to decide 1) if the intervention needs to be adapted and if so, how this could be done and 2) whether conducting a full implementation trial is worth considering.

METHODS

Intervention development

The adaptation process of the D-PRESCRIBE intervention has been described elsewhere [19]. Briefly, we first identified the “core functions” of the D-PRESCRIBE intervention, which are “*the underlying mechanisms of change that make an intervention effective*”[20]. In the frame of an adaptation, these core functions must remain unchanged to preserve the integrity of the intervention [20]. Then, we conducted interviews and group discussions with key stakeholders (patients, pharmacists, and general practitioners (GP)) to assess the acceptability and needed changes in the D-PRESCRIBE components. The brochure and pharmaceutical opinion were adapted accordingly while preserving their core functions. In addition, a questionnaire survey was disseminated to GPs and pharmacists to explore at a broader scale the acceptability of the first adaptation of the pharmaceutical opinion, renamed “pharmaceutical proposal”. This survey allowed further improvement of the pharmaceutical proposal.

Study design, setting, and participants

The SPIRIT checklist recommendations for interventional trials [21] and the CONSORT checklist extension to randomized pilot and feasibility trials [22] guided the development of this protocol (See the SPIRIT checklist in Appendix 1). This protocol

Section 3

was informed by the protocols of the EMPOWER and D-PRESCRIBE studies [23, 24]. Procedures of the original D-PRESCRIBE trial were reviewed with 7 community pharmacists during a group discussion conducted in addition to the intervention adaptation process. Trial procedures were adapted according to pharmacists' real-life practice. This protocol (version 1, in date of 4th April 2023) was registered on the ClinicalTrials.gov website (NCT05929417).

We will conduct a feasibility study of a cluster-randomized, parallel-group, controlled trial in the community setting. Community-dwelling older adults will be recruited through French-speaking community pharmacies in Brussels and Wallonia, each pharmacy forming a cluster. The eligibility criteria for pharmacies and older adults are described in Table 1.

Table 1: Eligibility criteria		
	Inclusion criteria	Exclusion criteria
Pharmacies	- Using a dispensing software that allows identification of eligible patients based on their age, medication, and number of visits during the 12 previous months. - to be located in Brussels or in a French-speaking municipality at maximum 1h-1h30 time travel from Brussels.	- None.

Patients	- Age ≥ 65 years. - Taking a BZRA for ≥ 4 weeks (ATC codes: N05BA, N05CD, N05CF and N03AE01). - Being a regular patient at the community pharmacy (defined as ≥ 4 visits/12 previous months).	- Severe mental illness (assessed through having an active prescription of any antipsychotic medication). - Dementia or significant cognitive impairment (assessed through an active prescription or any past prescription during the last 12 months of anticholinesterase inhibitors or memantine) and/or pharmacist's judgment). - Known ongoing alcohol withdrawal. - Ongoing BZRA withdrawal at the time of recruitment. - Patients unable to read or communicate in French.
Notes: BZRA : Benzodiazepine receptor agonists; ATC : Anatomical Therapeutic Classification		

Sample size

We have based our sample size estimation on the EMPOWER trial results, which yielded 27% of BZRA deprescribing at 6 months in the intervention group and 5 % in the control group [25]. This estimation only considered the effect of the EMPOWER brochure and not the effect of the pharmaceutical opinion which resulted in higher deprescribing rates in Canada (intervention group: 43%, control group: 9%, 34% risk difference). Considering a power of 80%, a statistical significance of 5%, a cluster size of 7-8 patients, and an intraclass correlation coefficient of 0.05 (lowest value) or 0.50 (highest value), we have estimated that the required sample size for a full implementation trial would be between 88 and 300 patients. For this feasibility study, we aim to recruit 56 to 80 participants, within 8 to 10 pharmacies. This sample will represent approximately 20 to 25% of the maximal required sample size. We expect this sample to allow us to inform sufficiently our research objectives and we will further refine the sample size calculation for a full trial.

Recruitment strategies

Pharmacies

Pharmacies will be contacted through several channels: professional associations, social and professional networks, and university networks. Information sessions will

Section 3

be held online to inform interested pharmacists about the details of the study. Depending on the number of interested pharmacies, we will include pharmacies with a variety of localization (urban or rural) and type of practice (independent or cooperative pharmacy).

A financial compensation will be granted to every participating pharmacy. All pharmacies will receive 40 euros per included patient for recruitment and data collection. Additionally, intervention pharmacies will receive 25 euros per included patient for the intervention implementation. The compensation was based on the Canadian payment fee for the pharmaceutical opinion in 2022 (21.25 CAD\$)[26]. This compensation is also close to the fee received for patient education for appropriate use of inhaled corticoids in the treatment of asthma in Belgium (21.89 €)[27]. A research convention will be signed between UCLouvain and pharmacies to formalize the collaboration during the study.

Patients

Pharmacists will be responsible for selecting patients and establishing first contact with potential participants. To limit the burden on pharmacists, the research team will be responsible for providing comprehensive information about the study and for obtaining patients' consent. Practically, pharmacists will establish a list of all patients meeting the inclusion criteria using their dispensing software. Following this list, they will contact patients in person at the pharmacy, by phone, by mail, or by e-mail. The pharmacist will explain the study in broad terms and ask for patients' oral agreement to be contacted by the research team. A letter and a conversation guide will be provided to pharmacists. Within four to six weeks, pharmacists will continue until 10-15 patients agree to be contacted by the research team or after the list of eligible patients is covered. From then, pharmacists will stop contacting patients, even if the target is not reached. As soon as patients agree to be contacted, the research team will phone them and ask to confirm their interest in participating in the study. If so, an appointment will be arranged at the patient's home to provide detailed information about the study and answer any questions patients may have. Patients will have to sign an informed consent form to finalize their inclusion in the study. To avoid recruiting only patients already open to BZRA deprescribing, patients will be told that the trial aims to favor BZRA reevaluation (not BZRA deprescribing). Indeed, BZRA deprescribing will only occur if the patient agrees, after shared decision-making with their GP. Patients will not receive any compensation for their participation in the study.

We plan a retention strategy similar to the YAWNS NB study, which is a randomized controlled trial also investigating BZRA deprescribing in older adults [28]. A postal reminder will be sent to participants that would no longer be reachable by phone. If the

length of the phone interview appears to be the reason of patients' drop-out, we will propose a shorter data collection to the participant.

Intervention and control group

Intervention group

Patients in the intervention group will first receive the adapted EMPOWER brochure during a face-to-face contact with their pharmacist. This brochure aims to increase knowledge and concerns about BZRA use and to empower patients by increasing their self-efficacy [29]. Then, the pharmacist will ask patients' oral consent to send the pharmaceutical proposal to the prescriber in a time-period of maximum 2 weeks. This component aims 1) to increase physicians and pharmacists' knowledge about current guidelines regarding BZRA use in older adults and therefore increasing motivation and capabilities to support BZRA deprescribing and 2) to provide tripartite communication about BZRA deprescribing and therefore limiting clinical inertia around BZRA deprescribing [23]. A letter introducing the pharmaceutical proposal to the prescriber will be provided to pharmacists. Three options will be available for the pharmacist to send the document: postal mail, a phone application or an electronic mailbox, the two latter being specifically dedicated to secure information exchange between healthcare professionals.

Control group

Patients in the control group will receive usual care. Usual care may comprise education about BZRA use (i.e.: providing information usually given in a day-to-day routine) but will not include proactive information on BZRA deprescribing from the pharmacist. Control pharmacies and patients will have access to the brochure and pharmaceutical proposal after the 6-month follow-up.

Random allocation of the intervention

Similarly to the CHARMER study, an unbalanced study design will be used to prioritize the testing of the intervention feasibility [30]. Six pharmacies will be allocated to the intervention group and four pharmacies to the control group. The randomization of each pharmacy will occur when the baseline data collection is complete. A computer-generated randomization (using R software) will be performed by a member of the research team involved neither in the recruitment nor in the data collection.

Blinding

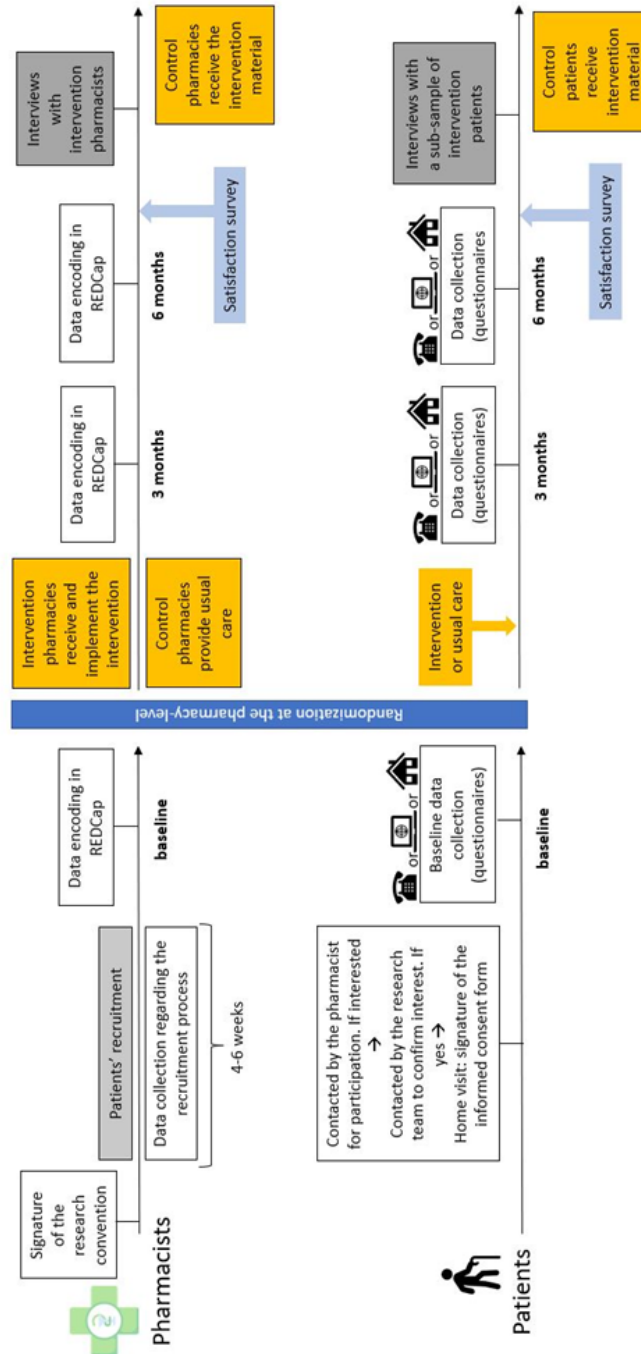
Our data collection addresses many topics related to BZRA use, making impossible to leave patients uninformed about study's goals using the words "medication

Section 3

optimization trial”, as was done in the EMPOWER and D-PRESCRIBE trials [23, 24]. However, as in the D-PRESCRIBE trial, we will blind patients to their group allocation by telling them that the intervention could occur anytime between a few weeks and 6 months after inclusion in the study. However, pharmacists’ blinding will not be possible. Pharmacists will be told about their allocation directly after the randomization but asked not to disclose this information to the patient.

Data collection and management

Figure 1 presents the study timeline for both pharmacists and patients and the different data collection points.



Pharmacy icon made by Freepik from www.flaticon.com

Figure 1. Study timeline

Section 3

Quantitative data

Quantitative data will be collected from both the patient and the pharmacist at 3 time points: at baseline, at 3 months, and at 6 months (Table 2 and Table 3). For these data, REDCap, a secure application for encoding, managing, and storing research data, will be used as electronic case report form [31]. Two databases will be created, one for patient data and one for pharmacist data. Patients' data will be collected by both the research team and the pharmacists. The research team will collect data preferably by phone or videoconferencing. Home visits will be organized if needed. Data collected during a phone or video-conference interview will be directly encoded in REDCap. In case of a home visit, paper questionnaire will be used, and data will be encoded afterwards. Pharmacists will encode patients' data and their personal data directly in REDCap. Pharmacists will only be able to access their patients' data and forms they must complete into REDCap.

Supplementary data will be collected. First, a recruitment form will be completed by the pharmacist for each potential participant. They will return this form by email to the research team. Second, pharmacists and patients will anonymously be surveyed after the study to assess their satisfaction regarding the study conduction procedures. Pharmacists will receive a link to an online survey, patients a mailed questionnaire. These supplementary data will be stored in an Excel file.

Table 2: Feasibility evaluation: collected data and time schedule				
Measure	Collected Data	Time points		
		Baseline	3m	6m
Feasibility of the study conduction				
Recruitment process	Patients' participation rate; Time to recruit patients; Differences between participants and non-participants according to age and gender; Means of contact of between pharmacists and patients	x		
	Time needed to recruit the pharmacies (in weeks); Pharmacists' satisfaction with the recruitment process			x
Data collection process	Patients' retention rate (+ reasons for withdrawal)	x	x	x
	Completeness of patient-centered data (i.e.: number of variables presented in Table 3 with few or no missing data)	x	x	x
	Pharmacists' satisfaction with the data collection process (3 items)			x

Study in general	Pharmacists' and patients' satisfaction with the contacts with the research team; Pharmacists' satisfaction with their participation in the study			x
	Patients' satisfaction with their pharmacist during the study			x
Feasibility of the intervention: Implementation fidelity				
Adherence at the pharmacist level	Number of brochures given; Number of pharmaceutical proposals sent to the GP; Means used to send the pharmaceutical proposal to the GP; Reasons for not giving the brochure; Reasons for not sending the pharmaceutical proposal		x	(x)
Patients 'responsiveness*	Number of brochures received; Interest in the brochure		x	(x)
	Number of patients that initiated a conversation about BZRA deprescribing with the prescriber; Number of patients that tried to reduce or stop their BZRA; Number of patients that successfully reduced or stopped their BZRA; Reasons for not discussing BZRA deprescribing with the prescriber; Reasons for not attempting BZRA deprescribing; Reasons for deprescribing failure		x	x
Pharmacists 'responsiveness	Number of drop-out pharmacies and reasons for drop-out; Satisfaction with the implementation of the intervention (4 items)			x
GPs' responsiveness	Number of physicians that answered the pharmaceutical proposal		x	x
	Number of physicians that altered (or not) the prescription		x	x
	Number of physicians that switched to another molecule (+molecule involved)		x	x
	If a withdrawal was undertaken: chosen tapering options (e.g. specialty or capsules made by the pharmacist)		x	X

Section 3

Feasibility of the intervention: Mechanisms of impact				
Mechanisms of impact at the patient level	Knowledge about BZRA (5 questions: true or false); Self-efficacy regarding BZRA deprescription (Medication reduction self-efficacy scale [32]) (1 item); Intention regarding BZRA deprescription (rPATD-BZRA) (2 global items of the scale)	x	x	x
Mechanisms of impact at the pharmacist level	Perceived knowledge regarding BZRA deprescribing (4 items); Perceived skills regarding BZRA deprescribing (1 item); Motivation for BZRA deprescribing (1 item); Ability in BZRA deprescribing (5 items adapted from a previous study [33]); Prioritization of BZRA deprescribing (2 items) (Shapoval et al, <i>in preparation</i>)	x	x	x
Feasibility of the intervention: Contextual factors				
Contextual factors at the patient level	For how long patients have known their GP; For how long patients have known their pharmacist; Type of GP remuneration (i.e., fee-for-service or per capita); Type of GP practice (i.e., solo or in a group of practice); Patients' trust in their GP (one item from the Wake Forest Trust in Physician scale [34]; one item from the Wake Forest Trust in Physician scale [34]); Patients' trust in their pharmacist (one item adapted from the Wake Forest Trust in Physician scale [34]); Patient health status (EQ-5D-5L), Patients' number of previous BZRA deprescribing attempts	x		
Contextual factors at the pharmacist level	Pharmacist's professional experience (time since graduation); Setting of the pharmacy (rural or urban); Type of pharmacy (independent or chain pharmacy); Pharmacists' seniority in the pharmacy (Since how long he/she has worked in this pharmacy); Duration of pharmacist-GPs collaboration (since how many years the pharmacist has known the prescriber (GP) of each included patient); Quality of	x		

	collaboration with the prescriber (Attitudes Towards collaboration Instrument for Pharmacists (ATCI-P, interactional determinants) 10 items [35]); Participation in local GP-pharmacists concertation			
Notes: BZRA : Benzodiazepine receptor agonists; GP : General practitioner * Data collected within the shortened data collection (retention strategy)				

Table 3: Additional patient-centered outcomes: collected data and time schedule				
Measure	Collected data or measure instrument	Time points		
		Baseline	3m	6m
Socio-demographic data ^a	Age, gender, education level, living arrangement	x		
Medication use ^{b*}	Number of chronic regular prescribed medications	x	x	x
BZRA use ^{b*}	Total number of BZRA taken, BZRA brand names, BZRA dosages, BZRA frequency of use	x	x	x
BZRA use history ^a	Duration of BZRA use, main reason for BZRA use, if the current prescriber is the initial prescriber of BZRA, if the initial prescription occurred on personal request, if the initial prescription occurred during hospitalization, if the patient already tried to stop his BZRA, number of previous BZRA deprescribing attempts	x		
Prescribed or over-the-counter sleep or anxiety medication use ^b	Use of melatonin, phytotherapy, or complement for sleep or anxiety (number of medications, brand names, dosage, frequency of use)	x	x	x
Antidepressant use (ATC N06) ^c	Use of antidepressant (number of medications, brand names, dosage, frequency of use)	x	x	x
Opioid use (ATC N02) ^c	Use of opioids (number of medications, brand names, dosage, frequency of use)	x	x	x

Section 3

Patient's attitude toward BZRA deprescribing ^{a#}	rPATD-BZRA (13 items) [36]	x	x	x
Quality of life ^{a*#}	EQ5D-5L (5 items) + Visual analogue scale (VAS)[37]	x	x	x
Quality of sleep ^{a#}	Insomnia Severity Index (7 items) [38]	x	x	x
Anxiety ^{a#}	Geriatric Anxiety Inventory-SF (5 items) [39]	x	x	x
Falls ^a	Fall since the last 6 months or last contact	x	x	x
Health care use ^a	Number of visits (related to sleep, anxiety, BZRA use) to GP, pharmacist, specialist physician, psychologist or psychotherapist, emergency room, hospitalization since the last contact		x	x
Healthcare expenses ^a	Amount usually spent for a GP consultation	x		
^a Data collected by the research team ^b Data collected by both the research team and the pharmacist ^c Data collected by the pharmacist [*] Data collected within the shortened data collection (retention strategy) [#] Copyright license and rights to use these questionnaires were obtained Notes: ATC : Anatomical therapeutical classification; BZRA : Benzodiazepine receptor agonist; GP : General practitioner				

Qualitative data

Semi-structured interviews will be conducted by a trained psychologist with pharmacists and a sub-sample of patients in the intervention group, after the 6-month quantitative data collection is ended. Interviews will take place at patients' home or at the working place (for pharmacists). Oral consent will be asked before participation for pharmacists. Patients will be selected purposively to ensure enough diversity in deprescription status (successful, did not try, failed), and previous BZRA deprescribing attempts (yes vs. no). We plan to interview two patients from each intervention pharmacy. This predefined sample could be adapted depending on emerging results. Patients will have to sign a specific consent form to participate in this interview.

Outcome measures

Feasibility of conducting the study

Table 2 reports outcome measures assessing the feasibility of the recruitment and data collection process. Patient-centered data will be collected as they would be for a full trial study assessing the effectiveness and cost-effectiveness (Table 3). It will comprise sociodemographic data, data on healthcare providers, medication use, BZRA use and history of BZRA use, patient's attitude towards BZRA deprescribing (rPATD-BZRA questionnaire [36]), quality of life (EQ-5D-5L [37]), insomnia (Insomnia Severity Index (ISI) [38]), anxiety (GAI-SF [40]), falls, healthcare use and expenses. Feasibility of the data collection will be assessed through participants' retention in the study and completeness of the collected data.

Satisfaction surveys will include questions developed by the research team, and others adapted from the Research Participant Satisfaction survey [41].

Feasibility of the adapted D-PRESCRIBE intervention

To assess the feasibility of the adapted D-PRESCRIBE intervention, we will conduct a process evaluation that will comprise the evaluation of implementation fidelity, mechanisms of impact and contextual factors, as recommended by the MRC framework [42].

Implementation fidelity “refers to the degree to which an intervention or a program is delivered as intended” [43] (p.40). According to the conceptual framework developed by Carroll et al., two essential aspects will be measured: 1) adherence which is “how far those responsible for delivering an intervention actually adhere to the intervention as it is outlined by the developers” and 2) participants' responsiveness to the intervention which is “how far participants respond to, or are engaged by, an intervention.” (p. 42) [43] (i.e. patients, pharmacists and GPs in our intervention). Evaluating mechanisms of impact (i.e., how an intervention works) is essential to highlight how the effects of an intervention occurred [44]. Several mechanisms of impact will be evaluated in relation with core functions of the intervention described above. In addition, we will explore the effect of contextual factors on participants' responsiveness to the intervention to assess if and how they would interact with the effect of the intervention. Table 2 details quantitative data that will be collected for the process evaluation.

In line with the MRC framework recommendations for process evaluation [42], we will also collect qualitative data through interviews. They will explore patients' and pharmacists' perceptions of the intervention to have a deeper understanding of

Section 3

mechanisms of impacts, contextual factors, and implementation issues. As examples, we will investigate patients' and pharmacists' perceptions of the brochure and pharmaceutical opinion, but also patients' perceptions about benzodiazepines or support provided by the GP. All interviews will be audio-recorded and transcribed verbatim.

Exploratory cost effectiveness analysis

Health-related quality of life will be measured with the EQ-5D-5L at each time-point [37]. The combination of answers to EQ-5D will lead to a health profile of five digits that will be converted into a utility using standard Belgian tariff values [45]. Data on healthcare use and medication use will be collected (Table 3) including any healthcare professional visits along with emergency room visits or hospitalization in the past 3 months. In order to convert resource usage figures into costs, individual-level resource use will be combined with unit costs based on the average national medication cost to calculate the total health services cost for each participant. The cost of the intervention will be calculated for the D-PRESCRIBE arm, it will be based on the expenses directly related to the intervention including printing of the brochure and pharmaceutical proposal, stamps needed to send the pharmaceutical proposal to the GP, financial compensation granted to the pharmacists per intervention delivered, average time required for pharmacists to implement the intervention and enter patients' data.

Analyses

Quantitative data

All analyses will be performed using R software [46]. Descriptive statistics will be performed on quantitative data. Categorical variables will be expressed as numbers and percentages and continuous variables as mean $\pm$ standard deviation or median [P25 – P75] depending on normality assessment. Intervention and control groups will be compared regarding patient's characteristics and intervention effects on potential mechanisms of impact using Pearson's chi-squared tests (or Fisher tests), Student's T test or Mann-Whitney tests.

The effectiveness of the intervention will be calculated on a preliminary basis only as this study is not powered to perform this analysis. BZRA cessation at 6 months as well as BZRA dose reduction (defined as at least 25% of dose reduction) will be calculated in each group. Lost to follow-up patients or withdrawn patients will be classified with patients that would have failed BZRA deprescribing. No statistical analysis will be performed on primary or secondary outcomes.

Missing data will inform the research team of the feasibility of data collection. Hence, the relevance of some variables that would have too many missing values will be discussed before a potential full implementation trial.

If considered feasible, we will conduct an exploratory cost-effectiveness analysis on completed cases and estimate patients' quality-adjusted life years (QALYs) and associated costs following the recommendations of the Belgian Healthcare Knowledge Centre (KCE) [47]. We will describe the proportion of respondents falling within each level and dimension for the EQ-5D-5L at baseline and at the 3-month and 6-month follow-ups, both overall and by intervention and control groups. Utility scores for each health-related quality of life questionnaire at baseline, 3-month, and 6-month follow-up will be calculated to present the change in mean EQ-5D-5L per intervention and control groups over time. The primary analysis will involve obtaining a ratio of the differences in costs and the differences in health outcomes (QALY) to generate the incremental cost-effectiveness ratio (ICER). The ICER represents the additional cost per one unit of health outcome gained [48]. Given the findings, a value of information (VoI) analysis will be conducted using a decision analysis model [49]. The VoI analysis will help to determine whether a full trial is worthwhile to assess cost-effectiveness.

Qualitative data

Interviews will be analysed using a deductive and inductive thematic approach using QRS Nvivo 11. The Theoretical Domains Framework (TDF) will be used as deductive framework. However, new themes or sub-themes may be identified inductively from the data. The two first patients' and pharmacists' interviews will be analysed by two independent coders. The two coders will meet to compare their coding. If satisfying agreement is reached, the remaining interviews will be performed by a single coder. If not, two additional interviews will be analysed by the two coders that will compare their coding once more. this process will be repeated until reaching satisfying agreement. This qualitative part will be reported following the COREQ checklist [50].

Patient and public involvement

In the frame of the interviews conducted during the adaptation process of the intervention, 6 patients were asked about what would make them accept to participate in a study like this and what would be important to measure if they were participating. The results did not change what was planned by the research team. Results of the study will be discussed with an advisory board that will include patients' and carers' representatives together with healthcare professionals and policymakers. This advisory board will be involved in results dissemination and help making decisions on

Section 3

the opportunity of refining the intervention components and proceeding to a full implementation trial.

ETHICS AND DISSEMINATION

This study protocol received approval by the Ethical Committee of the CHU UCLouvain Namur on 11 April 2023 (NUB: B0392023000036)

Exclusion criteria were carefully considered to help minimize patient risk prior to enrollment. BZRA withdrawal symptoms could occur if participants decide to taper BZRA. However, both the EMPOWER and D-PRESCRIBE trials have shown that the provided tapering scheme allows safe discontinuation [17, 51]. Besides, the EMPOWER brochure emphasizes the need for a professional follow-up if cessation is considered. Patients' prescribers will be also informed through the pharmaceutical proposal so that they could also adequately support their patient in case of need. If participants report any adverse effect during a research phone interview, they will be encouraged to talk about it with their healthcare provider (pharmacist or GP).

All data are confidential. Data will only be available to researchers involved in this study and they will be pseudo-anonymized prior to analysis using an encrypted code assigned to each participant (patients and pharmacists). Contact details of participants and the identification key allowing to link them to their code will be stored in a different file on a computer to which access is authorized using a password. The file allowing the identification of patients will be destroyed after 7 years. De-identified data will be kept on a secure data repository (OSF [52]). Following the FAIR Data Principles (or Findable, Accessible, Interoperable, Reusable) about data sharing [53], de-identified data (i.e. data without any name or information allowing patient's identification) will be shared on the data repository after an embargo period of 2 years.

Participants will receive a summary of the results. Results will also be disseminated through the organization of a local symposium and a peer-review publication.

DISCUSSION

This study will determine if the D-PRESCRIBE intervention, adapted to the Belgian context, is feasible in the Belgian community setting, and if proceeding to a full-effectiveness trial could be considered. This intervention comprises two components: a patient educational brochure, specifically designed for older adults, that aims to increase patients' concerns and knowledge about BZRA long-term use and raises self-efficacy towards BZRA deprescribing. This content goes far beyond the educational material currently available in Belgium. In addition, the pharmaceutical proposal will promote interprofessional collaboration around BZRA deprescribing in an innovative

way for our country. We believe testing the implementation of this intervention in Belgium is particularly timely since the Belgian National Institute of Health and Disability Insurance (NIHDI) launched a pilot program to promote BZRA deprescribing in the adult population (≥ 18 years) in February 2023 [54]. Under specific conditions, the patient can benefit from a free-of-charge tapering program using capsules containing a decreasing dosage of the compound made by the pharmacist. This program also includes two support consultations by the pharmacist. Interprofessional collaboration is encouraged by the signing of a tripartite contract between the GP, the pharmacist, and the patient. To capitalize on this new program, information about it was included in both the adapted brochure and pharmaceutical proposal. We believe that, if found feasible, the adapted D-PRESCRIBE intervention could usefully complement tools made available by the Belgian authorities.

To our knowledge, this is the first study that will test an adapted version of the D-PRESCRIBE intervention in another country. Our study will provide new insights on the transferability of this intervention in a different context. The process evaluation conducted in this feasibility study will reveal how the intervention can be implemented in Belgian pharmacies and what will be the contextual factors playing a role in its implementation [42]. This will enable us to refine the adapted intervention and/or the study design and procedures. Procedures were kept as pragmatic as possible in order that the trial integrates easily in the pharmacy workflow. For example, pharmacists will choose how to send the pharmaceutical proposal to the prescriber. This flexibility may encourage pharmacists' satisfaction with the intervention, their retention in the study, and eventual implementation of the intervention on a larger scale.

Retention of older participants in a clinical trial might be a challenge [55], however the participants' retention rate at 6 months was excellent in the original D-PRESCRIBE trial (89%) [17]. Based on the Canadian experience, we may expect no severe attrition in our participants. Besides, participants can choose between a home visit, or a phone or video conference for data collection appointments. These will be scheduled according to participants' availability. Such strategies have been highlighted as favoring participants retention in clinical trials [55]. The length of data collection is, however, a concern regarding the retention of participants. A reduced burden regarding data collection improves retention in clinical trials [56]. In the D-PRESCRIBE trial, follow-up calls were planned to last between 5 to 10 minutes [23]. We anticipate our data collection to last one hour because of the need to collect implementation outcomes as well. For this reason, inspired by the study of Murphy et al., we will propose a shortened data collection option when needed [28].

Section 3

This study has some limitations. First, the participation of pharmacies will be on a voluntary basis, and this may select pharmacists with an extra motivation for BZRA deprescribing. Moreover, our inclusion criteria regarding time travel from Brussels may limit the participation of rural pharmacies. Those two limitations could impact the generalizability of our results. Second, the nature of the intervention and topics discussed with patients during data collection will not allow double blinding, contrary to what was done in the D-PRESCRIBE trial [23]. Finally, we did not predefine progression criteria towards a full effectiveness trial as recommended by the MRC framework [15]. In fact, the qualitative part of the process evaluation leaves room for unexpected results which makes it difficult to set *a priori* criteria. Decisions will be made by the research team and will take into consideration recommendations made by the advisory board.

The recent systematic review of Omuya *et al.* highlighted the need for more research about process, implementation, and economic outcomes in deprescribing trials [57]. The main strength of this study is the scope of the evaluation plan that will include both these aspects and therefore contribute to addressing this gap.

CONCLUSION

The END-IT CS study will assess the feasibility of a BZRA deprescribing intervention led by the pharmacist in the Belgian community setting. In a context where BZRA deprescribing is a political priority, our study will be a first step to assess the opportunity to strengthen pharmacists' role in this area.

Supplementary material

Appendix 1: SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents

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Section 3

Appendix 1. SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*			
Section/ item	Item No	Description	Location in the document
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Cover page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Abstract (page 1) + Methods and analyses (page 5)
	2b	All items from the World Health Organization Trial Registration Data Set	Not applicable
Protocol version	3	Date and version identifier	Methods (page 5)
Funding	4	Sources and types of financial, material, and other support	Fundings (page 15)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Cover page + Authors' contributions (page 15)
	5b	Name and contact information for the trial sponsor	Study sponsor (page 15)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Authors' contributions + Fundings (page 15)

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Not applicable
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Introduction (page 3)
	6b	Explanation for choice of comparators	Methods (page 7)
Objectives	7	Specific objectives or hypotheses	Introduction (page 4)
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Methods and analysis (page 5)
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Methods (page 5)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Table 1

Section 3

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Methods (page 8)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Not applicable
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Not applicable
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Methods, Control group (page 7)
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Methods, Outcome measures (pages 9-10) / Table 2 and Table 3
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Methods, Sample size (page 5)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Methods, Recruitment strategies (page 6)
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Methods, Intervention and control group, random allocation of the intervention (page 7)
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Methods, Intervention and control group, blinding (page 7)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Methods, Intervention and control group, blinding (page 7)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Methods, Intervention and control group, blinding (page 7)

Section 3

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Methods, Data collection and management (page 8) + Tables
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Methods, Recruitment strategies (end page 6)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Methods, Data collection and management (page 8) + Ethics and dissemination (page 12)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Methods, Analyses (page 10-11)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Not applicable

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Methods, Analyses (page 10-11)
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Not applicable
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not applicable
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Ethics and dissemination (page 12)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not applicable
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Ethics and dissemination (page 12)

Section 3

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Not applicable
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Methods, Recruitment strategies (page 6 and 9)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Ethics and dissemination (page 12)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Competing interests' statement (page 15)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Ethics and dissemination (page 12)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not applicable

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Ethics and dissemination (page 12)
	31b	Authorship eligibility guidelines and any intended use of professional writers	Not applicable
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available on reasonable request
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable
*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons “Attribution-NonCommercial-NoDerivs 3.0 Unported” license.			

Chapter 6. Feasibility of the adapted D-PRESCRIBE intervention to favor benzodiazepine deprescribing in the Belgian community setting: results from a cluster randomized controlled trial (END-IT CS study)

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Manuscript in preparation

Section 3

AUTHORS' CONTRIBUTIONS

Pharmacies were recruited by CP and AS. CP performed the patients' recruitment, data collection, and data analysis. The study conduction was supervised by AS. Results were discussed with all authors (CP, PE, SH, and AS). CP wrote the first draft of the manuscript, which was then revised and amended by all authors (CP, PE, SH, and AS).

ACKNOWLEDGMENTS

The authors thank Dr. Tina Chevallereau, for her help in patient recruitment, and Ms. Monineat Cheap and Ms. Anita Moghadam Far, for their help in data collection. The authors would also like to thank the pharmacists and the older adults who participated in this study.

FUNDING

This study was funded partly by a grant from EBPracticenet (Projet d'implémentation 2023), and partly by a grant (Crédit de Recherche) from the Fonds de la Recherche Scientifique (n°40013898).

DECLARATION OF INTEREST

None.

TRIAL REGISTRATION

The protocol of this study was registered on the ClinicalTrials.gov website (NCT05929417).

ABSTRACT

BACKGROUND: Older adults frequently take benzodiazepine receptor agonists (BZRA) despite their potential adverse effects. In Canada, the pharmacist-led D-PRESCRIBE intervention was shown to be effective in BZRA deprescribing in older adults. It comprised a patient educational brochure and a pharmacist-prescriber communication tool. We adapted these tools to the Belgian community setting using the ADAPT guidance.

OBJECTIVES: This chapter aims 1) To assess the feasibility of the adapted D-PRESCRIBE intervention in Belgium, 2) to evaluate the study conduction plan needed for a full (cost-)effectiveness trial.

METHODS: We conducted a feasibility study of a cluster randomized controlled trial, recruiting patients (≥ 65 years) through community pharmacies (clusters). The adapted D-PRESCRIBE intervention was delivered by intervention pharmacies while control pharmacies provided usual care. Patients were blinded to group allocation. Quantitative data was collected at baseline, three months, and six months through patient and pharmacist questionnaires. The feasibility of the intervention was measured through implementation outcomes. The feasibility of the study conduction was assessed through participation and retention rates, completeness of the collected data, and a satisfaction survey. Data were analyzed using descriptive statistics.

RESULTS: Sixty eligible patients were recruited through seven pharmacies. Three patients dropped out before baseline data collection. Three pharmacies were allocated to the control group (25 patients) and four to the intervention group (32 patients). Thirty intervention patients received the adapted EMPOWER brochure and 22 pharmaceutical proposals were sent to prescribers. Fifty-five patients completed the 6-month follow-up. Completeness of the collected data at the three time points was excellent. Overall, the satisfaction survey showed that both patients and pharmacists were very positive about the study.

CONCLUSION: These partial results show that implementing the adapted D-PRESCRIBE intervention is feasible in the Belgian community setting. However, some study conduction procedures, in particular, the recruitment of the pharmacies, the inclusion criteria, and the intensity of the questioning related to BZRA should be revised for a future effectiveness trial.

Section 3

INTRODUCTION

This chapter presents the results of the feasibility study for which the complete protocol is described in Chapter 5 and focuses on two main research questions:

1. To what extent is the planned study design for a full (cost)-effectiveness trial feasible in practice?
2. To what extent is the D-PRESCRIBE intervention adapted to the Belgian context, which we will call the Belgian D-PRESCRIBE intervention, feasible in the Belgian community setting?

Regarding the latter objective, this chapter describes outcomes related to the implementation fidelity of the intervention only. The analysis of mechanisms of impact and contextual factors, and the exploratory economic analysis are not part of this PhD thesis and will be performed by two post-doctoral researchers.

METHODS

The methodology followed for this feasibility study has been exhaustively described in Chapter 5.

RESULTS

1. Feasibility of the study conduction plan

1.1. Recruitment process

We recruited 8 eight community pharmacies, in a period of 10 weeks from March 2023 to May 2023. One pharmacy withdrew before any patient recruitment due to reasons external to the study. Hundred and ninety potential participants were contacted by pharmacists between June and July 2023, mainly by phone (66.8%) and face-to-face (23.2%) (Table 1). The mean duration of patient recruitment was 28 days (minimum: 16 days, maximum: 42 days, 1 missing value). There were no statistical differences in age and gender between older adults accepting to be contacted by the research team and those who refused (Table 1). However, participation rates varied between pharmacies and means of contact.

Table 1. Comparison of participants and non-participants (at the pharmacy level) to the study (N=190)				
	Total (N=190)	Participants (n=101)	Non- participants (n=89)	p-value*
Gender <i>n</i>(%)				0.486
Female	116 (61.1)	64 (63.4)	52 (58.4)	
Male	74 (38.9)	37 (36.7)	37 (41.6)	
Age				0.146
Median	74.0	73.0	75.0	
[IQR]	[69.0 ; 78.8]	[68.0 ; 78.0]	[69.0 ; 80.0]	
Pharmacy ID <i>n</i>(%)				<0.001
462	27 (14.2)	13 (12.8)	14 (15.7)	
794	16 (8.4)	12 (11.9)	4 (4.5)	
767	30 (15.8)	16 (15.8)	14 (15.7)	
734	21 (11.1)	18 (17.8)	3 (3.4)	
205	20 (10.5)	16 (15.8)	4 (4.5)	
487	41 (21.6)	11 (10.9)	30 (33.7)	
308	35 (18.4)	15 (14.9)	20 (22.5)	
Means of contact <i>n</i>(%)				0.050
Face-to-face	44 (23.2)	21 (20.7)	23 (25.8)	
Phone call	127 (66.8)	73 (72.3)	54 (60.7)	
Postal mail	16 (8.4)	5 (5.0)	11 (12.4)	
E-mail	3 (1.6)	0 (0.0)	3 (3.4)	
*Pearson chi-square test, Fisher test, or Mann-Whitney test				
IQR: Interquartile range				

Of the 101 older adults who agreed to be contacted by the research team, 76 accepted a home visit for more information about the study. Finally, 63 patients were included, of which 3 dropped out before the baseline data collection and 3 were excluded during baseline data collection as they did not answer the inclusion or exclusion criteria (anymore) (Figure 1). This led to a final sample of 57 participants.

Section 3

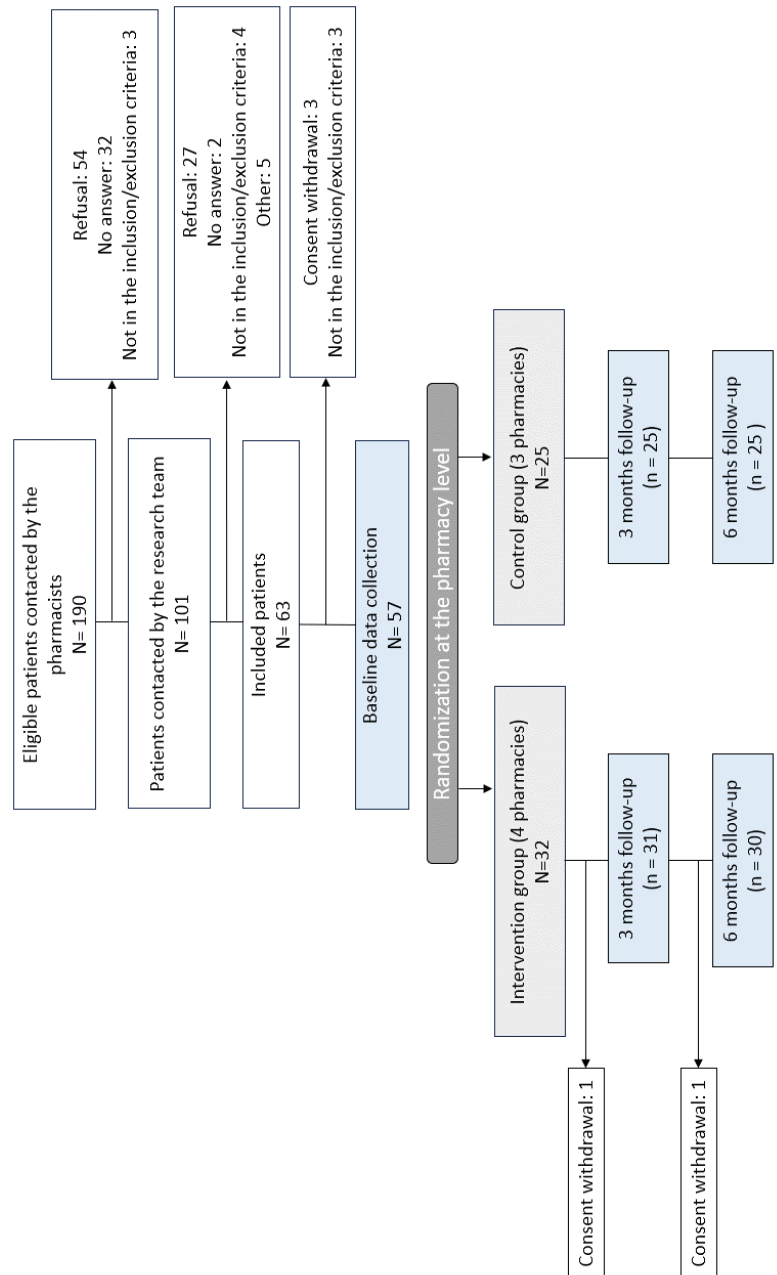


Figure 1. Study flowchart

The characteristics of participating pharmacists are presented in Table 2. Five out of 7 pharmacists were women, and five were experienced pharmacists (i.e.: had graduated for 10 years or more). In the intervention group, 2 pharmacists had a professional experience of less than five years, and 2 a professional experience equal or above 10 years. All three control pharmacies were in the rural setting while three intervention pharmacies out of 4 were in the urban setting.

Table 2: Pharmacists' characteristics				
		Total population (N=7)	Intervention group (N= 4)	Control group (N=3)
Age				
	<i>Range</i>	27.0 - 58.0	27.0 – 56.0	36.0 – 58.0
Gender <i>n</i>(%)				
	Male	2 (28.6)	1 (25.0)	1 (33.3)
	Female	5 (71.4)	3 (75.0)	2 (66.7)
Time since diploma <i>n</i>(%)				
	<5 years	2 (28.6)	2 (50.0)	0 (0.0)
	≥5 and <10 years	0 (0.0)	0 (0.0)	0 (0.0)
	≥10 years	5 (71.4)	2 (50.0)	3 (100.0)
Seniority in the pharmacy <i>n</i>(%)				
	<5 years	2 (28.6)	2 (50.0)	0 (0.0)
	≥5 and <10 years	2 (28.6)	1 (25.0)	1 (33.3)
	≥10 years	3 (42.9)	1 (25.0)	2 (66.7)
Setting of the pharmacy <i>n</i>(%)				
	Urban	3 (42.9)	3 (75.0)	0 (0.0)
	Rural	4 (57.1)	1 (25.0)	3 (100.0)
Type of pharmacy <i>n</i>(%)				
	Independent practice	5 (71.4)	2 (50.0)	3 (100.0)
	Collaborative practice	2 (28.6)	2 (50.0)	0 (0.0)
Has previously participated in MPC <i>n</i>(%)				
	Yes	3 (42.9)	2 (50.0)	1 (33.3)
	No	4 (57.1)	2 (50.0)	2 (66.7)
MPC: medico-pharmaceutical concertations				

The characteristics of the participants at baseline are described in Table 3. Participants had a median age of 72 years, and around 60% were women. Most of them (54.4%) had a university degree or equivalent. Participants were mostly taking one BZRA (87.7%),

Section 3

and zolpidem was the molecule more frequently prescribed (43.9%). Seventy-seven percent of participants took their BZRA for more than five years. Most participants reported taking their BZRA for sleep issues (57.9%), and 24.6% for equally for anxiety and insomnia. Results from the Insomnia Severity Index (ISI) showed that around sixty percent of patients suffered from insomnia (defined as an ISI score ≥ 10) [1] and 56.1% suffered from anxiety (defined as a Geriatric Anxiety Inventory (short-form) score ≥ 3) [2]. Comparison between the intervention and control groups showed few differences: participants in the control group reported a significantly better health-related quality of life (measured through the EQ5D-5L questionnaire [3]) and a difference also existed regarding the current GP being the initial prescriber of their BZRA. A difference in educational levels was also observed between the two groups.

Table 3: Patients' characteristics, BZRA prescribing patterns and history, and alternatives use - at baseline				
		Total population (N=57)	Intervention group (N= 32)	Control group (N=25)
Population Characteristics				
Age				
	<i>Median [IQR]</i>	72.0 [68.0; 77.0]	73.5 [68.5-77.0]	71.0 [68.0-76.0]
Gender n(%)				
	Male	23 (40.4)	13 (40.6)	10 (0.40)
	Female	34 (59.7)	19 (59.4)	15 (0.60)
Living situation n(%)				
	Alone	18 (31.6)	13 (40.6)	5 (20.0)
	In couple	37 (64.9)	18 (56.3)	19 (76.0)
	With a family member other than a spouse/partner	1 (1.8)	0 (0.0)	1 (4.0)
	Other	1 (1.8)	1 (3.1)	0 (0.0)
Higher achieved educational level n(%)				
	Never went to school or primary school	2 (3.5)	0 (0.0)	2 (8.0)
	Middle school	7 (12.3)	2 (6.3)	5 (20.0)
	Highschool	17 (29.8)	8 (25.0)	9 (36.0)
	University or equivalent	31 (54.4)	22 (68.8)	9 (36.0)
Number of prescribed chronic medicines taken (patient-reported)				
	<i>Median [IQR]</i>	5 [3-8]	5.5 [3-8]	5 [3-7]
History of falls in the last 6 months n(%)				
	Yes	10 (17.6)	7 (21.9)	3 (12.0)
Anxiety (GAI-SF ≥ 3)				
	Yes	32 (56.1)	19 (59.4)	13 (52.0)

Insomnia (ISI ≥10)			
Yes	34 (59.6)	19 (59.4)	15 (60.0)
Quality of life (EQ5D-5L)			
Median [IQR]	0.76 [0.62;0.84]	0.72 [0.44;0.82]	0.78 [0.75;0.85]
BZRA use patterns and history			
Most prescribed BZRA <i>n</i>(%) – Patient reported			
zolpidem	25 (43.9)	13 (40.6)	12 (48.0)
lorazepam	13 (22.8)	7 (21.9)	6 (18.8)
alprazolam	8 (14.0)	5 (15.6)	3 (12.0)
lorazepam	5 (8.8)	3 (9.4)	2 (8.0)
Number of BZRA taken <i>n</i>(%) – Patient reported			
1	50 (87.7)	28 (87.5)	22 (88.0)
≥2	7 (12.3)	4 (12.5)	3 (12.0)
Duration of BZRA use <i>n</i>(%)			
< 1 year	4 (7.0)	2 (6.3)	2 (8.0)
≥ 1 and < 5 years	8 (14.0)	3 (9.4)	5 (20.0)
≥ 5 years	44 (77.2)	27 (84.4)	17 (68.0)
Doesn't remember	1 (1.8)	0 (0.0)	1 (4.0)
Current GP is the initial prescriber <i>n</i>(%)			
Yes	22 (38.6)	6 (18.8)	16 (64.0)
No	33 (57.9)	24 (75.0)	9 (36.0)
Does not remember	2 (3.5)	2 (6.3)	0 (0.0)
Main reason for taking BZRA today <i>n</i>(%)			
Insomnia/ sleep issues	33 (57.9)	16 (50.0)	17 (68.0)
Anxiety/ Stress	9 (15.8)	8 (25.0)	1 (4.0)
Anxiety and insomnia equally	14 (24.6)	8 (25.0)	6 (24.0)
Other	1 (1.8)	0 (0.0)	1 (4.0)
Previous attempts for BZRA deprescribing* <i>n</i>(%)			
Never	23 (40.4)	11 (34.4)	12 (48.0)
One attempt	8 (14.0)	7 (21.9)	1 (4.0)
Two or more attempts	25 (43.9)	14 (43.8)	11 (44.0)
One or more BZRA initially prescribed during hospitalization <i>n</i>(%)			
Yes	5 (8.8)	3 (9.4)	2 (8.0)
No	51 (89.5)	28 (87.5)	23 (92.0)
Does not remember	1 (1.8)	1 (3.1)	0 (0.0)
Alternatives use			
Melatonin use*			
Yes	13 (22.8)	7 (21.9)	6 (24.0)
No	44 (77.2)	25 (78.1)	19 (76.0)
Phytotherapy use			
Yes	11 (19.3)	5 (15.6)	6 (24.0)
No	46 (80.6)	27 (84.4)	19 (76.0)
Other complement use (magnesium, homeopathy, etc.)			

Section 3

Yes	7 (12.3)	6 (18.8)	1 (4.0)
No	50 (87.7)	26 (81.3)	24 (96.0)
*Missing value: 1 (1,8%)			
BZRA: Benzodiazepines Receptors Agonists (ATC N03AE01, N05BA, N05CD and N05CF), EQ5D-5L: Euroqol quality of life questionnaire (5 dimensions, 5 levels); GAI-SF: Geriatric Anxiety Inventory short-form; GP: General practitioner; ISI: Insomnia Severity Index.			

Five pharmacists answered the satisfaction survey and evaluated the recruitment process (Figure 2): except for one pharmacist who found it difficult to establish the list of eligible participants and one who was dissatisfied with the financial compensation, the pharmacists' experience of recruiting patients was satisfactory. One pharmacist reported difficulties in contacting eligible patients, especially those who infrequently come to the pharmacy to buy BZRA (because they take limited amounts or get several boxes at once).

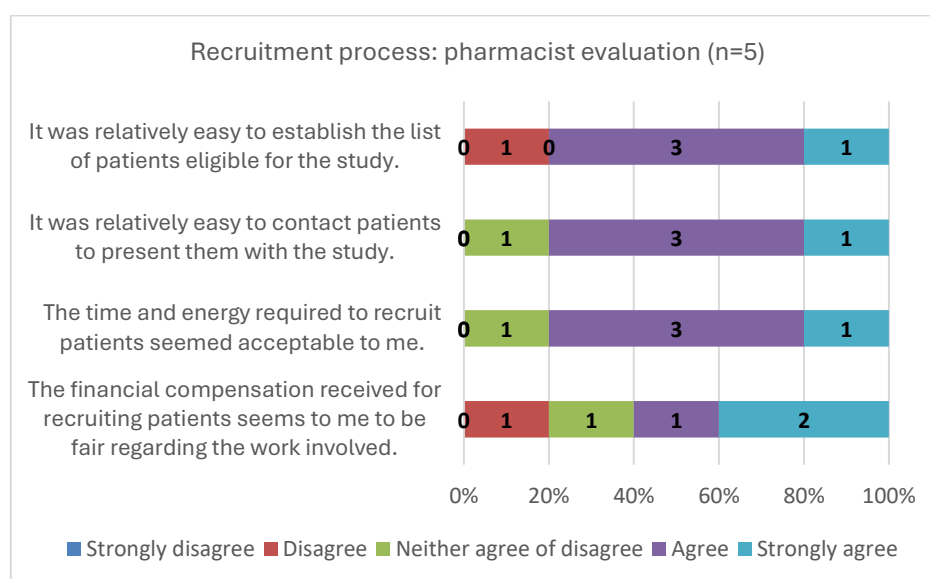


Figure 2. Evaluation of the recruitment process by participating pharmacists

Eligibility criteria were discussed in additional comments. One pharmacist found that the eligibility criteria were too strict and another felt that the criteria were too loose, especially regarding the number of previous visits to the pharmacy. This pharmacy suggested that eligible patients should have come to the pharmacy at least once in the 2 or 3 previous months to ensure seeing the patient enough during the study.

1.2. Data collection process

Data were collected between July 2023 and March 2024. Out of the 57 randomized patients, only two withdrew during the study (96.5 % retention rate), one before the 3-month data collection and one before the 6-month data collection. Reasons for dropping out were not related to the study. Collecting data lasted 30 minutes on average at each time point, which was half the time we had anticipated. Around three-quarters of the participants accepted that the data collection happened by phone (42/57 patients at baseline (74%)), and home visits were organized for the others. Results from the patient satisfaction survey showed that research visits were scheduled at a time that worked for patients and that research visits went overall smoothly, except for one patient (Figure 3).

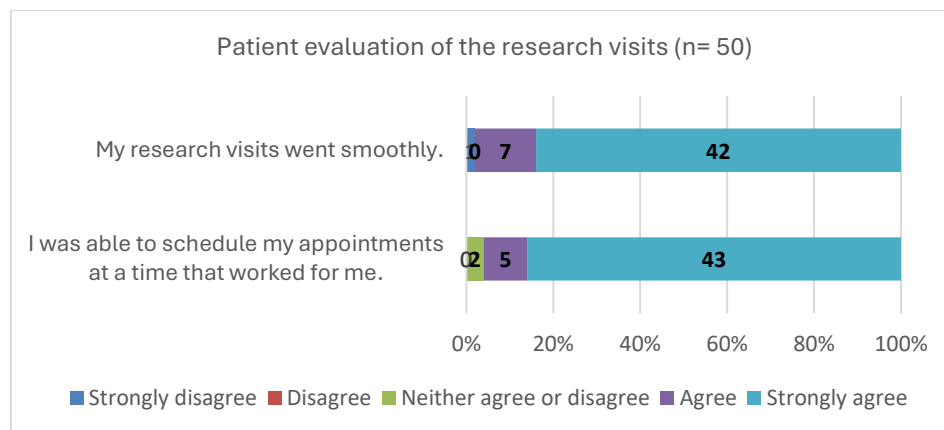


Figure 3. Patient evaluation of the research visits

Overall, the completeness of the data was excellent (Table 4). It was not necessary to reduce data collection to core outcomes for any participants, as planned in the protocol in case of patients' tiredness or willingness to drop-out. However, some issues appeared during the study conduction: first, the questions about knowledge about BZRA were problematic because some patients were unable to state "true" or "false", which led to some missing values. Second, two questionnaires made no sense when the participants had stopped their BZRA (i.e.: the measure of self-efficacy and the rPATD-BZRA questionnaire). It was decided to not ask these questions to patients who had stopped their BZRA.

Section 3

Table 4: Completeness of the collected data at each time point			
Variables or instruments	Patients with at least one missing value for the variable or instrument (n (%))		
	Baseline (n=57)	3-month (n=56)	6-month (n=55)
Data collected by the research team			
Socio-demographic data (4 items)	0 (0.0)	NA	NA
Medication use (5 main items)	0 (0.0)	0 (0.0)	1 (1.8)
BZRA use history (7 items)	1 (1.8)	NA	NA
Data about healthcare providers (6 items)	1 (1.8)	NA	NA
Cost of a GP consult (1 item)	3 (5.3)	NA	NA
Knowledge (5 items)	9 (15.8)	5 (8.9)	8 (14.5)
Self-efficacy (1 item)	1 (1.8)	1 (1.8)	5 (9.1)*
Falls (1 item)	0 (0.0)	0 (0.0)	0 (0.0)
EQ5D-5L (5 items) [3]	0 (0.0)	0 (0.0)	0 (0.0)
Visual Analogic Scale (1 item)	0 (0.0)	1 (1.8)	0 (0.0)
ISI (7 items) [1]	0 (0.0)	0 (0.0)	0 (0.0)
GAI-SF (5 items) [2]	0 (0.0)	0 (0.0)	0 (0.0)
rPATD-BZRA (13 items) [4]	0 (0.0)	0 (0.0)	4 (7.3)*
Healthcare use (6 items)	NA	1 (1.8)	0 (0.0)
Data collected by the pharmacist			
Medication use (7 main items)	1 (1.8)	2 (3.6)	1 (1.8)
Legend: BZRA: Benzodiazepine receptor agonists; EQ5D-5L: EuroQol questionnaire (5 dimensions, 5 levels); ISI: Insomnia Severity Index; GAI-SF: Geriatric Anxiety Inventory short form; rPATD-BZRA: revised Patients Attitudes towards Deprescribing questionnaire adapted for BZRA; NA: not applicable (the questionnaire was not administered at that time-point) * 4 missing values are due to the non-administration of these questionnaires to patients that stopped their BZRA.			

Additional comments in the patient satisfaction survey showed some frustration due to the format of the questionnaires for 4 participants who felt that questions were imprecise or appealed for more extensive answers than the proposed options. One patient expressed his/her discontent, judging questions biased towards deprescribing whereas he/she was very satisfied with his/her BZRA.

The evaluation of data encoding by the pharmacist raised mixed perceptions, especially regarding its integration into the pharmacy workflow (Figure 4). In additional comments, one pharmacist reported having called patients in addition to reporting what was in their files, which generated an extra load for both patients and pharmacists.

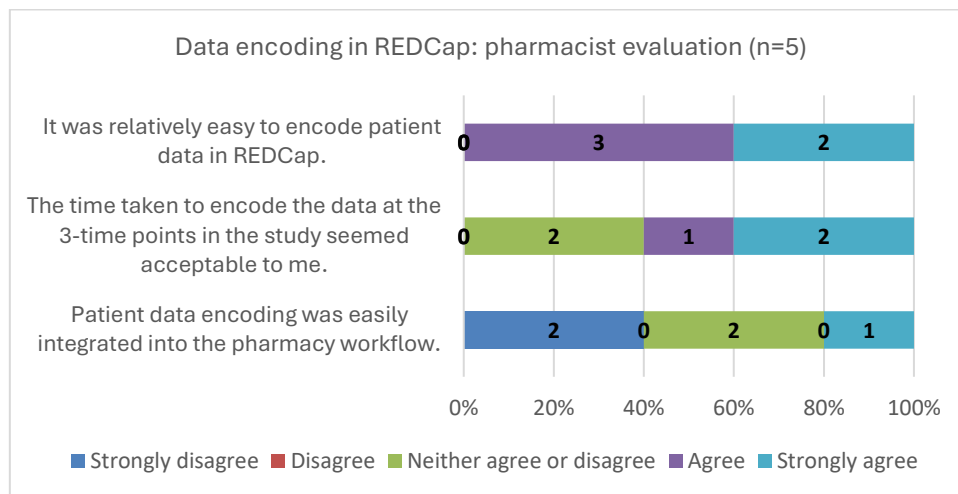


Figure 4. Pharmacists' evaluation of the data encoding in REDCap

1.3. Study in general

Overall, patients and pharmacists were very satisfied with their experience with the research staff, which was perceived as easy to contact and professional (Figures 5 & 6). Most participants (pharmacists and patients) reported that study procedures were understood before the study started.

Section 3

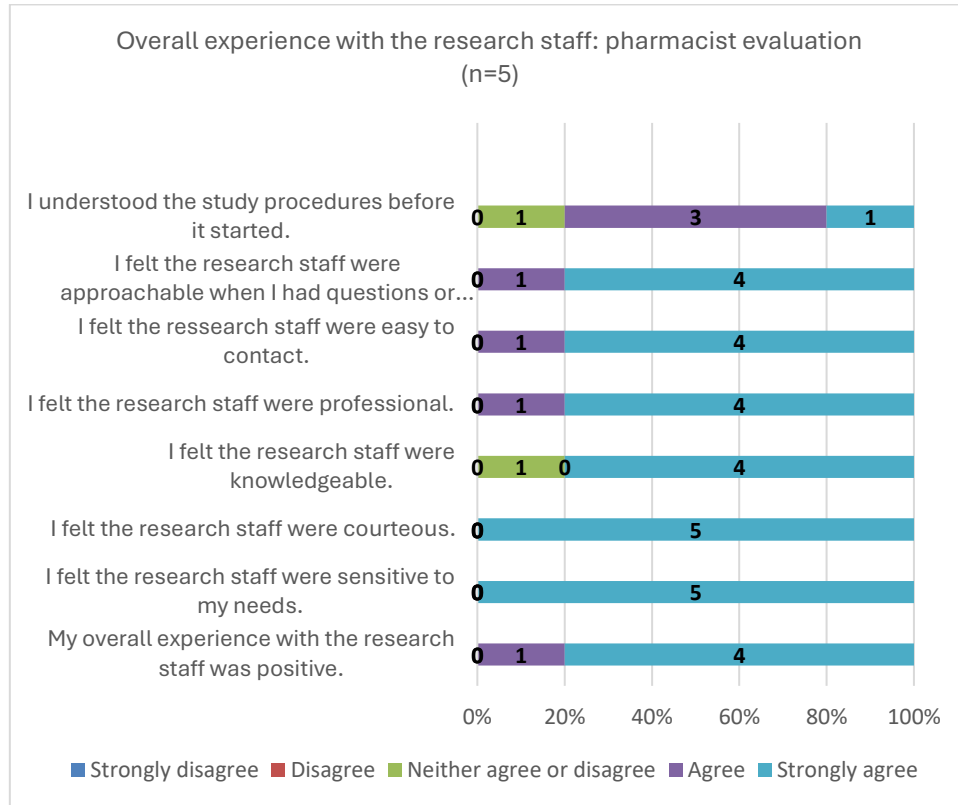


Figure 5. Pharmacists' overall experience with the research staff

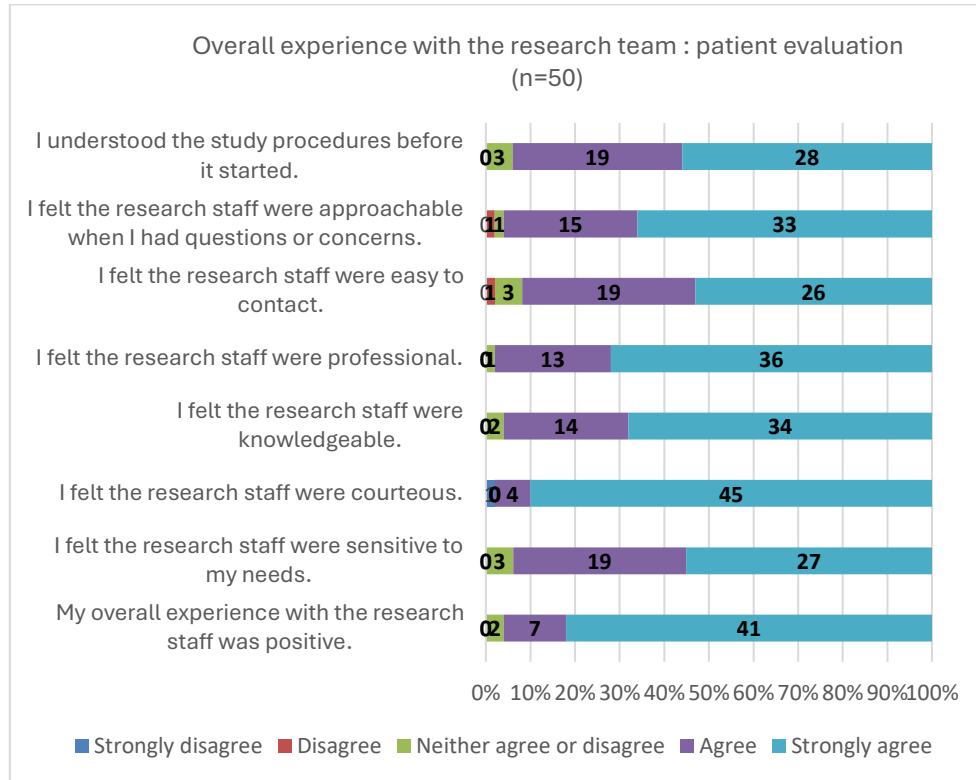


Figure 6. Patients' overall experience with the research staff

Patients were also overall satisfied with their pharmacist during the study, the very large majority of them reporting having appreciated the suggestion in study participation from the pharmacist (Figure 7).

Section 3

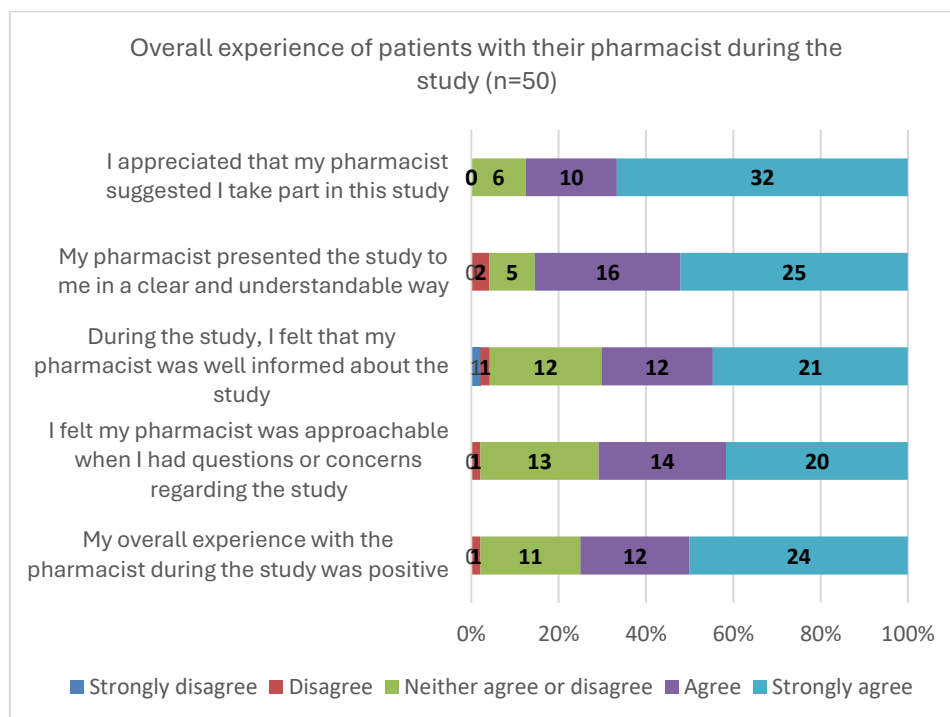


Figure 7. Overall experience of patients with their pharmacist during the study

Many patients shared positive comments in addition to the survey. Seven participants (intervention and control groups combined, as the survey was anonymous) highlighted that the study helped them reduce, stop, or think about their benzodiazepine. However, few patients, most likely from the control group, expressed some dissatisfaction with the study because they felt they had answered questions with no purpose.

Pharmacists' satisfaction with the study was also overall positive, except for one pharmacist who did not find participating motivating. Four pharmacists would be happy to participate in a future similar study (Figure 8).

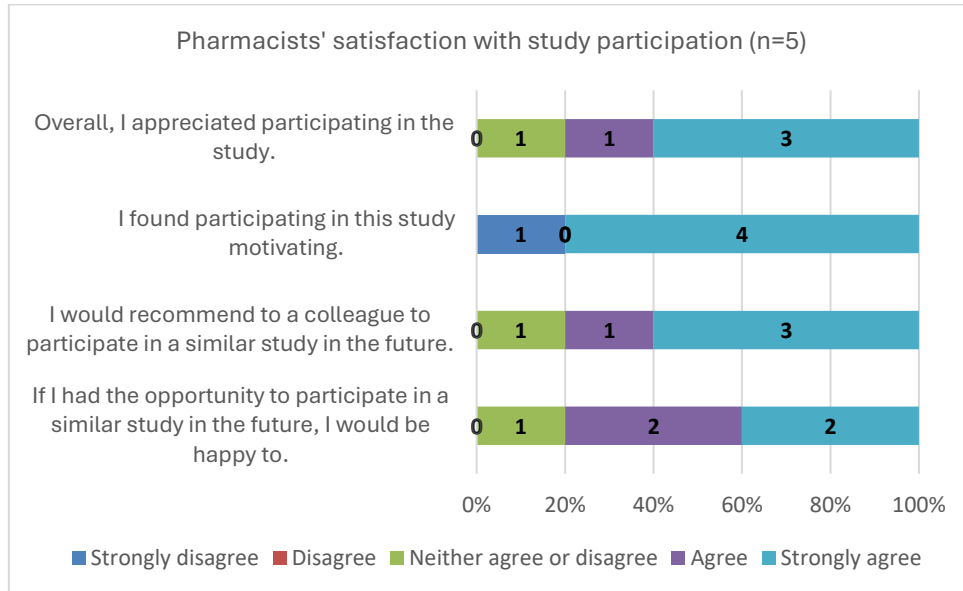


Figure 8. Pharmacists' satisfaction with study participation

2. Feasibility of the adapted D-PRESCRIBE intervention

2.1. Intervention implementation

Figure 9 presents the intervention implementation at 3 months. Of the 32 patients randomized in the intervention group, one dropped out before receiving the intervention, and one changed pharmacy. Hence, 30 brochures were given by the pharmacist (96.8%). Twenty-two pharmaceutical proposals (71.0%) were sent by pharmacists, all by postal mail. The main reasons for not sending the pharmaceutical proposals were patient refusal (n=3) and lack of time (n=3).

Section 3

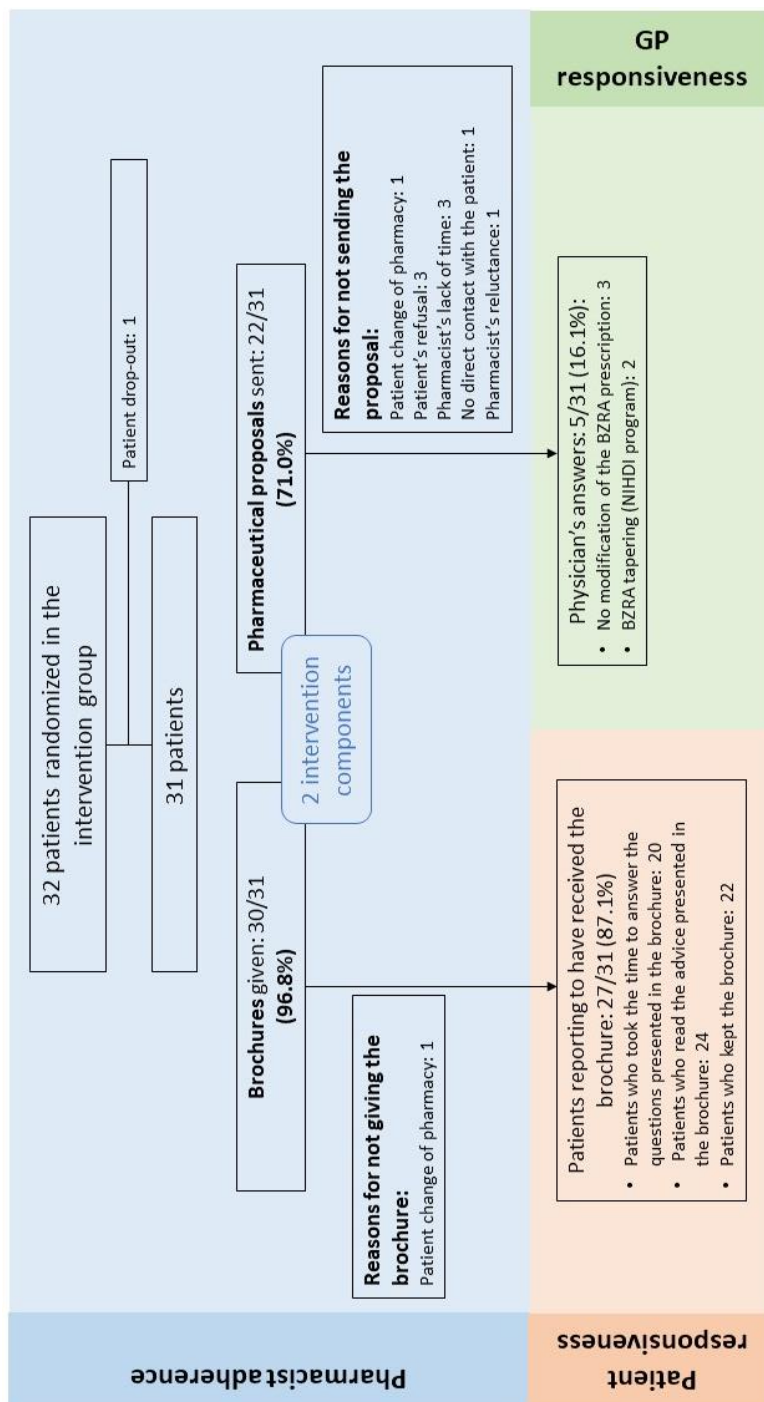


Figure 9. Intervention implementation at 3 months

Implementation of the intervention varied between pharmacies, especially regarding the sending of the pharmaceutical proposal, one pharmacist sending no pharmaceutical proposal (Table 5).

Table 5: Intervention implementation (at 3 months)					
	Total (n=32)	Pharmacy 1 (n= 7)	Pharmacy 2 (n=12)	Pharmacy 3 (n=5)	Pharmacy 4 (n=8)
Number of brochures given by the pharmacist <i>n (%)</i>	30 (93.8)	7 (100.0)	11 (91.7)	5 (100.0)	7 (87.5)
Number of pharmaceutical proposals sent <i>n (%)</i>	22 (68.8)	0 (0.0)	11 (91.7)	5 (100.0)	6 (75.0)

Three pharmacists from the intervention group anonymously answered questions about the intervention implementation in the satisfaction survey (Figure 10). Results were slightly better regarding the implementation of the brochure than the pharmaceutical proposal. In additional comments, one pharmacist suggested that the pharmaceutical proposal be given to the prescriber by the patient, to make sure he/she has received it. The pharmacist thought answering the proposal represented an important workload for the GP explaining that they did not answer.

Section 3

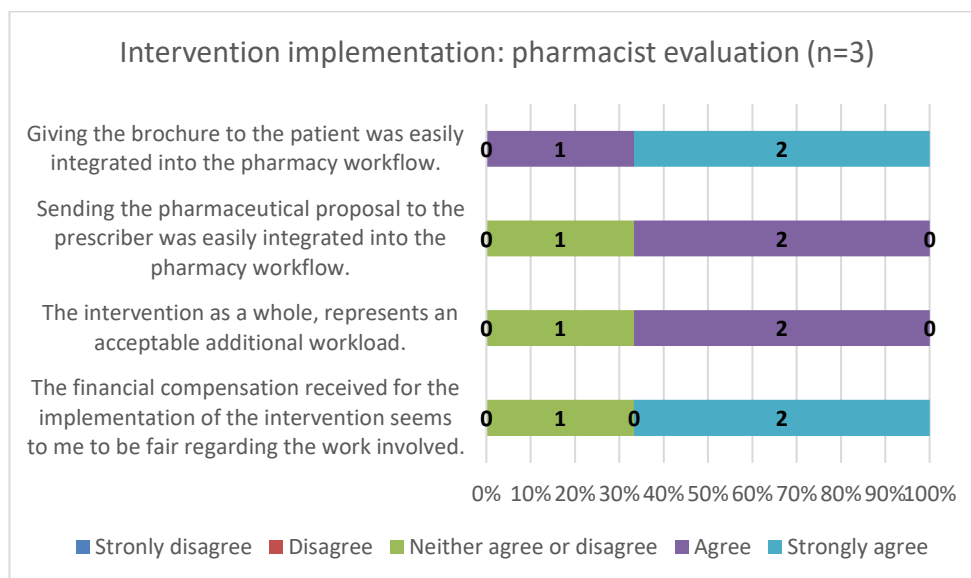


Figure 10. Pharmacists' evaluation of the intervention implementation

2.2. Participant responsiveness to the intervention

Twenty-seven patients reported having received the brochure (87.1%), which is slightly less than pharmacist-reported data, showing recall issues for some patients. Most patients took the time to answer questions presented in the brochure and to read the advice presented in it (See Figure 9). Of the 22 proposals that were sent, 5 were answered by the prescriber (16.1%), of which 2 involved a modification of the BZRA prescription and the initiation of a tapering scheme (with capsules made by the pharmacist through the NIHDI pilot program).

Table 6 presents patients' responsiveness regarding BZRA use and potential deprescription in the intervention group. At 3 months, around 40% of the intervention patients reported having had a conversation with their GP about BZRA deprescribing, and 25% tried to reduce or stop their BZRA. Data were overall consistent in BZRA changes whether they were self-reported or analyzed through data on medication collected from patients. Differences in patients' responsiveness were observed between pharmacies, particularly in pharmacy n°3, where almost no patients' responsiveness was observed at 6 months.

Table 6. Patient responsiveness to the intervention regarding BZRA use (intervention group)										
	3-month					6-month				
	Ph 1 (n=7)	Ph 2 (n=12)	Ph 3 (n=5)	Ph 4 (n=8)	Total (n=32)	Ph 1 (n=7)	Ph 2 (n=12)	Ph 3 (n=5)	Ph 4 (n=8)	Total (n=32)
Self-reported										
Since our last meeting, did you talk with your doctor about a potential stop of your benzodiazepine? – Yes n(%)	2 (28.6)	7 (58.3)	3 (60.0)	1 (12.5)	13† (40.3)	3 (42.9)	6 (50.0)	1 (20.0)	2 (25.0)	12† (37.5)
Since our last meeting, have you tried to reduce or stop your benzodiazepine? – Yes n(%)	1 (14.3)	4 (33.3)	0 (0.0)	3 (37.5)	8 (25.0)	3 (42.9)	6 (50.0)	0 (0.0)	4 (50.0)	13 (40.6)
Since our last meeting, have you successfully reduced your benzodiazepine? – Yes n(%)	1 (14.3)	4 (33.3)	0 (0.0)	0 (0.0)	5 (15.6)	2 (28.6)	4 (33.3)	0 (0.0)	3 (37.5)	9 (28.1)
Since our last meeting, have you successfully stopped your benzodiazepine? – Yes n(%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	1 (0.0)	2 (7.1)
Based on medication data (collected from participants)										
Complete BZRA cessation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	1 (12.5)	2 (6.3)
Deprescription 1 (any BZRA reduction or complete cessation)	0 (0.0)	4 (33.3)	1 (20.0)	1 (12.5)	6 (18.8)	2 (28.8)	6 (50.0)	0 (0.0)	3 (37.5)	11 (34.4)
Deprescription 2 (BZRA reduction ≥25% or complete BZRA cessation)	0 (0.0)	4 (33.3)	1 (20.0)	1 (12.5)	6 (18.8)	2 (28.8)	5 (41.7)	0 (0.0)	2 (25.0)	9 (28.1)
BZRA: benzodiazepine receptor agonists; Ph: pharmacy † A total of 17 participants (53.1%) discussed with their doctor about a potential BZRA deprescribing, irrespective of the follow-up period *BZRA dose reductions were calculated using diazepam equivalences.										

Section 3

2.3. Preliminary evaluation of the intervention effectiveness

Table 7 presents preliminary results of the intervention's effectiveness. A higher proportion of patient from the intervention group talked with their doctor about a potential BZRA deprescribing or tried to reduce or stop their BZRA. If taking a broad definition of deprescribing (i.e. any BZRA reduction or complete cessation) deprescription rates were 34.4% in the intervention group and 24% in the control group. If taking a more strict definition of deprescribing (i.e.: BZRA reduction of at least 25 % + complete cessation), the deprescribing rate was 28.1% in the intervention group versus 24% in the control group. It is interesting to note that, compared to baseline values, BZRA dosage increases were also observed at 3 months and 6 months in both groups.

Table 7. Preliminary evaluation of intervention efficacy – Comparison with the control group				
	At 3 months		At 6 months	
	Intervention (N=32)	Control (N=25)	Intervention (N=32)	Control (N=25)
Self-reported				
Since our last meeting, did you talk with your doctor about a potential stop of your benzodiazepine? – Yes <i>n</i> (%)	13 (40.3)†	7 (28.0)‡	12 (37.5)†	5 (20.0)‡
Since our last meeting, have you tried to reduce or stop your benzodiazepine? – Yes <i>n</i> (%)	8 (25.0)	5 (20.0)	13 (40.6)	7 (28.0)
Since our last meeting, have you successfully reduced your benzodiazepine? – Yes <i>n</i> (%)	5 (15.6)	2 (8.0)	9 (28.1)	3 (12.0)
Since our last meeting, have you successfully stopped your benzodiazepine? – Yes <i>n</i> (%)	0 (0.0)	0 (0.0)	2 (7.1)	2 (8.0)
Based on medication data (collected from patients)				
Complete BZRA cessation	0 (0.0)	0 (0.0)	2 (6.3)	2 (8.0)
Deprescription 1 (any BZRA reduction or complete cessation)	6 (18.8)	4 (16.0)	11 (34.4)	6 (24.0)
Deprescription 2 (BZRA reduction ≥25% or complete BZRA cessation)	6 (18.8)	4 (16.0)	9 (28.1)	6 (24.0)
BZRA dose increase*	3 (9.4)	5 (20.0)	5 (15.6)	4 (16.0)
Legend: BZRA : benzodiazepine receptor agonists				
† A total of 17 participants (53.1%) discussed with their doctor about a potential BZRA deprescribing, irrespective of the follow-up period.				

‡ A total of 9 participants (36%) discussed with their doctor about a potential BZRA deprescribing, irrespective of the follow-up period.
 * Changes in BZRA dosages were calculated based on diazepam equivalences compared to baseline values

We asked patients in the intervention group the reasons why they did not talk to their doctor about a potential BZRA deprescribing. The main reasons were not wanting to stop, other life or health priorities, feeling ok with their current BZRA, and having not seen the doctor yet. Not wanting to stop and other life or health priorities, along with not sleeping well otherwise or fearing not to sleep were the main reasons patients reported for not attempting BZRA deprescribing. Patients who, during the study, tried but failed to reduce or stop their BZRA reported sleep difficulties and anxiety. Some patients who successfully reduced their BZRA but did not reach a full BZRA cessation reported having not finished the tapering program, feeling ok with the current dosage, or wanting to consider stopping later.

To assess a potential shift towards other medication classes, we compared changes in other medication classes between patients that did deprescribe (broader definition: i.e. any BZRA reduction or BZRA cessation) and those who did not at 6 months, but figures are too low to draw any conclusions.

Table 8. Change in other medication classes at 6 months compared to baseline				
	Deprescribed (n=17)		Did not deprescribe (n=38)	
	Start or dose increase n (%)	Dose decrease or stop n (%)	Start or dose increase n (%)	Dose decrease or stop n (%)
Antidepressants	2 (11.8)	1 (5.9)	5 (13.2)	4 (10.5)
Sedative antidepressant (trazodone + mirtazapine)	2 (11.8)	1 (5.9)	2 (5.3)	2 (5.3)
Melatonin	2 (11.8)	2 (11.8)	5 (13.2)	2 (5.3)
Phytotherapy	2 (11.8)	1 (5.9)	2 (5.3)	2 (5.3)
Other complements	2 (11.8)	0 (0.0)	2 (5.3)	2 (5.3)

DISCUSSION

This cluster randomized controlled trial assessed the feasibility of implementing of the Belgian D-PRESCRIBE intervention in 57 patients recruited through 7 community

Section 3

pharmacies. If some changes in the study procedures would be necessary, our results support the feasibility of both study design and intervention implementation.

Indeed, adherence was excellent regarding the implementation of the brochure (30/21, 96.8%) and good regarding the pharmaceutical proposal (22/31, 71.0%). We previously investigated the intervention's acceptability among HCPs (Chapter 4). It showed that pharmacists had some reluctance to send the pharmaceutical proposal. Considering this, the number of pharmaceutical proposals sent is very encouraging. Indeed, it is quite similar to the number of pharmaceutical opinions that were sent in the original D-PRESCRIBE trial (66.2%) [5].

The number of pharmaceutical proposals that physicians answered was very low (16.1%). This percentage is considerably below the 83% of physicians who declared that they would be happy to respond to the pharmaceutical proposal in our previous survey (see Chapter 4). Even if the collaboration between pharmacists and GPs in the frame of BZRA deprescribing is fostered by Belgian authorities (notably through the recent awareness campaign promoting the rational use of psychotropics (*"Psychotropes: quels risques pour vos patients ? Ensemble, favorisons un usage adapté"*) [6], our results show low responsiveness to this new tool. However, expecting all GPs to answer the pharmaceutical proposal would be unrealistic. In the original D-PRESCRIBE trial, the response rate from physicians was 48.3%, whereas pharmaceutical opinions were common practice at that time [5]. The absence of GPs' answers to pharmacists does not mean that sent pharmaceutical proposals did not reach their purpose. Indeed, as our follow-up period was limited to 6 months, it is possible that they had no opportunity to discuss BZRA deprescribing with their patient during this time interval (for example if no appointment was taken by the patient or because of other health priorities). As BZRA are often routinely prescribed and are not often reevaluated when started [7], we believe that such a tool could trigger the reflection process about BZRA appropriateness and potential deprescribing, even after the follow-up period and even if they did not take the time to answer the pharmacist. A longer follow-up period might allow observing more GPs' responsiveness. We did not foresee interviewing GPs in the qualitative part of the process evaluation but it would be relevant. Indeed, it could have been interesting to know more about their perception of this tool and how it might support them (or not) talking about BZRA deprescribing with their patients.

Our results also support the feasibility of the study design. Despite a pharmacy drop-out, sufficient participant recruitment was achieved, and the retention rate was excellent in both groups. Data collection revealed also feasible with very good data completeness, and a lower-than-expected time to collect data, alleviating the

expected burden on patients and the research team. Minor adjustments are needed in some questionnaires (e.g.: adding an “I don’t know” choice to the questionnaire investigating knowledge about BZRA). The medication encoding by pharmacists was somewhat redundant with the data collected by the research team; some of them called patients to ensure correct information. The medication data collection strategy should therefore be revised. Limiting medication data collection to the research team only would limit pharmacists’ burden and improve their satisfaction with the study.

In addition, some major changes are required for a future effectiveness trial. First, eligibility criteria need to be revised. A threshold of minimal BZRA weekly use should be added to the inclusion criteria. Indeed, talking about BZRA deprescribing with very small BZRA users (less than 3 times a week) makes some questions irrelevant. Besides, criteria regarding the number of visits to the pharmacy should be also adjusted to ensure sufficient contact of the patient with the participating pharmacy.

Second, the recruitment strategy of the participating pharmacies should be revised. We recruited mostly highly educated older adults; our sample was therefore not representative of the general older population. Previous literature about health promotion research has shown that among older adults, the oldest old (≥ 80 years), ethnic minorities, and socio-economically disadvantaged people are the “hard-to-reach” population [8]. We hypothesize that the location of the pharmacy played an important role, as most participating pharmacies were in high-income municipalities (data not formally collected). The recruitment strategy of the pharmacies should be revised, and a special effort should be undertaken to ensure the participation of pharmacies located in middle and low-income municipalities (often also more culturally diverse). Indeed, previous literature has shown a significant association with low socioeconomic status and BZRA use [9]. Not including this part of the population would represent a missed opportunity. In those areas, the pharmacist could have a crucial role in helping “build trust” for these “hard-to-reach” participants with the research team [8]. Simplified recruitment documents could also help recruit participants for which written information and consent forms represent a barrier to participation [8]. In addition, as stratification criteria (i.e. location of the pharmacy (rural or urban) and type of the pharmacy (independent or collaborative practice) could be considered for a full effectiveness trial, the recruitment strategy should ensure sufficient variety in participating pharmacies.

Third, if this was not the primary objective of this study, we observed quite small differences in terms of BZRA deprescribing between the intervention and control group, with a quite high rate of BZRA deprescribing in the control group. As an example, 11 patients in the intervention group (34.4%) vs 6 patients in the control group (24.0%)

Section 3

achieved BZRA deprescribing defined as any BZRA reduction or BZRA cessation. Two patients in the intervention group (6.3%) and 2 patients in the control group (8.0%) completely ceased their BZRA. As a comparison, the deprescribing rates (defined as BZRA cessation at 6 months) of the EMPOWER and D-PRESCRIBE trials control groups were respectively 5% and 9 % vs 27 and 43% in the intervention groups [5, 10]. Three hypotheses may explain this observation. First, we believe that the intensity of the questioning during the research visits could have worked unexpectedly as an intervention component in the control group, making patients reflect on their BZRA use and change their behavior, particularly in already motivated patients. This was previously observed in another context, where control participants in a randomized controlled trial evaluating a complex intervention to promote social well-being after a stroke reported that research follow-ups and questioning improved their understanding of their condition (clarifying feelings), provided emotional support, and encouraged them to seek professional help [11]. The intensity of the questioning should be adapted for a full effectiveness trial to avoid this drawback. In the original D-PRESCRIBE trial, four research visits were planned (baseline, 7 days, 6 weeks, and 6 months post-intervention), but the questioning about BZRA was less intense and comprised only a questionnaire about BZRA tapering if it had begun [12]. A solution would be to remove some questionnaires from the data collection planned in the control group (i.e. questions about knowledge and self-efficacy, as well as the rPATD-BZRA questionnaire) as these questions may stimulate thoughts about BZRA use. Second, many changes in BZRA use were observed both in the intervention and control groups, with BZRA dose reductions and increases as well. As we calculated BZRA reduction based on diazepam equivalent dosage, it is likely that for some patients, BZRA reduction (or increase) occurred by chance, to the benefit of a change of molecule with a lower diazepam-equivalent dosage. Finally, we cannot exclude the possibility that the intervention was ineffective, given the limited difference in deprescription between groups. Process evaluation, in particular the interviews with patients and pharmacists, will provide complementary data that will help us to better understand mechanisms of action and outcomes. These interviews will also provide complementary information on differences that were observed in pharmacies.

Several outcomes were measured in our feasibility study: BZRA cessation at 6 months, BZRA deprescribing at 6 months (as defined as BZRA dose reduction of $\geq 25\%$ and/or BZRA cessation), and BZRA deprescribing at 6 months (as defined as any BZRA dose reduction and/or BZRA cessation). As “BZRA cessation at 6 months” was the main outcome of the D-PRESCRIBE trial, choosing this outcome for the full trial would allow compare the effectiveness of the intervention between Quebec and Belgium. However, our results suggest that a 6-month period of follow-up might be too short, as some

patients mentioned “not having seen their doctor yet” as a reason for not discussing BZRA deprescribing with their doctor. One solution could be to extend the follow-up period to 12 months. Because in real life, patients take time to make a decision and because the tapering process needs several weeks, this timeframe would give a better idea of the effect of the intervention. However, this choice might have several drawbacks: 1. it increases the resources needed for the study, 2. it may harden the recruitment process, as patients might be reluctant to engage for one year, and 3. it increases the probability of lost-to-follow-up.

If a 12-month follow-up period is not feasible, we believe that a more flexible definition of BZRA deprescribing should be preferred for a full-effectiveness trial (i.e. BZRA deprescribing as defined as $\geq 20\%$ BZRA dose reduction and/or BZRA cessation). Indeed, if a full cessation should be aimed for, this outcome may better reflect what is possible to achieve in 6 months. Patients take time to make a decision, begin with small reductions, and do not necessarily aim to stop completely their BZRA. This outcome differs from what was measured in our feasibility study. However, we believe that it could be a good compromise between BZRA deprescribing at 6 months (as defined as BZRA dose reduction of $\geq 25\%$ and/or BZRA cessation), that does not take into account BZRA dose reductions proposed by the first step of the NIHDI tapering program (20%), and BZRA deprescribing at 6 months (as defined as any BZRA dose reduction and/or BZRA cessation), that may lead to include non-significant dose reductions.

This study presents several limitations. First, we recruited pharmacies on a voluntary basis, and the recruitment target was barely obtained. This did not allow us to select pharmacies based on pre-defined criteria. However, the satisfaction survey highlighted overall good satisfaction of pharmacists with the study and the research staff, which is encouraging, considering that it is very unusual for community pharmacists to participate in clinical research in Belgium. Second, patients were also recruited voluntarily. It is therefore possible that we recruited some patients with more motivation towards BZRA deprescribing, who seized the opportunity of the study to stop or reduce their BZRA, and therefore do not represent general BZRA users. Finally, as discussed in Chapter 5, we did not predefine progression criteria to help decide whether to move toward a full implementation trial. However, the three main points that should have been comprised in these criteria (i.e. recruitment, adherence to the protocol, and “completeness and quality of outcome data”) were assessed, allowing discuss them a posteriori [13]. The complete results, which will also comprise the full process evaluation and preliminary cost-effectiveness analysis, will be discussed with the research team and an advisory board that includes representatives of key stakeholders, and the final decision will be made by the research team.

Section 3

CONCLUSION

The first results of the END-IT CS study show that implementing the adapted D-PRESCRIBE intervention is feasible in the Belgian community setting, yet with some uncertainties about the effect of the intervention. Additional qualitative data will be important to consider before moving to a full-effectiveness trial. If such a trial were to be undertaken, a longer follow-up period should be considered and some study conduction procedures would have to be revised, in particular, the recruitment of the pharmacies, the patient inclusion criteria, and the intensity of the questioning related to BZRA.

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GENERAL DISCUSSION

1. Summary of main findings

I showed in Chapter 1 that **BZRA use prevalence**, if slowly declining is still high in the Belgian older population aged 65 years or more (18% in 2013), and is even higher with increasing age. BZRA deprescribing interventions are thus needed in Belgian older adults.

Barriers and enablers to BZRA deprescribing in older adults were identified in Chapter 2 and mapped into domains of the TDF. The most relevant domains were Beliefs about capabilities, Beliefs about consequences, Intention, Goals, Memory, attention and decision processes, Social influences, and Environmental context and resources. To maximize the chances of success, the barriers and enablers highlighted in this SR should be targeted by BZRA deprescribing interventions.

To better understand the **attitudes of older adults toward BZRA deprescribing**, I adapted the rPATD questionnaire to BZRA. This work, presented in Chapter 3, resulted in a 13-item questionnaire (rPTAD-BZRA). This new questionnaire presented some statistical limitations. However, we believe that it might be a useful tool to initiate a conversation about BZRA deprescribing between HCPs and older adults. Besides, using the data collected for the questionnaire validation, this chapter also presented a short description of our participants' attitudes towards BZRA deprescribing. Corroborating the results of our SR, which highlighted low intention towards BZRA deprescribing, we found that only a third of older adults were willing to consider BZRA deprescribing.

Chapter 4 describes the adaptation process of the Canadian D-PRESCRIBE intervention, a pharmacist-led intervention, to the Belgian community setting. This intervention indeed demonstrated its effectiveness in BZRA deprescribing among community older adults, by increasing their motivation and self-efficacy. This study resulted in the production of an **adapted EMPOWER brochure** for older people and a **pharmaceutical proposal**, a new communication tool between Belgian pharmacists and physicians. If the brochure was quite unanimously well perceived by patients, pharmacists, and GPs, the survey that I conducted among GPs and pharmacists about the pharmaceutical proposal, showed some enablers but also some barriers to its implementation in real practice. This demonstrates the need for a feasibility study before undertaking a full implementation trial.

The protocol of this **feasibility study**, presented in Chapter 5, describes in detail the research objectives and the methods used for this study. Briefly, we aimed 1) to assess the feasibility of the adapted D-PRESCRIBE intervention in the Belgian community setting, 2) to assess the feasibility of the study design and procedures needed for a full

General discussion

(cost)-effectiveness trial, and 3) if data permits, to explore the potential economic impact of the intervention. For these objectives, we conducted a feasibility study of a cluster-randomized controlled trial, that included 57 older adults within 7 community pharmacies (clusters). Chapter 6 shows the first results of this study. The full process evaluation and preliminary cost-effectiveness do not fall in the scope of this thesis (and will be described elsewhere). Preliminary results showed that implementing the adapted D-PRESCRIBE intervention was feasible in the Belgian community setting, yet with some uncertainties about intervention effectiveness. The decision to move forward with a full implementation trial will be made based on the results of the process evaluation. If such a trial were to be undertaken, some study procedures should be adapted.

2. To what extent are the different chapters linked?

As we used the CWDIF a posteriori, one can ask how well the tools that we have developed (i.e.: the questionnaire (Chapter 3), the adapted EMPOWER brochure, and the pharmaceutical proposal (Chapter 4)) targeted the TDF domains highlighted in the systematic review (Chapter 2).

Table 1 presents the main TDF domains found in the systematic review and the TDF domains we believe could be investigated by the items of the rPATD-BZRA questionnaire. Three major domains highlighted in our systematic review are not covered by the rPATD-BZRA questionnaire: Memory, attention and decision processes, Environmental context and resources, and Social Influences. Further discussion about the items of the rPATD-BZRA questionnaire is provided at point 3.

Table 1. Match between the main Theoretical Domains Framework domains identified in the systematic review and items of the rPATD-BZRA questionnaire		
Main TDF domains	Coverage by the rPATD-BZRA questionnaire	Related item(s)
Beliefs about capabilities	Yes	• I feel like I have no other choice but to take my benzodiazepine to feel okay or sleep well. • I feel dependent on my benzodiazepine.
Beliefs about consequences	Yes	• If my benzodiazepine was stopped, I would be worried about my health and well-being. • If my benzodiazepine was changed (e.g. change of dose, composition, brand name) I would get stressed

General discussion

		I believe that my benzodiazepine is giving me side effects
Intention	Yes	- I would be reluctant to stop taking my benzodiazepine - If my doctor recommended it, I would be willing to reduce the dose of my benzodiazepine. - If my doctor recommended it, I would be willing to stop taking my benzodiazepine.
Goals	Yes	With my doctor's help, I would like to try stopping my benzodiazepine to see how I would feel without it.
Memory, attention, and decision processes	No	-
Environmental context and resources	No	-
Social influences	No	-
Legend: TDF: Theoretical Domains Framework; rPATD-BZRA: revised Patients Attitudes towards Deprescribing questionnaire adapted for benzodiazepine receptor agonists.		

To identify TDF domains targeted by the adapted D-PRESCRIBE intervention, we used the Theory and technique tool [1]. Briefly, this tool, available online (<https://theoryandtechniquetool.humanbehaviourchange.org/tool>) allows linking mechanisms of action, which include the 14 TDF domains, and behavior change techniques. Behavior change techniques may be operationalized in intervention components. We used this tool backward: first identifying intervention components of the D-PRESCRIBE intervention, then linking them to a behavior-change technique according to its definition, and finally retrieving the TDF domains related to this behavior change technique (see Table 2). Of the seven major TDF domains that we highlighted in the systematic review, all but one (the TDF domain "Goals") are addressed by the D-PRESCRIBE intervention. Indeed, behavior change techniques associated with "Goals", such as Goal setting or review outcome/behavior goals, are more likely to be performed inside the clinical relationship (patient-GP and/or patient-pharmacist).

General discussion

Table 2. Backward retrieval of Theoretical Domains Framework domains targeted by the D-PRESCRIBE intervention			
EMPOWER brochure			
Element in the brochure	Identified Behavior change technique	Definition of the Behavior change technique	Related TDF domains
Title “You may be at risk”	• Salience of consequence	• Use methods specifically designed to emphasize the consequence of performing the behavior with the aim of making them more memorable.	• Beliefs about consequences*
Quiz, “Did you know”, “With age”.	• Information about health consequences	• Provide information (e.g. written, verbal, visual) about health consequences of performing the behavior.	• Knowledge • Beliefs about consequences* • Intention*
Testimony	• Social comparison	• Draw attention to others’ performance to allow comparison with the person’s own performance.	• Social influences*
Advice on how to sleep and handle anxiety differently	• Restructuring the physical environment • Restructuring the social environment • Social support (practical)	• Change, or advise to change the physical/social environment in order to facilitate performance of the wanted behavior or create barriers to the unwanted behavior. • Advice on, arrange, or provide practical help (e.g. from friends, relatives, colleagues, buddies, or staff) for performance of the behavior.	• Environmental context and resources* • Social influences*
Tapering program	• Instruction on how to perform the behavior • Graded task	• Advise or agree on how to perform the behavior (including Skills) • Set easy to perform tasks, making them increasingly difficult but achievable, until	• Knowledge • Skills* • Beliefs about capabilities*

General discussion

		behavior is performed.	
Pharmaceutical proposal			
Reminder of risks associated with BZRA long-term use	Information about health consequences	Provide information (e.g. written, verbal, visual) about health consequences of performing the behavior.	- Knowledge - Beliefs about consequences* - Intention*
Pharmacist's opinion Reminder of the guidelines	Information about others' approval	Provide information about what other people think about the behavior. The information clarifies whether others will like, approve, or disapprove of what the person is doing or will do.	Social influences*
Proposal itself	Restructuring the social environment	Change, or advise to change the social environment in order to facilitate performance of the wanted behavior or create barriers to the unwanted behavior.	Environmental context and resources
Sending/Receiving the proposal	Prompt/cues	Introduce or define environmental or social stimulus with the purpose of prompting or cueing the behavior. The prompt or cue would normally occur at the time or the place of performance	- Memory, attention, and decision processes* - Environmental context and resources*
Tapering options	- Instruction on how to perform the behavior - Graded task	- Advise or agree on how to perform the behavior (including Skills) - Set easy to perform tasks, making them increasingly difficult but achievable, until behavior is performed.	- Knowledge - Skills* - Beliefs about capabilities*
Legend: * TDF domain highlighted as major in the systematic review.			

General discussion

Both Tables 1 and 2 show that the tools that we have developed fit, imperfectly for the rPATD-BZRA questionnaire, and quite well for the Belgian D-PRESCRIBE intervention components, the results of our systematic review. If the systematic review did not help tailor the components of our intervention, it supports the relevance of adapting the D-PRESCRIBE intervention to the Belgian community setting.

3. Discussion

3.1. How to optimally measure older adults' attitudes towards BZRA deprescribing?

As discussed in Chapter 3, the rPATD-BZRA questionnaire presents several limitations. First, BZRA deprescribing generated polarized views in participants, as we observed high floor and ceiling effects in many items. The very limited variance on several items led us to remove them from the analysis whereas they might have evaluated important dimensions for older adults. Second, the questionnaire explained a low percentage of variance. This suggests that relevant dimensions might not be assessed in this questionnaire. One explanation could be that neither the original rPATD nor its adaptation leaned on theory in item development. The questionnaire elaborated by Lynch *et al* in 2024 does not present this drawback, as the authors based the item development on the TDF [2]. The questionnaire, validated in a ≥ 18 -year-old population, aims to explore barriers and enablers towards long-term BZRA deprescribing [2]. It includes 29 items distributed in 9 theoretical domains from the TDF. Three important TDF domains, highlighted in our systematic review, are covered by Lynch's questionnaire while they are not covered in our questionnaire: Social influences, Environmental context and resources, and Memory, attention and decision processes. Adding these dimensions to the rPATD-BZRA questionnaire might improve it. Besides, the two rPATD-BZRA items related to Beliefs about capabilities do not investigate directly older adults' capabilities towards BZRA deprescribing. In that matter, the items developed by Lynch and colleagues, such as "I am confident that I can stop my use of benzodiazepines/Z-drugs" or "I am confident that I can stop my use of benzodiazepines/Z-drugs while still managing the symptoms associated with medical condition (e.g. anxiety, insomnia)" seem particularly relevant. If covering more dimensions than the rPATD-BZRA questionnaire, some statistical limitations were also observed in Lynch's questionnaire, as authors reported fit values outside statistical standards. This shows the difficulty of creating a statistically perfect tool to assess attitudes towards BZRA deprescribing. In addition, clinicians would benefit from a questionnaire as short as possible for quick and efficient use in clinical practice. We recognize that thirteen items might already be too much. On one hand, the

development of a new version of the rPATD-BZRA questionnaire should consider adding new items to make sure that all important dimensions are considered. On the other hand, a short rPATD-BZRA questionnaire with only three to five items representing only the most relevant ones should be developed to be used in daily clinical practice.

If both researchers and clinicians would benefit from a tool allowing the identification of patients more likely to deprescribe, such a tool is not currently yet available [3]. Indeed, Turner *et al.* calculated the predictive value of the PATD (the first version of the rPATD questionnaire) and the Beliefs about Medicines Questionnaire (Specific section) showing that none of these questionnaires allowed to predict successful or unsuccessful deprescribing [3]. None of these questionnaires are specific to one medication, and we hypothesize that a questionnaire assessing attitudes toward deprescribing a specific medication class might better predict its deprescribing. Future research perspectives could therefore include the evaluation of the predictive value of the rPATD-BZRA questionnaire and Lynch's questionnaire.

3.2. How do our tools fit in the current BZRA deprescribing policies in Belgium?

In this thesis, we adapted tools to better engage older adults and healthcare professionals in BZRA deprescribing: the rPATD-BZRA questionnaire may help HCPs explore patients' attitudes towards BZRA deprescribing and engage the conversation about BZRA use with patients; the adapted EMPOWER brochure aims to increase patients' knowledge and concerns about BZRA use and their self-efficacy towards deprescribing; finally, the pharmaceutical proposal aims to foster tri-partite communication between patients, pharmacists and prescribers around BZRA use and potential deprescribing, and to increase pharmacists' and prescribers' knowledge and accountability towards medication appropriateness. As the tools we have developed are specific to older adults, they complete other tools, already available in Belgium in the frame of the national awareness campaigns, that target the general population. In fact, as a large proportion of Belgian BZRA users are older adults [4], and because BZRA use exposes them to specific risks, we believe that it is important for the education material to target this particular population⁴. Indeed, as explained by Kreuter and Wray in 2003, *"a message may be more likely to be perceived as relevant by an individual if it is seen as responding to his or her particular circumstance, life experience, or*

⁴ In the frame of a regional campaign about fall prevention in 2016, an educational brochure "Van slaappillen, kan je vallen" (which may translate to "From sleeping pills you could fall"), was developed in Flanders. This brochure is an adaptation of the Canadian EMPOWER brochure. (see this website: https://storage.googleapis.com/smooty-1220.appspot.com/uploads/3124/1558363012_2016EducatiebrochureVanslaappillenkanjevallen.pdf).

General discussion

predisposition to adopt a recommended behavior and is matched according to reading ability, learning preferences, cultural markers and other such characteristics” [5] (p. 228).

The three tools we developed aim at changing behavior of individuals, either patients or HCPs. However, from a health promotion perspective, individual behavior change strategies are not enough, as broader measures, often taken at a political level, are needed to create a favorable environment for the promoted behavior [6]. As presented in Figure 1, several federal measures promote BZRA deprescribing in Belgium whether providing supportive environmental conditions or directly aiming at changing patients' or HCPs' behavior.

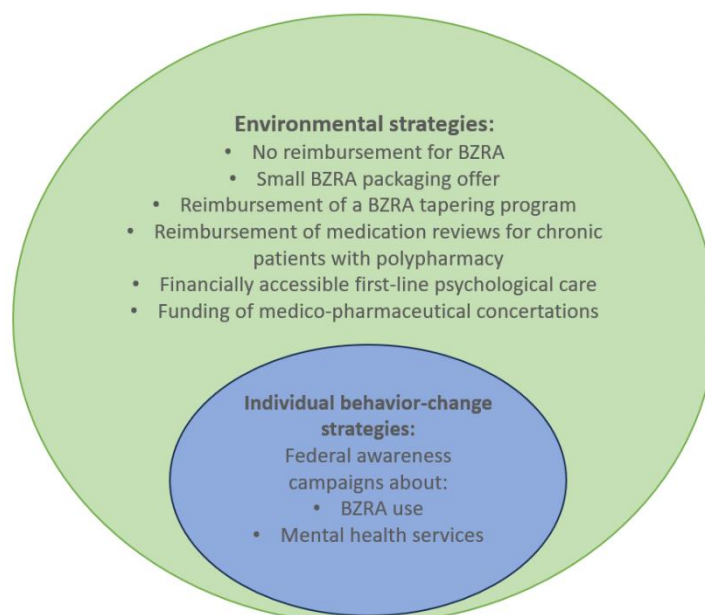


Figure 1. Summary of the Belgian federal measures promoting or supporting BZRA deprescribing

First, as previously stated in the introduction, the NIHDI does not reimburse BZRA, so patients fully assume the costs of their BZRA. However, the prices are low as generic medications are available for most BZRA and cost is not a major barrier for BZRA users. In 2018, the Federal Agency for Medicines and Health Products (FAMHP), together with the Belgian Psychotropic Expert platform (BEL-PEP) proposed to the pharmaceutical industry sector to broaden the BZRA **small packaging offer** [7]. This initiative aimed to

prevent long-term use, especially at BZRA initiation [7]. Still, few small packaging options are available in 2024, showing the reluctance of the pharmaceutical industry to offer smaller BZRA boxes. Out of the 22 BZRA available on the Belgian market, only three are available in boxes of ≤ 10 tablets (flunitrazepam (which is a BZRA assimilated to narcotics, is mandatorily limited to 10 tablets), triazolam, and zolpidem), one is available in a 14-tablets box (alprazolam) and four are available in 20-tablets boxes (clotiazepam, lorazepam, lormetazepam, and prazepam) [8]. Except for zolpidem, which is also available in 28 tablets, all other BZRA are only available in boxes of ≥ 30 tablets (up to 60 tablets for some BZRA) [8]. Prescription data showed that only 1% of all boxes of purchased zolpidem were in small packaging (≤ 10 tablets) in 2022 [9]. Besides, only 6 % of the zolpidem new users were prescribed a small packaging (≤ 10 tablets) in 2022 [9]. This shows that prescribing habits poorly integrate the small packaging option. In light of our data (Chapter 3: additional data) that suggest very low intention towards BZRA deprescribing in older adults once BZRA are initiated, it seems crucial to strengthen BZRA long-term use prevention along with BZRA deprescribing. Making the prescription of small packaging mandatory for initial BZRA use could be one effective option to limit BZRA long-term use. Indeed, in Denmark, where the limitation of BZRA prescriptions to one month at a time after a consultation (no telephone prescription allowed) was tested in 10 medical practices, BZRA prescriptions were found to drop by more than 40% after fifteen months, without drastically increasing the number of consultations [10].

Two new pharmaceutical care services were recently reimbursed by the NIHDI and foster BZRA deprescribing in the general population. **First, a pilot BZRA tapering program** was launched in February 2023 [11]. On several conditions (being aged ≥ 18 years, using a single BZRA (in one dose of maximum 3 times the daily defined dosage) for at least three months, authorizing data sharing on the eHealth platform, and following the program in the same pharmacy), patients may benefit from this program that uses capsules compounded by the pharmacist containing a decreasing percentage of BZRA [11]. The making of the capsules and two support follow-ups by the pharmacist are financed by the NIHDI. This pilot program, initially planned for a one-year duration starting from February 2023, has been extended to 31 August 2024, and its allocated budget was increased given the high number of patients entering it. “Displaying visual prompts” and “attaching educational brochures to prescription bags” are two strategies highlighted by Canadian pharmacists to integrate deprescribing services into the pharmacy workflow [12]. Similarly, making the Belgian EMPOWER brochure available in the pharmacy, near information about the tapering program, or providing proactively the brochure on the occasion of a renewal, might

General discussion

enhance older adults' awareness and encourage discussion with the pharmacist about BZRA deprescribing.

Second, in April 2023, the NIHDI **reimbursed medication reviews** as a new pharmaceutical care service. Under specified conditions, any patient that takes ≥ 5 reimbursed chronic medications may benefit from a medication review every two years at maximum [13]. If this new service does not directly aim at BZRA deprescribing, medication reviews could be opportunities to re-evaluate BZRA use and discuss potential deprescribing. A realist review explored the context-mechanisms-outcomes configurations needed for medication reviews and deprescribing interventions to be effective for older adults in primary care [14]. Authors underlined that for allowing recommendations of medication reviews to be accepted and implemented, several elements were crucial, notably, the quality of the pharmacist-GP relationship, the integration of the pharmacist as a member of the multidisciplinary team, and a clear definition of roles and responsibilities. We believe that there is room for improvement in that matter in our country. Indeed, the survey conducted in Chapter 4 about the implementation of the pharmaceutical proposal revealed some barriers related to role boundaries. **Medico-pharmaceutical concertations** (MPC) can foster interprofessional collaboration between pharmacists and GPs at a local level. These are local meetings funded by the NIHDI, that can be organized on several topics approved by the NIHDI [15]. One of them is about the rational prescription and drug delivery of benzodiazepines. However, if MPCs ultimately aim at care quality improvement, their uptake by pharmacists and GPs is currently below the NIHDI expectations [15].

In March 2024, the NIHDI launched a new **campaign** named “*Stress, solitude, anxiété, ne les laissons pas s’installer*” (which might translate to “Stress, loneliness, anxiety, let’s not let them setting in”) [16]. This campaign aims to promote **recourse to first-line psychologic care**. The campaign website provides an interactive tool that helps people find a contracted psychologist close to home. If patients consult contracted psychologists, they can benefit from a first free consultation. Eight to 20 individual consultations are further reimbursed for a period of one year (out-of-pocket cost equals 11 euros per consultation). The number of contracted psychologists is however limited. This campaign follows and completes the latest campaign about the **rational use of psychotropics**, launched in 2023 by the Public Federal Service Health, Food Chain Safety and Environment, “*Psychotropes: quels risques pour vos patients ? Ensemble, favorisons un usage adapté*” (which might translate to “Psychotropic drugs: what are the risks for you patients? Together, let’s promote appropriate use”). This campaign aims to limit psychotropic use in the Belgian population by providing healthcare professionals with evidence-based resources such as e-learning or educational

material [17]. Interdisciplinary collaboration between GPs, pharmacists, and psychologists is emphasized and promoted notably through videos highlighting the roles of each HCP and the promotion of MPC. In 2019 in Canada, the MedSaferNL initiative promoted BZRA and proton-pump inhibitors deprescribing at the province level, one of its components being a public awareness campaign [18]. The evaluation of the project by a panel of HCPs ranked the campaign in the top 5 actions that help them on the field. Indeed, they reported that the campaign “legitimized deprescribing” and “supported the cultural change necessary to improve appropriate medication use” (p. 138) [18]. Besides, interviewed HCPs perceived that campaigns lightened the pressure to put deprescribing on the table [18]. Therefore, we believe that a federal campaign, using the word “deprescribing” instead of “rational use” might have a stronger impact in reducing BZRA use in our country by making this concept more common in patients’ and HCPs’ minds. Besides, as a recent qualitative study conducted among Belgian adults showed that they perceived BZRA as “harmless medications” [19], more effort should be undertaken to change that conception. Adding clear information about risks upon BZRA boxes and inside (with information sheets) should be considered.

Healthcare providers’ **audit and feedback** is a quality of care improvement strategy that has been widely used, alone or in combination with other components [20], including in the field of deprescribing [21-23]. In Belgium, the *Conseil National de Promotion de la qualité* (National Council for Quality Promotion) set up in November 2023 an audit and feedback to promote the rational use of antibiotics, based on three indicators, and aiming to reduce their use by 40% [24]. We may wonder if such a strategy should also be used to foster BZRA deprescribing, provided that data about BZRA prescribing were available for all GPs (which is not currently the case). A study conducted in Japanese primary care in 2020 tested the feasibility of monthly audit alone or monthly audit and coaching to promote BZRA deprescribing [25]. Authors found that both interventions had a limited effect on BZRA deprescribing but that combining audit with coaching was more positively perceived by HCP than audit alone [25]. Indeed, the systematic review of Ivers *et al* about the use of audit and feedback in HCP concluded that it was more likely to be effective if “*the source is a supervisor or a colleague, it is provided more than once, it is delivered in both verbal and written formats, and when it includes both explicit targets and an action plan*”[20]. Sending their BZRA prescribing statistics to prescribers should be included in a larger program that supports prescribers in their efforts.

3.3. Multidisciplinary collaboration, a key for BZRA deprescribing

We highlighted in Chapter 2, that GPs' heavy workload and limited time available are major obstacles towards BZRA deprescribing [26]. Hence, multidisciplinary collaboration may be a key to enhancing BZRA deprescribing in the community setting.

Community pharmacists are first-line HCPs particularly available for patients. A systematic review and meta-analysis showed that pharmacists' interventions (through education or medication review) had a significant effect on BZRA deprescribing (low quality of evidence) [27]. As explained previously, the clinical role of pharmacists has expanded in the last few years in Belgium, with the reimbursement of a BZRA tapering program and medication reviews. In Chapter 6, we showed that there is room for the pharmacist to take a proactive role in patient education regarding BZRA use and deprescribing and collaboration with the GP through the pharmaceutical proposal. Despite the limited responsiveness from prescribers to pharmaceutical proposals observed in our feasibility study, we believe that pharmaceutical proposals might be an interesting tool for advancing pharmacists-GP collaboration and promoting BZRA deprescribing. As to our knowledge, no formal communication tool currently exists between these two categories of HCP in Belgium, the pharmaceutical proposal might fill an unmet need in that matter. However, a shift towards an interprofessional collaboration work culture should be reinforced by adequate training. Indeed, our survey among GPs and pharmacists (in Chapter 4), showed that only 54% of the GPs agreed that it was pharmacists' role to ask them about potential BZRA deprescribing for their patients. This may indicate that the pharmacist's role in pharmaceutical care is still underestimated by a significant proportion of GPs. The curriculum framework for deprescribing developed by Farrell and colleagues highlights that the opportunity for interprofessional training should be considered when teaching deprescribing skills [28]. Today, local initiatives are undertaken to promote it, notably at UCLouvain, where future GPs and pharmacists meet to think about BZRA use and deprescribing during a one-day training session. More of these collaborative learning activities should be developed and implemented in GPs and pharmacists' curricula. Indeed, a focus-group study among HCP's teachers, clinical staff, and students (working in the ambulatory setting) showed that they identified four benefits for interprofessional learning: "development of personal relationships", "improved education", "improved patient care" and "improved job satisfaction" [29].

Psychologists are other healthcare professionals targeted by the latest federal campaign promoting interprofessional collaboration to foster the rational use of psychotropics [17]. Indeed, psychologists may help patients reflect on their symptoms and need for BZRA, and invite them to discuss BZRA use with their GP. In addition,

psychologists providing CBT-I as an alternative to BZRA use may play an important role in supporting patients during BZRA withdrawal.

Although **nurses** play an important role in medication management, none of the current Belgian policy integrates them as potential actors in BZRA deprescribing. A scoping review of deprescribing interventions in primary care showed, indeed, that nurses were seldom involved as intervention deliverers or intervention recipients of deprescribing interventions [30]. In the Netherlands, Dijkstra *et al* conducted a qualitative study about perceptions of home care nurses of their role in interprofessional collaboration in the frame of clinical medication review [31]. Interviewed nurses perceived they were in an ideal position to “*observe signs and symptoms such as non-adherence, usage problems, and side effects*” [31](p.4). Nurses also believed to have a role in patient education, in formulating in simpler words information provided by pharmacists or prescribers, or in answering patients’ questions about medication change [31]. Besides, they felt that they could provide physicians and pharmacists precious information to perform medication reviews, such as the use of over-the-counter medication or physical issues (e.g.: visual or cognitive impairment) [31]. These roles could be extrapolated to BZRA deprescribing. For example, nurses could report BZRA side effects such as balance troubles, memory problems, or urinary losses that may suggest the need for BZRA deprescribing. Nurses could also support BZRA deprescribing programs providing additional patient support or monitoring withdrawal symptoms. It has also been suggested that, beyond supporting deprescribing, nurses could take a proactive role in encouraging patients to discuss potential deprescribing with their doctor [32, 33]. However, for allowing nurses to have a role in BZRA deprescribing, their training should be reinforced. Indeed, a European study among final-year student nurses showed that nurses had shortcomings in knowledge about pharmaceutical care [34]. Besides, almost 40% of the nurse students felt not skilled enough to “propose initiation or discontinuation of certain medications” [34]. An online survey, conducted by our research group, is currently ongoing to explore future HCPs’ (i.e.: physicians, pharmacists, and nurses trainees) attitudes towards deprescribing and self-perceived deprescribing competencies, knowledge, and skills. This work aims to improve training programs to better equip Belgian HCPs to deal with deprescribing.

As BZRA deprescribing in older adults concerns not only GPs and pharmacists, communication between all first-line HCPs (i.e.: GPs, pharmacists, psychologists, and nurses) should be improved and supported by the authorities. Therefore we suggest MPC related to BZRA use to be extended to psychologists and nurses, in order for them to build trust, agree on each others’ roles, and coordinate efforts for better pharmaceutical care. Besides, as first-line HCPs’ communication is a key to an

General discussion

effective multidisciplinary collaboration, a single patient multidisciplinary electronic file, allowing for secure exchanges of information between the different HCPs should be made available, as advocated by the Federal expertise center in healthcare (KCE) report about integrated care in Belgium in 2024 [35].

Finally, **specialists** are not major initial prescribers of BZRA, unlike GPs, who were the initial BZRA prescribers for 83% of the delivered BZRA in 2022 [9]. If specialists are not targeted by the federal campaigns promoting the rational use of psychotropics, they could also be sensitized to reevaluate periodically the appropriateness of prescribing BZRA to their patients and deprescribe if necessary. Indeed, BZRA deprescribing is feasible in the hospital setting, as demonstrated by a retrospective study conducted in acute geriatric wards of a Belgian hospital showing that almost 43% of the patients taking BZRA at admission reduced or stopped their BZRA at discharge (mostly in reaction to an adverse event) [36]. Moreover, the literature has shown that GPs were reluctant to deprescribe medications prescribed by a specialist due to a sense of medical hierarchy [37, 38]. However, according to a recent European survey conducted within our research group, most GPs are in favor of continuing the BZRA deprescribing initiated by a hospital physician (Shapoval et al., manuscript in preparation). This shows the importance of hospital specialists taking a proactive role in BZRA deprescribing.

4. **Strengths and limitations of the PhD thesis**

One main strength of this thesis is that stakeholders were implicated in the adaptation of each tool (the questionnaire, the brochure, and the pharmaceutical proposal). Indeed, the development of each tool comprised a qualitative part that investigated older adults' and HCPs' opinions on the necessary changes.

However, the participants, along with those that we recruited to test the developed tools (Chapters 3, 4, and 6), were recruited on a voluntary basis. It is therefore likely that we selected participants (older adults and HCPs) with extra motivation for the topic. The generalizability of our results may thus be limited.

Recruiting older adults to participate in our studies was challenging throughout this thesis. The systematic review of Forsat *et al.* highlighted several strategies found effective in older adults' recruitment such as recruitment through mailing followed or not by a telephone call, recruitment through HCPs, or directly at a location where potential participants are present [39]. We utilized several in this thesis: recruitment of older adults through a mail distributed by pharmacies and GPs (Chapter 3), directly in nursing homes or serviced residences (Chapter 3), through their pharmacist or GP (Chapter 4), or after a face-to-face contact that followed first information by their

pharmacist (Chapter 6). If recruiting older adults for the END-IT CS study went well (Chapter 6), we believe it is mainly because they were first contacted by their pharmacist and then enrolled following a face-to-face contact at their own home. Indeed, “taking time to explain the goal of the study”, “partnership with medical staff participants know and trust”, “conducting recruitment in natural places (e.g.: private residence)”, were three strategies reported to improve recruitment [40]. Recruiting participants for the rPATD-BZRA study (Chapter 3) was far more difficult, first because of the COVID-19 situation, and second, we believe, because we did not have direct contact with participants that were distributed questionnaires by pharmacists and GPs, limiting the possibility to explain goals and to build trust.

The literature has also highlighted several barriers to the recruitment of pharmacists and GPs in research, a lack of time being commonly reported by both HCPs [41, 42]. Finding or not the research topic interesting has also been highlighted as an enabler or a barrier to participation for both GPs and pharmacists [42, 43]. More time should maybe have been dedicated to putting forward the interest for GPs and pharmacists to participate in our different research. A study conducted in the Netherlands in 2019 found that having to collaborate with a GP was a barrier to participating in research for more than 25% of pharmacists [43] but we do not know if it played a role in pharmacists' recruitment in the END-IT study. The difficulty of recruiting pharmacists might more likely be due to the absence of a culture of participation in research among community pharmacists in our country and the absence of an existing research network.

A second strength of this work is the use of implementation frameworks for the adaptation of the D-PRESCRIBE intervention (Chapter 4) and the conceptualization of the feasibility study (Chapter 5) (i.e.: the Medical Research Council framework and the ADAPT guidance [44, 45]). Using these frameworks improved the methodological rigor of our work and allowed providing transparent results. If we used the CWDIF model to structure our thesis and if its different sections fit quite well into this model, our thesis was not initially thought within the CWDIF. However, the other frameworks we used allowed us to provide results coherent with the CWDIF approach.

5. Perspectives

We adapted three tools to promote BZRA deprescribing in the Belgian community setting. These tools complement others available in Belgium but not specifically designed for older adults. After their re-assessment following the process evaluation, the Belgian EMPOWER brochure and the pharmaceutical proposal will be made available on the BEL-PEP website.

General discussion

Further work is nevertheless needed (and sometimes already ongoing) to test and improve these tools.

First, the effectiveness of the brochure and pharmaceutical proposal should be tested to ascertain their effect on BZRA deprescribing. A full implementation trial may take place within the DI-PRESCRIBE project. This project is an *Action de Recherche Concertée* (Concerted Research Action) project funded by UCLouvain, whose topic is “Deprescribing in older adults through an implementation research approach – Understanding and addressing what matters at patient/caregiver, health care professional and organizational/ environment levels”. The full process evaluation and the preliminary cost-effectiveness analysis of the END-IT CS study are planned in the frame of the DI-PRESCRIBE project. The interviews that are currently ongoing with patients and pharmacists in the frame of the process evaluation will allow highlighting area for improvement for both the brochure and the pharmaceutical proposal. The results of the process evaluation should be available in September 2024. As explained in Chapter 6, the decision about moving on to a full-effectiveness trial will depend on the assessment of complete results by the research team and insights from the DI-PRESCRIBE advisory board.

The adaptation of the EMPOWER brochure to the Belgian community setting helped other research projects. First, the brochure was further adapted for the nursing home setting and used in the END-IT NH project (a similar project to the END-IT CS study, conducted in the nursing home setting) [46]. Second, it was also further adapted in the frame of the European BE-SAFE project for 5 additional European countries following a similar approach to the one described in Chapter 4. This adapted brochure will be integrated into the BE-SAFE intervention and tested in a coming randomized controlled trial aiming to reduce BZRA taken for insomnia. Besides, the adaptation process that we followed may help other researchers to adapt other EMPOWER brochures (e.g.: about opioids, proton-pumps inhibitors, or non-steroidal anti-inflammatory drugs) or other interventions. Pharmaceutical proposals about other medications could also be developed.

We believe the brochure should be further adapted for a less literate public and for culturally diverse subgroups (such as the Maghrebian community) who may have different needs. If it was originally designed by Martin and Tannenbaum to be readable for older adults with a grade 6 reading level (i.e. reading level of an 11 to 12 years child) [47], it could still be difficult for people whose mother tongue is not French and for older adults with low literacy. A study conducted between 2016 and 2017 in Belgium showed indeed that health literacy was inadequate for 14.5% of older adults (≥ 65 years) and problematic for 24.5% of them [48]. Further improving the readability of the brochure

and its accessibility could improve its uptake and expand its use. With the same purpose, we should check if the content of the brochure is culturally appropriate for other communities. The brochure should also evolve with the Belgian context and include up-to-date information on first-line psychologic consultations. A regular revision of its content should be undertaken to ensure its coherence with the evolution of the healthcare system.

Finally, we saw that if it already produces some interesting results (see Chapter 3-additional data), the rPATD-BZRA questionnaire is far from perfect. Further work is ongoing in our research group to build on this questionnaire and the one developed by Lynch *et al.* Indeed, in the context of the European BE-SAFE project, a questionnaire aiming to explore barriers and enablers towards BZRA deprescribing in older adults taking them for insomnia combined items from the Lynch *et al.* questionnaire and adapted items of the rPATD-BZRA (Shapoval *et al.*, manuscript in preparation). Furthermore, in the context of the DI-PRESCRIBE project, a systematic review regarding the use of health behavioral theories to understand or predict older adults' deprescribing willingness in general (i.e.: unspecific to one medication in particular) was performed by another PhD student (Alves Jorge *et al.*, manuscript in preparation). This systematic review aims to create a questionnaire that would cover all the identified theoretical dimensions. We believe that the insights of these two projects could help improve the rPATD-BZRA questionnaire. Besides, as the rPATD-BZRA questionnaire was administered during the END-IT studies (in the community and nursing homes settings), at baseline (N= 92) and 6 months (N= 79), data is now available to calculate, upon a limited number of participants, the predictive value of answers to the different items providing more insight about the ability of this questionnaire to predict BZRA deprescribing.

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Curriculum vitae

List of publications and communications

Scientific publications related to this thesis

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Poster presentations at international meetings

- Péteïn, C, Spinewine, A., Henrard, S., Trends in Benzodiazepine Receptor Agonists Use and Associated Factors in Belgian Older Adults: Analysis of the Belgian Health Interview Survey Data, International Congress of the European Geriatric Medicine Society (EUGMS), 7-9th October 2020 (online).
- Péteïn, C., Spinewine, A., Laroche, M-L, Niquille, A., Henrard, S., Adaptation and validation of the French revised Patients' Attitudes towards Deprescribing (rPATD) questionnaire for benzodiazepine receptor agonists, 1st International Conference on Deprescribing (ICOD), 5-7th September 2022, Kolding, Denmark.
- Péteïn, C., Dujardin. N., de Montigny, M., Dewez, E., Spinewine, A. & Henrard, S, Deprescribing Benzodiazepine Receptor Agonists in Older Adults: Adaptation of the D-PRESCRIBE Intervention to the Belgian Community Setting, International Congress of the European Geriatric Medicine Society (EUGMS), 20-22th September, Helsinki, Finland.

Oral presentation at national meetings

- Ma Thèse en 180 secondes. « Pour arrêter les somnifères, une solution, la communication ! », UCLouvain, 21st March 2023.
(<https://www.youtube.com/watch?v=df74oDAw7-s>)