Enhancing the uptake of benzodiazepine deprescribing in nursing homes:

Insights from behaviour-change theories and implementation science

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Septembre 2024

Thèse présentée en vue de l'obtention du grade de docteure en sciences biomédicales et pharmaceutiques

Secteur des sciences de la santé

« Individuellement nous sommes une goutte d'eau.
Ensemble nous sommes un océan. »

Ryunosuke Satoro

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REMERCIEMENTS

Lorsque j'ai commencé cette thèse, il y a déjà 6 ans, je n'avais qu'une vague idée de ce qui m'attendait. Ce fut pour moi une expérience extrêmement enrichissante, jalonnée de nombreuses opportunités. Si j'ai parfois eu l'impression de me retrouver face à une montagne, j'ai aussi eu la chance d'être entourée de formidables personnes. Je tiens à vous remercier, chacun d'entre vous, qui m'avez aidée à avancer, marche après marche.

Tout d'abord Anne, mon exceptionnelle promotrice. Merci de m'avoir donné cette opportunité il y a 6 ans. Merci pour tes conseils, ton écoute, ta bienveillance et tes mots toujours si justes. Merci aussi pour les nombreuses relectures, et les documents retournés toujours avec beaucoup de commentaires constructifs.

Merci aussi à toi Séverine, ma co-promotrice, pour ton accompagnement, ta patience et tes qualités humaines. Merci aussi, bien sûr, pour ton aide si précieuse avec les statistiques.

Je remercie également les membres de jury de cette thèse, les Professeurs Françoise Van Bambeke, Marie de Saint Hubert, Veerle Foulon, Olivia Dalleur, Marc Vanmeerbeek, Tinne Dilles, et Sion Scott. Que vous m'ayez accompagnée sur l'ensemble de ce parcours ou uniquement lors des dernières étapes, vos précieuses critiques et vos conseils ont grandement contribué à la réussite de ce travail.

Cette thèse m'a également offert de formidables opportunités de collaborations. Merci aux résidents, professionnels de santé et maisons de repos qui ont contribué à ce projet. Merci à Jeremy Grimshaw et Andrea Patey, à Ottawa, de m'avoir accueillie et formée à l'utilisation des sciences d'implémentation. Merci aussi à Amber Damiaens d'avoir réalisé avec moi notre étude qualitative.

Dans cette folle aventure, j'ai aussi eu la chance d'être accompagnée quotidiennement par des collègues formidables. Merci à Pauline, Anne-Elisabeth, et Stefanie de m'avoir accueillie au CLIP. Merci à Antoine, François-Xavier, Juliette, Laudine, Maria, Marine, Rostand, Sara, Victoria, et Vlad pour l'atmosphère si chaleureuse que vous savez donner à notre groupe de travail, et pour vos

nombreux encouragements. Un merci INFINI à Catherine, la meilleure partenaire dont je pouvais rêver pour cette thèse. Merci pour la multitude de rôles que tu as su endosser : supportrice n°1, relectrice, amie, maman bruxelloise, oreille attentive… Merci pour tous les moments partagés et la belle complicité que nous avons développée.

Merci également à mes nombreux collègues du plateau TFAR, et particulièrement Hélène, Aline, Alix, Emilia, Romain et Audrey pour les nombreuses soirées jeux.

Pour poursuivre avec les collègues, j'ai aussi eu la chance de travailler comme assistante à la faculté de pharmacie et sciences biomédicales. Merci aux différents professeurs qui m'ont fait confiance dans cette tâche, et merci aux assistants et techniciens qui m'ont accompagnée en TP. Merci à Maude, Romano, Pauline, Julien, Adam, Justine, Romane, Sarah, Loïc, Perrin, Anne-Marie, et Martial.

Merci à mes amis, pour tous les moments partagés, qui ont contribué à recharger mes batteries pour mieux me faire avancer sur ce parcours. Merci particulièrement à Elodie pour ton aide avec la couverture de cette thèse. Et merci bien sûr à Alexandra, d'avoir partagé ce chemin avec moi, d'avoir célébré mes réussites, et d'avoir aidé à atténuer les mauvais moments.

Merci aux différents colocataires avec lesquels j'ai vécu pendant ces années : Sébastien, Marie-Cécile, Jean, Cattleya, SP, Marine, Ana, Yasmine, Alex et Alex. Merci d'avoir toujours été là pour m'écouter et m'encourager. Merci surtout pour tous les bons moments que nous avons partagés.

Merci à Albert, pour tout. Le soutien, les encouragements, et tous les petits moments du quotidien qui m'ont été si chers.

Il me reste enfin à remercier ma famille. Merci à vous pour le cocon que vous représentez. Merci pour votre douceur comme pour votre humour piquant. Enfin, merci à vous, et particulièrement à Bompa, pour nos nombreux débats qui ont sans aucun doute contribué à mon esprit critique.

A chacun d'entre vous, MERCI.

Perrine

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SUMMARY

Benzodiazepine receptor agonists (BZRAs, benzodiazepines and Z-drugs) are mainly used for anxiety and insomnia but have an unfavourable risk-benefit ratio in older adults. Despite this, chronic BZRA use is highly prevalent in Belgian nursing homes (NHs). In this context, this thesis aims at developing a behaviour-change intervention towards BZRA deprescribing in NHs, with insights from implementation science and stakeholders' involvement.

We first evaluated the current practices of BZRA use in Belgian NHs, showing that 52.4% of NH residents receive BZRAs, often for longer than the recommended 4-week period (98% of BZRA users). We then developed an intervention to enhance the uptake of deprescribing through (i) an evaluation of barriers and enablers of BZRA deprescribing, and (ii) the selection and design of intervention components targeting these barriers and enablers. Our process was embedded in a robust implementation framework and employed several behaviour-change tools such as the Theoretical Domains Framework and the Behaviour Change Techniques Taxonomy v1. It resulted in the END-IT NH intervention, which encompasses goals and process setting, healthcare professionals' education, environmental adaptations, audit and feedback, residents and relatives raising awareness, and multidisciplinary work. Finally, we performed a cluster-randomized controlled trial to assess the feasibility of implementing and evaluating the END-IT NH intervention. Our results showed that the intervention was feasible but would require several refinements before moving on to a larger-scale implementation. Observed deprescribing rates were also encouraging.

By employing behaviour-change theories and an implementation science approach, this thesis sets the first stones of a future intervention towards BZRA deprescribing in Belgian NHs. The approach used helps strengthen evidence on how best to move deprescribing forward in clinical practice.

ABBREVIATIONS

AGS	American Geriatrics Society
ATC	Anatomical Therapeutical Chemical
BCT	Behaviour change technique
BZD	Benzodiazepine
BZRA	Benzodiazepine receptor agonists
CBT-I	Cognitive behavioural therapy for insomnia
CDSS	Clinical decision support system
CFIR	Consolidated framework for implementation research
CI	Confidence interval
CIRS-G	Cumulative Illness Rating Scale-Geriatric
CNS	Central nervous system
COM-B	Capacity, Opportunity, Motivation, Behaviour
COME-ON	Collaborative approach to Optimise Medication use for Older people in Nursing homes
COPD	Chronic obstructive pulmonary disease
COS	Core outcome set
CP	Coordinating physician
DSM-V	Diagnostic and statistical manual of mental disorders – Fifth edition
FG	Focus group
GABA	g-aminobutyric acid
GAI-SF	Geriatric anxiety inventory – short form
GP	General practitioner
HCP	Healthcare professional
ISI	Insomnia severity index
LIM	Local Interdisciplinary meeting
MMAT	Mixed-methods appraisal tool
MoA	Mechanism of action
MR	Medication review
MRC	Medical research council
MRPA	Maison de repos pour personnes âgées
MRS	Maison de repos et de soin
NH	Nursing home
NHR	Nursing home resident
NNH	Number needed to harm
NNT	Number needed to treat
NPI	Neuropsychiatric inventory
OR	Odds Ratio
PIP	Potentially Inappropriate prescription

PPI	Patient and Public involvement
RCT	Randomized controlled trial
rPATD	Revised patients attitudes towards deprescribing
SR	Systematic review
START/STOPP	Screening Tool to Alert to Right Treatment/ Screening Tool of Older People's Prescriptions
TDF	Theoretical domains framework
US	United States

GENERAL INTRODUCTION

This general introduction begins with information on medication use in nursing homes, and on existing interventions for quality improvement. It then elaborates on benzodiazepine receptor agonists use in insomnia and anxiety in nursing home residents, with a specific focus on deprescribing, the subject at the heart of this PhD thesis. Implementation science is finally introduced, with a specific attention to intervention development. The information presented in this introduction was gathered through literature search and ongoing personalised newsfeed.

1. Medication use and improvement in nursing homes

1.1. Nursing home care and the medication pathway

Long-term care is defined as a panel of services available for people with functional limitations (either cognitive or physical), and therefore needing help in their activities of daily life (1). Within long-term care, nursing homes (NHs) are an alternative when at-home care is no longer a possibility. NHs welcome older adults with various levels of dependency, but not requiring hospital care (1). In the context of the ageing population, the percentages of adults aged 65 and older are expected to rise from 9.4% in 2020 to 16.5% in 2050 world widely, and from 19.2% to 27.5% in Belgium (2). In 2018, 14% of Belgian men aged 85 and older, and 27.7% of Belgian women aged 85 and older lived in NHs (3). There is currently a density of 65 beds for 1000 adults aged 65 and older, which is higher than the European mean, but recent reports expect a future drastic rise in bed needs, despite policies to extend at-home care. In addition, healthcare professionals' (HCPs) availability for NH care is also of concern. The current HCPs shortage might indeed worsen with the growing NH care needs (3, 4). In Belgium, nursing home residents (NHRs) can have various bed statuses, whether they have light to moderate limitations (in French "MRPA" for "Maison de Repos pour Personnes Agées) or they have more severe limitations and are more dependent (in French "MRS" for "Maison de Repos et de Soins") (1). However, most NHs welcome both types of bed statuses, which means that older adults with various levels of dependency live together. Several norms are required for a NH to receive the MRS accreditation (5). In terms of staff, a rate of 5 full-time equivalent nurses for 30 NHRs, including a chief-nurse is required. In addition, a nurse must be present in the institution at all times (day and night). The same rate of care aids (5 full-time equivalents for 30 NHRs) is also required. These norms also ensure appropriate access to physical therapists,

educational therapists, and speech therapists (5). For MRPA beds, staffing norms are lower. Five full-time equivalents nurses and care aids combined (minimum 2 nurses) are required (6) On average, according to a survey conducted in 2021, Belgian NHs indicate to organise care per 30 residents with a team of 0.9 Full-time equivalents head nurses, 3.8 full-time equivalents nurses, 7.2 full-time equivalents care aids, 1.4 full-time equivalents allied HCPs and 0.4 full-time equivalents living assistants (6). The overall resident-to-staff (nurses and care aids) ratio of 11.3, with important variations between moments of the day. The ratio is of 6.9 in the morning and of 40 at night (6)

Medication use is an important aspect of NH care. It encompasses a large variety of tasks that can be influenced by various elements such as personal factors (including competencies, knowledge, and responsibilities), technology and tools, environmental and organizational factors (7). Overall, eight overarching processes have been identified in the NH medication pathway: prescribing, purchase and ordering, delivery, storage, preparation, administration, monitoring, and medication reconciliation at transfer (7). All these steps are important to consider in ensuring a safe and effective medication pathway in NHs. In Belgian NHs, various stakeholders take part in this medication pathway. Since 2000, NHs must appoint a coordinating physician (CP). The CP is responsible for NH staff training and for medication/care use policy at the level of the NH. Still, each NHR can choose their own general practitioner (GP) and generally keep their GP from before institutionalisation. In some NHs, this leads to a high number of visiting GPs, with an average of one GP per 3 NHRs (8), and a reported number of visiting GPs sometimes above 50 (9, 10). These GPs are responsible for medication prescribing. Nurses are responsible for medication ordering, storage, preparation, and administration. Both nurses and GPs are involved in medication monitoring. NHs work with local community pharmacies, hospital pharmacies, or pharmacy groups. The pharmacy role is often limited to medication delivery. Medication review activities in NHs are not mandatory and not funded. According to a systematic review based on 11 studies, mostly in North America, medication errors involve 16 to 27% of NHRs (11). They can occur at any step of the medication pathway, but the literature suggests that most errors occur at prescribing, monitoring, administration, and medication reconciliation (11). The present thesis focuses mainly on the prescribing component of the medication pathway in NHs.

1.2. Medication prescribing in older adults and its challenges

Medication prescribing in older adults is particularly complex, because of the specific features of the older population (12). First, there is a high variability among older adults in terms of health, disease, and disability. At the same age, some are relatively fit while others are frail. This heterogeneity, as well as various personal preferences, may lead to important variations in therapeutic goals and prescribing decisions (12). Second, ageing leads to changes in the pharmacokinetics and pharmacodynamics properties of medications. Therefore, specific cautions and adaptations in prescribing are needed. In terms of pharmacodynamics, ageing induces changes in drug sensitivity. These changes vary between drugs, and between individuals, making generalisations difficult (13). For example, older adults are more vulnerable to adverse effects of central nervous system active drugs. In terms of pharmacokinetics, ageing has an impact on all 4 phases: absorption, distribution, metabolism, and excretion (13). A major change is the reduction in drug clearance by the kidneys or the liver. Indeed, older adults often have reduced glomerular filtration rate and liver metabolizing capacity. The clinical impact of these changes highly depends on the potential toxicity of the medication (13). As an example, opioids can be contra-indicated in case of renal insufficiency, even moderate. Third, potential cognitive impairment may lead to difficulties in medication intake, and poor engagement with health services. Older adults with dementia often are not able to participate in health decisions (12). Finally, there is a high level of comorbidities among older adults, which makes prescribing decisions complex (12). The high level of comorbidities often leads to polypharmacy. Polypharmacy is defined by the World Health Organisation as "the administration of many drugs at the same time or the administration of an excessive number of drugs" (14). In Belgium, in 2022, 42% of adults aged 65 or older were taking 5 or more medications, which is the usual threshold used to define polypharmacy (3).

Potentially inappropriate prescriptions (PIPs) are also very common among older adults. PIPs encompass 3 types of inappropriateness: underprescribing, misprescribing and overprescribing. Underprescribing refers to the lack of a needed medication. Misprescribing refers to incorrectly prescribing a needed drug (inappropriate dosage, route of administration, or potential DDI…). Overprescribing refers to prescribing a medication without a valid indication, or for a longer period

than necessary (12). To ease PIPs identification for clinician, several explicit criteria have been developed. The most used sets of explicit criteria are the American Geriatrics Society Beers criteria (15), and the Screening Tool of Older Persons' Prescription/ Screening Tool to Alert to Right Treatment (STOPP/START criteria) (16), both updated in 2023. The Beers criteria are a list of medications to avoid or use with caution in older adults (15). The STOPP criteria are a list of 133 criteria designed to detect potential overprescribing and misprescribing. The START criteria are a list of 57 criteria designed to detect potential underprescribing or omitted medications (16).

Medication prescribing for older adults is also complicated by the low inclusion of older adults in clinical trials. Indeed, according a systematic review including 109 clinical trials, approximately 20% of them excluded older adults based on age criteria only, and almost half of the remaining trials have exclusion criteria leading to a disproportional exclusion of older adults (17). These criteria could, as example, include decreased life expectancy or functional limitations. Additionally, only 26.6% of trials examined age-related outcomes, such as functional status or quality of life (17). Recruitment of older adults is also challenging (18, 19). This results in low-quality evidence for medication choice and poor availability of guidelines specific to older adults. Additionally, current guidelines are often disease-oriented, which is not representative of the clinical case of many older adults with comorbidities (20).

1.3. Medication prescribing in nursing home residents: even more challenging

The challenges of medication prescribing in older adults are even greater in NHRs, partly because NHRs are often frailer and have more comorbidities. It is therefore unsurprising that polypharmacy among NHRs is more prevalent than among community-dwelling older adults (21). Therefore, studies suggest a different threshold of 9 or more medications should be used to define polypharmacy in NHs (22). In a systematic review of 44 studies, up to 91% of NHRs take 5 or more medications (21). Using the cutoff of 9 or more medications, up to 74% of NHRs are under polypharmacy (21).

With this high number of medications also comes potential drug-drug interactions. A recent study in Belgian NHs showed that 52.7% of NHRs had at least

one drug-drug interaction in their medication regimen. The most common interaction was the concomitant use of 3 or more central nervous system active drugs (32.6% of NHRs) (23), which is in line with the high psychotropics prescribing rate observed in Belgian NHs (24).

Regarding the identification of PIPs among NHRs, a specific list of explicit criteria (called stoppNH) has been developed (25), but the American Geriatrics Society Beers criteria and the STOPP/START criteria are also used. Based on these explicit criteria or other similar tools, a systematic review found the prevalence of PIPs among NHRs to be 43.2% (26). This prevalence is higher in Europe than in North America and tends to increase (26). In Belgium, a prospective study conducted in 2015 in 1410 NHRs from 54 NHs reported that more than 85% of NHRs have at least one PIP (27). This high rate of PIPs is worrying as PIPs can be associated with major clinical outcomes, such as frailty (28), or hospitalization (29).

NH care involves a large variety of HCPs with various expertise. A good interprofessional collaboration between these HCPs has been highlighted as a facilitator of medication review (MR) in a qualitative study in the Netherlands (30). A recent systematic review evaluated barriers and enablers for interprofessional collaboration in long-term care and rehabilitation (31). Based on 24 studies, 3 major themes emerged: Team performance (collaboration, behaviour and attitude, shared goals, clarity of roles), Organisational conditions (workplace process, availability of resources, leadership), and Information sharing (basic communication skills, communication process, developing and utilizing knowledge). This systematic review also highlighted the need to recognize the interdependency of all stakeholders involved, including NHRs and relatives (31). In particular, the role of nurses in pharmaceutical care is often underrecognized (32). Literature also reports shortcomings in the competences of several HCPs such as nurses, physicians, or pharmacists in pharmaceutical care (32).

Finally, the engagement of NHRs and their relatives in the medication pathway is also an issue. This is partly explained by a high prevalence of cognitive impairment and dementia (33-35), but other personal and organisational factors can also explain this (36). A qualitative study conducted with 17 NHRs and 10 relatives from 4 Belgian NHs showed that both groups believed they did not have a say in medication prescribing and were mainly resigned. This was due to the perception of the NH as a healthcare institution (and not a home replacement),

perceived lack of knowledge of NHRs and relatives regarding medications, and trust in healthcare providers (36). Still some NHRs and relatives would like to be more actively involved. Interviews with Belgian HCPs also revealed barriers and enablers for NHRs involvement such as the fear for medication safety, and the need for organizational control on medication process (37).

Because of the complexity of medications prescribing in NHs, and to overcome these challenges, there is a need to develop and evaluate interventions to improve the quality of medication prescribing and use in NHs.

1.4. Interventions to improve medication prescribing in nursing homes

This section has been adapted from a broader narrative review (38) (Spinewine, A. Evrard, P., Hughes, C.. (2021). "Interventions to optimize medication use in nursing homes: a narrative review." Eur Geriatr Med 12(3): 551-567.).
Authors contributions: All authors made substantial contributions to the conception of the review, analysis and interpretation of the data, and writing of the manuscript. PE and AS performed the literature search, selection of relevant articles, and initial synthesis of the data. PE wrote the first draft of the manuscript, and this was then critically reviewed and amended by all co-authors.

Here are only presented the review findings related to interventions to optimize the prescribing component of the medication pathway, and elements published in literature after the review. The full narrative review, including elements linked to other steps of the medication pathway is available following this link.

*Studies published in the literature after the review are marked with a * in tables. They were identified through a combination of Pubmed search and literature reading during the thesis.*

Interventions to optimize medication prescribing – and medication use as a whole - can be implemented at different levels of the health care system. Throughout the literature, there is inconsistency in the number and definitions of these levels (39). In this work, we distinguish between two levels. First, the micro-level refers to interventions implemented at the NH level and directed at NHRs, health care providers (HCPs) and organization of the NH itself. Second, the macro-level (also called system-level) encompasses strategies that are external to NHs but impact on their practice. These are typically (but not exclusively) defined at a national or regional level.

Three recent systematic reviews (SRs) evaluated the effect of micro-level interventions – largely based on medication review (MR) - to optimize prescribing in the NH setting and reported positive results on quality of prescribing (40-42). MR has been defined as "a structured evaluation of a patient's medicines with the

aim of optimising medicines use and improving health outcomes. It entails detecting drug-related problems and recommending interventions" (43). MR can have various levels of extensiveness, from Type 1- Simple MR, based solely on the patient's medication history available in the pharmacy, to type 3 – Advanced or clinical MR, based on a complete medication history, extensive patient interview, and clinical data (44). A Cochrane SR highlighted four different approaches for optimization: MR, multidisciplinary case-conferencing, education for HCPs, and use of clinical decision support system (CDSS) (40). These were used either alone, or in combination. Overall, the interventions led to identification and resolution of drug-related problems, but there was no consistent effect on resident-related outcomes (40). In a second SR focusing on MR and including experimental and observational study designs, interventions were associated with a reduction in prescribed medications, inappropriate medications, and adverse outcomes (including deaths and hospitalizations) (41). However, high-quality cluster-randomized controlled trials evaluating CDSS effects or evaluating the impact of multidisciplinary interventions on well-defined important resident-related outcomes were lacking (40, 41). In terms of deprescribing, a SR of specific interventions reported a reduction of 59% of NHRs receiving at least one PIP (42). Only interventions including a MR were associated with a reduction in all-cause mortality and number of fallers (42). Several trials performed in European countries NHs were published after these SRs and are summarized in Table 1 (45-55). They mainly evaluated the impact of different forms of MR, alone or in combination with other intervention components. Overall, results from these trials were consistent with those of previous SRs, with positive effects on polypharmacy and PIPs. However, the interventions mostly did not influence clinical outcomes.

Table 1: Trials recently conducted in European nursing homes and reporting the effect of an intervention on prescribing the whole medication regimen (Chronological order)

Study name, Author, year	Setting	Participants No; Average age	Study design, and duration	Intervention	Stakeholders involved in intervention	Main measures	Results of the intervention
Fog, 2017 (45)	41 NHs, Norway	N=2465; 85.9 yrs	BAS, 28mo	- **Training** sessions - One **MR** per NHR, conducted by the NH physician and a nurse, in collaboration with external pharmacist.	GP, Nurses, Pharmacist	- DRP identified (by START/STOPP and NORGEP criteria) during MR, and related interventions - Medication changes	- 6158 DRPs identified (2.6/ NHR) - 6283 interventions to resolve DRP - Reduction of total number of drugs used by NHR by 9.3% (p<.01)
DIM-NHR: Wouters, 2017 (46) Wouters, 2019 (30)	59 NH wards, Netherlands	N=426; 83.5 yrs	cRCT, 4mo	- Brief **training** on MR - **MR** incorporating NHRs' experiences and preferences (Multidisciplinary Multistep Medication review)	Elder Care Physician, Pharmacist	- Successful discontinuation of at least one inappropriate drug at 4 mo (46) - Clinical Outcomes (46) - Quality of life (46) - Barriers and facilitators of conducting MR (30)	- Discontinuation for 39.1% of NHRs in intervention group, versus 29.5% in control group (ARR [95%CI] = 1.37 [1.02; 1.75]) - No change in clinical outcomes - No change 4 themes of barriers and facilitators: - Assessing the patient perspective - level of comprehensiveness of MR - inclinations of healthcare providers - inter-professional collaboration, alliances
IQUARE: Cool, 2018 (47)	159 NHs, France	N=629; 87.0 yrs	cCT, 18mo	- **Audit and feedback on quality indicators** for both IG and CG - Two half-day **meetings with geriatrician** and NH staff to discuss results and decide strategies for improvement	GP, Nurses, Hospital geriatrician, Coordinating physician	- PIP, as any: (i) unfavourable benefit-to-risk ratio (ii) questionable efficacy (iii) absolute contraindication (iv) significant drug-drug interaction	The intervention significantly decreased PIPs (65.2% in IG, 69.9% in CG, OR [95%CI]= 0.63 [0.40; 0.99])

COSMOS: Husebø, 2019 (48), Gulla, 2019 (54)	33 NHs, Norway	N=723; 86.7 yrs	cRCT, 9mo	- **Education and training** of NH staff**:** 2 days' seminar combined with repeated lunch meetings for 4 months, focusing on MR, pain assessment and communication with NHRs - Interdisciplinary **MR** (every 6mo), with collegial monitoring - Organization of **activities**, based on NHRs interests	GP, Management, Nurses	- Change in QoL at 4mo, measured by 3 indicators (48) - Secondary outcomes: ADL, total medication, staff distress, CGIC (48) - Process evaluation (54)	- deterioration in QoL measures at 4mo, then improvement from 4mo to 9 mo. - Improvements in all secondary outcomes - 92% of NHR in IG underwent a MR - Improvement of communication between stakeholders - Reported barriers: lack of time, low engagement of stakeholders, ethical dilemmas
COME-ON: Strauven, 2019 (49), Anrys, 2019 (55)	54 NHs, Belgium	N=1804; 87.5 yrs	cRCT, 15mo	- **Training**: e-learning (4 modules of one hour each) and face-to-face workshops (2 hours each) - **Local interdisciplinary meetings**, where use of a medication class was discussed -Three interdisciplinary case conference per NHR, with **MR**	Coordinating physician, GP, Nurses, Pharmacist	- Resolution of at least one PIP present at baseline, without new PIP (identified by START/STOPP and AGS Beers criteria) (42) - Secondary outcomes: clinical outcomes, medication use (42) - Process evaluation: Barriers and enablers at intervention, professional, organization and external context levels (55)	- Significant positive effect of the intervention (OR [95%CI]= 1.479 [1.062; 2.059]) - No significant difference between IG and CG for most clinical outcomes and for median number of medications - Good rate of implementation and participants' satisfaction despite variations between NHs and stakeholders - various barriers and enablers identified at intervention, professional, organization and external context levels

CAREMED: Desborough, 2020* (50)	31 NHs, England	N=953; 87.1 yrs	cRCT, 12mo	- Two interdisciplinary MR (every 6 months)	GP, Nurses and NH staff, Pharmacist	- Falls - PIPs (identified by the START/STOPP criteria) - Secondary outcomes: clinical outcomes (emergency hospital admissions, deaths) - Cost effectiveness	- No significant differences between IG and CG - Significant positive effect of the intervention: potentially inappropriate medication reduction by almost 20% (RR [95%CI]= 0.82 [0.67; 1.00]) - No difference in emergency hospital admissions, or time until death - The intervention is not considered cost-effective
QC-DeMo: Cateau, 2021* (51)	56 NHs, Switzerland	/ (NH as unit of analysis)	cRCT, 12mo	- **Quality circle deprescribing module:** creation of local deprescribing consensus	Physician, Head nurse, Pharmacist	- Proportion of galenic units considered potentially inappropriate (using Beers and NORGEP-NH criteria) - Safety outcomes (number of hospital days and falls per average resident and year, mortality, use of physical restraints)	- No significant effect of the intervention. In exploratory analysis, positive effect of the intervention in reducing proton pomp inhibitors. - No significant different in falls and use of physical restraints between IG and CG. - Significantly higher number of days spent in hospital in IG. - Significantly lower mortality in the IG.
IDeI: Cateau, 2021* (52)	7 NHs, Switzerland	N=62; 85.5 yrs	cRCT, 4mo	- Deprescribing-focused **MR**, performed by the pharmacists, followed by the creation of a treatment modification plan in collaboration with nurses and physicians.	Pharmacist, Nurse, Physician	- Number of PIMs, identified using STOPP criteria - Secondary outcome: number of chronic drugs, number of inappropriate DDD per day, number of chronic DDD per day, number of common complaints, and Quality of life - Safety outcomes (mortality, hospitalization, number of hospital days, falls, use of physical restraints)	- No significant difference between IG and CG on the number of PIMs. - In IG: reduction in the PIMs defined daily dose in IG , No difference between IG and CG in number of chronic drugs, number of chronic DDD per day, number of common complaints, and quality of life - No significant difference between IG and CG

CHIPPS: Holland, 2023* (53)	72 NHs, United Kingdom	N=2045; 85.3 yrs	cRCT, 6mo	- **Pharmacists independent prescribers** doing **MR**, and improving medication pathway in NHs	Pharmacist	- Fall rate/person - Secondary outcomes: Quality of life, physical functioning score, drug burden index, hospital admissions, mortality, health service use and cost - Safety: serious adverse events	- No significant difference between IG and CG - Lower drug burden index in the IG. No significant difference between IG and CG for other secondary outcome - No safety concern found
Legend: ADL: Activities of Daily Living; **ARR:** Adjusted Relative Risk; **BAS:** Before-After Study; **CG**: Control Group; **CGIC:** Clinical Global Impressions of Change; **CI:** Confidence Interval; **CT:** Controlled Trial; **DRP**: Drug-related problems; **GP**: General Practitioner; **IG:** Intervention Group; **MR:** Medication Review; **mo:** months; **N:** nurse; **NH:** Nursing Home; **NHR:** Nursing Home Resident; **OR:** Odds Ratio; **PIM:** Potentially inappropriate medication; **PIP:** Potentially Inappropriate Prescription; **QoL**: Quality of Life; **RCT:** Randomized Controlled Trial, **cRCT:** cluster-RCT; **START/STOPP**: Screening Tool to Alert Doctors to Right Treatment/ Screening Tool of Older Persons' Prescriptions *: studies published after our narrative review							

Macro-level approaches were implemented in the US and Australia, but much less so in Europe. Positive effects were seen with mandatory/legislative initiatives, and it could be argued that these should be considered at the European level. However, there has been a tradition of different countries tackling approaches in nursing home care in different ways which may be a function of different cultural and political contexts (56). Many of the concerns around prescribing of key medicines such as antipsychotics and anti-infectives are universal, and a more comprehensive, cross-country approach may be warranted.

Outcome reporting and measurement vary greatly between studies. This makes synthesis of findings difficult and highlights the need for a more common approach across studies examining similar research questions. This may be realized through the development and use of core outcome sets (COSs). Two relevant COSs exist, one for trials aimed at optimizing prescribing among NHR (57) and one for trials of MR in multi-morbid older patients with polypharmacy (58). Several outcomes of these COSs have so far been under-evaluated (i.e. *what* to measure), such as pain relief, all-cause mortality, falls, quality of life, hospital admissions and emergency visits to hospital. These are clearly important outcomes for this particular population and for the health systems. It is important that future trials refer to and use a COS. Furthermore, approaches to measurement of outcomes (i.e. *how* to measure) were also highly variable. PIP was measured in most studies, but a wide range of tools was used. Although many were targeted at older adults (i.e older than 65 years), such tools may not be appropriate for NHRs who have a higher degree of frailty. The use of tools that have been specifically developed for those who are frail (59) or living in residential care (stoppNH (25)) may be a better option.

Beyond the evaluation of the effect of interventions, a clear understanding of the enablers and barriers to implementation and success is crucial for the development of future interventions. In recently conducted trials, the attitude, role, and competency of HCPs (physicians, pharmacists, and nurses) were identified both as barriers and enablers. The need for macro-level funding of MRs was also reported (30, 54, 55). Moreover, the importance of patient-centred interventions is increasingly recognized. However, more research on how best to involve NHRs and NHRs with dementia is required. Indeed, in some countries, patient and public involvement is now expected as part of applications for research funding (60).

Table 2 presents a summary of current evidence regarding intervention aiming at optimizing prescribing in NHs, and suggestions for improvement.

Table 2: Micro- and Macro- level interventions: Summary of current evidence and suggestions for improvement

Level of implementation	Current strategies and evidence of their effects		Suggestions for improvement
	Current strategies	**Reported effects**	
Micro-level	• Common prescribing improvement strategies, used either alone or in combination: - Medication review - Multidisciplinary case-conferencing - Education for health care providers - Use of decision aid • Shift to person-centred care • Antibiotic stewardship programs	• Improve quality of prescribing • Decrease medication use • Resolution of drug related problems, including adverse outcomes • Decrease adverse outcomes • Decrease all cause-mortality (when medication review is involved) • Inconsistent data • Positive effect on intermediate health outcomes	• Development of patient-centred interventions • Base the intervention development on studied barriers and enablers for implementation • Use of theory-informed interventions • Standardization in outcomes reported, use of existing care outcome sets • Use of health information technologies • Focus on under-studied medication classes
Macro-level	• Legislation (such as reimbursement changes) • Guidelines and recommendations • Antibiotic stewardship programs	• Greater effect of mandatory strategies • Positive effect on intermediate health outcomes	• Use of cross-country approach for mandatory legislative initiatives • Focus on under-studied medication classes

Legend: The **micro**-level refers to interventions implemented at the NH level and directed at NHRs, HCPs and organization of the NH itself. The **macro**-level (also called system-level) encompasses strategies that are external to NHs but impact on their practice. These are typically but not exclusively defined at a national or regional level

2. *Use and deprescribing of benzodiazepines in insomnia and anxiety in nursing home residents*

2.1. Insomnia in nursing home residents: definition, prevalence, and management

Insomnia disorder is defined by the Diagnostic and Statistical Manual of mental disorders – Fifth edition (DSM V) as follow:

A. A predominant complaint of dissatisfaction with sleep quantity or quality, associated with at least one of the following symptoms: (i) difficulty initiating sleep, (ii) difficulty maintaining sleep, or (iii) early-morning awakening with inability to return to sleep.
B. The sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioural, 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.
G. The insomnia is not attributable to the physiological effects of a substance.
H. Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia.

Insomnia can be explained by the "3P model". According to this model, insomnia results from predisposing factors (such as age or health status), precipitating factors (such as hospitalisation, disease, death, or NH entry), and perpetuating factor (excess of day sleep, bedrest, lack of social interaction or physical activity) (61). Perpetuating factors are the factors that can be tackled by non-pharmacological alternatives. Older age comes with structural changes in sleep. Indeed, aging is associated with decreased ability to maintain sleep, reduced nocturnal sleep duration, and decreased deep sleep (slow wave sleep) (62). Older adults also often experience an advance of sleep phase, meaning that they tend to fall asleep earlier in the evening and wake up earlier in the morning. Finally, daytime napping is more important in older adults, with 20% of them reporting excessive daytime sleepiness (62).

As a result, 50% of older adults complain about difficulties with sleep initiation or maintenance, and 12 to 20% of them suffer from insomnia (63). These sleeping issues are even more prevalent in NHs. Indeed, a cross-sectional observational study conducted in 2020 among 100 older adults in Portugal showed that NHRs had an overall worse sleep quality and greater daytime sleepiness in comparison to community-dwelling older adults (64). In a prospective study published in 2014 and including 4.156 NHRs from 8 countries (European countries and Israel), the reported insomnia prevalence was 24%, with variations between countries, from 13 to 30% (65). No specific data is available on the insomnia prevalence in Belgian NHs. The higher prevalence of insomnia in NHRs in comparison to community-dwelling older adults can be partly explained by higher perpetuating factors, such as lack of physical activity, reduced social activities, or limited daytime exposure to light, recurrent noises, and NHRs awakening by others and staff (66). The NH entry itself is also a potential precipitating factor because of associated stress and the change in environment and habits.

This high rate of insomnia is worrying, as insomnia has major consequences for patients and public health. Indeed, insomnia has been linked to significant morbidity, depression, heart disease, or metabolic syndrome (63). Insomnia also is associated with high direct and indirect costs for the healthcare system (67). Studies conducted in the long-term care setting specifically have shown association between sleep disturbances and decreased functional status, social disengagement, greater risk of falls, frailty, agitation, and higher mortality (66).

European and Belgian guidelines for insomnia treatment in adults recommend the use of non-pharmacological approaches, and in particular cognitive behavioural therapy for insomnia (CBT-I) and sleep hygiene as a first-line treatment *(very strong recommendation)* (68, 69). European guidelines precise that pharmacological interventions can be offered in case of non-pharmacological approaches ineffectiveness *(very strong recommendation)*. Benzodiazepines can be used in the short-term treatment of insomnia, for 4 weeks or less *(very strong recommendation)*. Long-term treatment can be initiated in some cases, but the advantages and disadvantages need to be discussed on individual basis *(strong recommendation)* (69). In older adults, according to Belgian recommendations, the 1st choice pharmacological treatment should be lorazepam, an intermediate-acting

benzodiazepine, with a 4-week limit duration. The use of sedating antidepressants, antihistaminics, melatonin, antipsychotics, or valerian are not recommended (61).

2.2 Anxiety in nursing home residents: definition, prevalence, and management

Anxiety disorders is a class of mental health disorders also described in the DSM V. It encompasses various conditions such as generalized anxiety disorder, panic disorder, or anxiety disorder due to another medical condition. Generalized anxiety disorder is defined as follow:

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):
    a. Restlessness or feeling keyed up or on edge
    b. Being easily fatigued
    c. Difficulty concentrating or mind going blank
    d. Irritability
    e. Muscle tension
    f. 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 (70).

In a systematic review of 2015, based on 18 studies, anxiety disorders prevalence among NHRs range from 3.2 to 20% (71). As for anxiety symptoms, they are present in up to 58% of NHRs (71). These rates have possibly increased since

the Covid-19 pandemic, which impacted NHRs mental well-being (72, 73). Adequate treatment of anxiety is particularly important given the morbidity and mortality risks associated with untreated anxiety (74). Anxiety symptoms are associated with some medical conditions such as gastrointestinal problems, hypo- or hyperthyroidism, diabetes, cardiovascular disease, and respiratory disorders (74). Studies also found significant excess costs for older adults with anxiety (75). Evidence also suggests a possible association with increased healthcare use (75).

Current guidelines recommend cognitive behavioral therapy in the long-term treatment of anxiety. Selective serotonin reuptake inhibitors are the recommended pharmacological treatment, for up to 18 months *(both recommendations based on category I evidence)* (76). The drug of choice for older adults, according to Belgian recommendation, is sertraline (61). Benzodiazepines and especially lorazepam can also be used, but only for a very limited time. Duloxetine, venlafaxine, antiepileptics, beta-blockers, and tricyclic antidepressants are not recommended in older adults.

2.3. Benzodiazepines use in insomnia and anxiety

Benzodiazepines are largely used in the treatment of insomnia and anxiety. Their use is not recent. Benzodiazepine structures were discovered in the 1950s and development led to the marketing of chlordiazepoxide in 1960 under the name of Librium®. In 1963, the Valium®, containing diazepam, a derivative with stronger activity was launched (77), followed by a long list of further developed benzodiazepines. In Belgium, there are now up to 20 benzodiazepines available. Benzodiazepines act by mediating g-aminobutyric acid (GABA) transmission (78, 79). More precisely, they are allosteric agonists of the $GABA_A$ receptors and enable a change in the configuration of the $GABA_A$ receptor, leading to an increase sensitivity to GABA, and therefore decreased neurons excitability, and central nervous system relaxation (79, 80). Benzodiazepines have several pharmacological effects: sedatives, anxiolytics, anticonvulsants, and myorelaxants. Two isoforms of the benzodiazepine receptor exist, depending on the relative GABA receptor subunit α isoform. GABA receptors containing the subunit α1 are responsible for the sedative and anticonvulsive properties of benzodiazepines. GABA receptors containing the subunit α2 are responsible for anxiolytics and myorelaxants properties (80). Depending on its relative affinity for the two types of benzodiazepine receptor, each benzodiazepine has a specific profile of

pharmacological effects. Differences in therapeutical use are also explained by variations in pharmacokinetics profile: a drug with a shorter onset and half-life will be preferred for insomnia treatment, while a drug with a longer half-life will be preferred for anxiety treatment. Therefore, some benzodiazepines (e.g. alprazolam) are more often prescribed for anxiety, while others (e.g. flunitrazepam) are presented as sedatives. However, in clinical practice, the distinction between the two types of benzodiazepines is often vague, and most benzodiazepines are used for both indications.

Z-drugs, medications also agonists of the benzodiazepines' receptors, were introduced as hypnotics later, in the late 1980s. There are currently two Z-drugs available in Belgium: zopiclone, and zolpidem. They have similar effects and risk profile than benzodiazepines (69). We gather benzodiazepines and Z-drugs under the unique term of BZRA, for benzodiazepine receptor agonists.

BZRA were first presented as safe therapeutic options for insomnia and anxiety. However, concerns about their safety have risen. In America, the Federal Drug Administration (FDA) recently required an update in the black box warning for benzodiazepines, to include the risks of dependence, withdrawal reactions, misuse, abuse, and addiction. This adds to an already existent warning about opioid concomitant use (81, 82). Safety concerns are even more important for older adults, because of changes in pharmacokinetics and pharmacodynamics BZRA properties. For some BZRA, requiring cytochrome p450 clearance and with active metabolites, elimination half-life increases, resulting in higher chances of residual effects and side-effects (68). To decrease the impact of pharmacokinetics change in older adults, the drug of choice should be lorazepam, which is directly metabolized through glucuronidation, without prior cytochrome p450 metabolism (52, 68). Older adults are also more sensitive to BZRA, with greater confusion and disorientation (80). A summary of BZRA benefits-to-risks ratio in older adults is presented in Figure 1 (83-94).

The START/STOPP criteria and the STOPP-NH criteria recommend limiting BZRA use to 4 weeks (16, 25), and the American Geriatrics Society Beers list recommends avoiding their use *(Strong recommendation, moderate evidence)* (15). This is also in line with guidelines for treatment of insomnia and anxiety which, as said above, recommend BZRA for short-term treatments (61, 69, 76). Belgian recommendations for older adults also do not select any BZRA as a long-term

treatment for neither insomnia nor anxiety, but only recommend lorazepam in acute situations (61).

Despite this, BZRA use in older adults remains high, especially in NHs where it is close to 30% (95). Variations exist between countries, with published rates ranging between 14.6 and 54.4% (24, 96-98). In Belgium, at the beginning of this thesis, the last published data were collected in 2006 among 1730 NHRs from 76 NHs and reported a prevalence of 50% (99). BZRA prescribing rate in older adults slightly declines over time but remains worrying (100). Finally, BZRA are often used for way longer than 4 weeks. In a study conducted in Australian NHs, in 2015, a quarter of BZRA users (n=4821) received enough medicines to cover an entire year of continuous use, and the median coverage length was 240 days (101).

Box 1- *BZRA use in NHs during SARS-CoV-2 pandemic*

The SARS-CoV-2 pandemic that began in March 2020, together with infection control measures and visit bans has been shown to have impacted NHRs well-being and mental health (72, 73, 102). This potentially could have led to changes in BZRA use, but only few data are available on that matter:

- A cross-sectional study conducted in 7 NHs in Spain showed that the pre-existing trend towards BZRA reduction slowed during the pandemic (103).
- A population-based cohort study conducted in Ontario, Canada, reported a slope change in the weekly proportion of NHRs who were dispensed BZRA, which is in opposition with the decrease observed before the pandemic (104).
- In a population-based cohort study conducted in Alberta, Canada, the pandemic was associated with a statistically significant small decrease in BZRA use (105).

Therefore, this thesis, which took place from 2018 to 2024, is to consider within the specific context of the SARS-CoV-2 pandemic, which might have impacted it. It is however difficult to quantify this impact.

2.4. Benzodiazepines receptor agonists deprescribing

Deprescribing is "the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes" as defined by Reeve *et al.* in 2015 (106). According to the latest guidelines, deprescribing should be offered to older adults taking BZRA, regardless of the length of use (Pottie et al. - s*trong recommendation* (107); MAGIC guideline - *weak recommendation* (108)). Belgian guidelines on medication use in older adults are also in line with that, and do recommend deprescribing chronic BZRA (61). The MAGIC guideline classified this as a weak recommendation. This means that, although BZRA deprescribing is recommended, BZRA deprescribing and usual care can both be reasonable options depending on the context and patients' values and preferences. According to the deprescribing competency framework published by Farrell et al. (109), *therapeutic* targets and goals of care should be defined based on patient specific factors, including age, multiple medications, frailty, comorbidities, neurocognitive disorder, *patients' goals*, and life expectancy. Therefore, shared decision-making is an important aspect of BZRA deprescribing, to consider the above-mentioned patients' goals or values and preferences. It is also in line with European 2023 guidelines for insomnia treatments, stating that long-term BZRA can be initiated in some cases, but pros and cons need to be discussed on individual basis *(strong recommendation)* (69). Patients' preferences are also major in another definition of deprescribing, introduced by Scott et al in 2015 : "The systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individual patient's care goals, current level of functioning, life expectancy, values, and preferences" (110). As an example, NHRs with other major health issues, or NHRs valorizing current comfort over potentially suffering withdrawal symptoms might not prioritize BZRA deprescribing. On the other hand, NHRs suffering from polypharmacy or prioritizing fall-risk reduction might choose BZRA deprescribing.

In older adults, original research found BZRA deprescribing to be associated with several benefits such as increased sleep quality (111, 112), improvement in psychomotor and cognitive tasks (113), and small anxiety decrease (107, 113). However, the latest guideline reports that the quality of evidence of BZRA deprescribing benefits are very low to low. The MAGIC guideline on BZRA

deprescribing therefore concludes that discontinuation intervention can have little or no effect on daytime functioning, quality of life, mental health, sleep symptoms, and sleep efficiency (108). The benefits of BZRA deprescribing for older adults should therefore be investigated in more robust study designs. BZRA deprescribing can also have potential risks. In an observational study, within 697 patients who made at least one BZRA stop experience, 78% experienced withdrawal symptoms, mainly under the form of insomnia (114). These withdrawal symptoms are often responsible for patients resuming their treatment. However, using a slow tapering program can help reduce withdrawal symptoms, and leads to deprescribing success ranging from 50 to 80% (115). In their guideline, Pottie et al. report no difference in withdrawal symptoms when discontinuing BZRAs compared with BZRA continuation or usual care (which could potentially include BZRA deprescribing, but often does not) (107). Unfortunately, no data are available regarding BZRA deprescribing benefits-to-risks ratio at the level of the NH (as an example in terms of workload for NH staff). Data on BZRA efficacy, safety, use and deprescribing latest guidelines in older adults and in NHs are summarized in Figure 1.

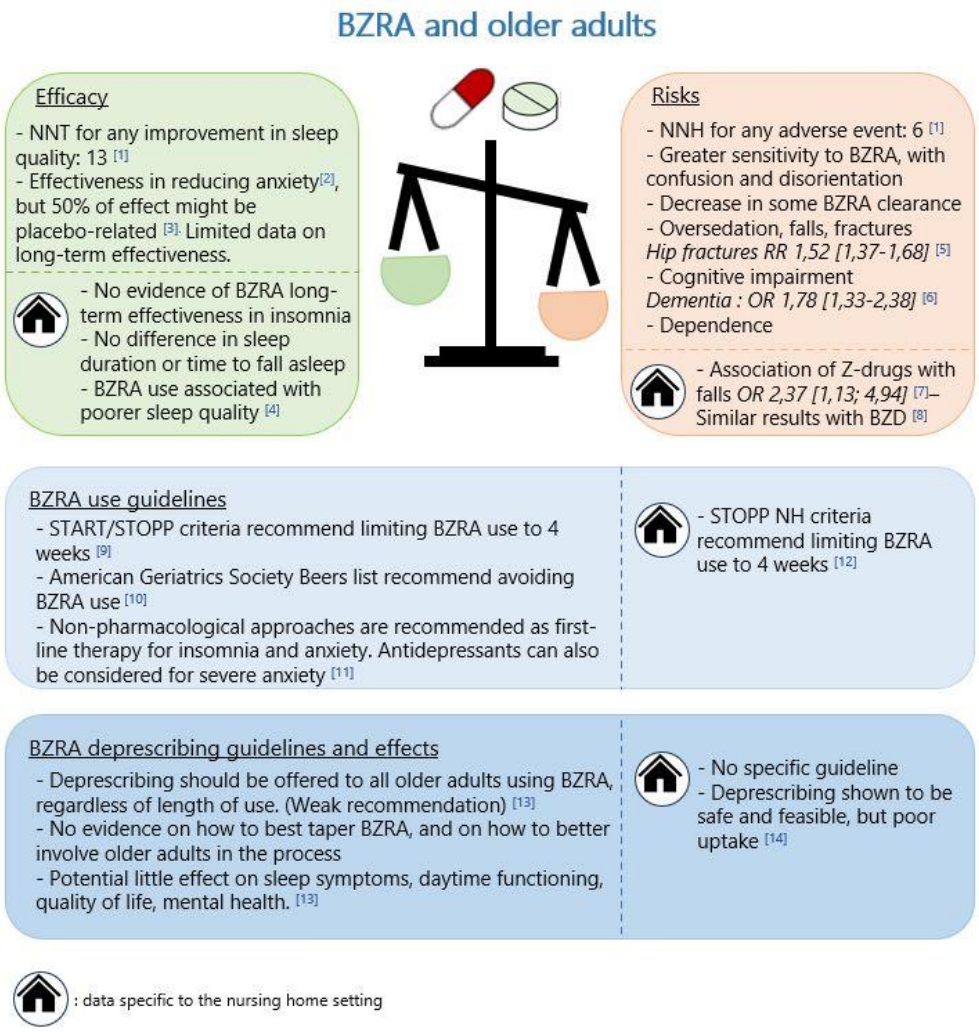


Figure 1: Data on BZRA efficacy, safety, use and deprescribing latest guidelines in older adults and in nursing homes.

Legend: BZD: benzodiazepine; **BZRA:** Benzodiazepine Receptor Agonists; **NNH**: Number Needed to Harm, **NNT:** Number Needed to Treat

[1] Glass et al., BMJ (Clinical research ed), 2005. [2] Gupta et al., Ann Clin Psychiatry, 2020. [3] Lader, Eur Neuropsychopharmacol, 1999. [4] Bourgeois et al., Sleep Med., 2013. [5] Donnelly et al., PloS one, 2017. [6] Islam et al., Neuroepidemiology, 2016. [7] Damanti et al., Aging Clin Exp Res., 2022. [8] Capiau et al., European Geriatric Medicine, 2022. [9] O'Mahony et al., European Geriatric Medicine, 2022. [10] American Geriatrics Society, Journal of the American Geriatrics Society, 2023. [11] Formulaire de soins aux personnes âgées, https://cbip.be, 2021. [12] Khodyakov et al., Journal of the American Geriatrics Society, 2017. [13] Johansson et al., MAGIC app, 2023. [14] Bourgeois et al., European Journal of Clinical Pharmacology, 2014.

Previous research showed that BZRA deprescribing in NHs is safe and feasible (111). Indeed, in a study conducted in Belgian NHs, 38 of 135 eligible NHRs started a BZRA discontinuation plan (after both GP and NHR agreement). After two months, 25 of the 38 NHRs had stopped BZRA, and 7 had reduced their dose. At 8 months, only one of the 25 BZRA free NHR had relapsed. The study reported no impact of BZRA discontinuation on withdrawal symptoms (111).

Despite that, the uptake of BZRA deprescribing in NHs is still very low, as shown by previously reported prevalence of use. Already existing micro- and macro-level strategies towards BZRA rational use in Belgian NHs are developed in Box 2. Internationally, several interventions to promote BZRA deprescribing have been assessed, mainly in the outpatient setting. These interventions include patients' raising awareness, MR, slow tapering, cognitive therapy, or medication substitution. They led to BZRA cessation rate from 27 to 80% (116). In the NH setting, antipsychotics deprescribing was extensively studied, but fewer data on BZRA have been reported. Still, some interventions aiming at medication or psychotropics optimization reported positive effects on BZRA deprescribing (Table 3, also adapted from the review by Spinewine et al. introduced in 1.4)(97, 117-120). All these interventions involved several components, which is recommended (38). However, none was evaluated in a robust randomized controlled trial and encompassed patient-reported outcomes. In addition, the transferability of intervention effectiveness is not guaranteed because of the high impact of context. One of these interventions was evaluated in Belgium. In a before and after study conducted in 5 Dutch-speaking NHs only, it showed that education of NH staff on psychotropic medication together with MR and transition towards person-centered care led to a reduction in hypnosedative use (120). However, the focus of the intervention was psychotropics in general and not BZRA specifically, and it is well known that there are cultural differences in healthcare between Dutch-speaking and French-speaking parts of the country. Therefore, there is a need to develop an intervention towards BZRA deprescribing specifically in our setting of interest, the Belgian French-speaking NHs.

Box 2- *What about Belgium? – Interventions towards appropriate BZRA use in NHs*

- Several national awareness campaigns on BZRA and psychotropics (since 2002): At the beginning of this thesis (2018), the campaign *"Somnifères et calmants pensez d'abord à d'autres solutions"* was ongoing. It provided several tools such as a poster and a brochure to help raise public awareness about the use of BZRA, and practical tools for HCPs to discuss dependence or non-pharmacological approaches for insomnia and anxiety. These tools have been updated in 2023 for a new campaign "*Psychotropes: quels risques pour vos patients? Ensemble favorisons un usage adapté*". This new campaign does not only focus on BZRA but on all psychotropics. It gathers various tools for general practitioners, pharmacists, or psychologists. These tools are available at https://usagepsychotropes.be. None of these campaigns specifically targeted the NH setting.
- BZRA access: BZRA are available under prescription. There is no reimbursement of BZRA by the national health insurance.
- BZRA tapering program: Since 2023, under certain conditions, magistral preparations for BZRA tapering can be reimbursed. However, NHRs cannot access this reimbursement, that is only available for community-dwelling adults.
- Access to non-pharmacological alternatives: Psychologist (and CBT) access varies greatly between NHs
  - Psychologist employment by the NH is not mandatory but can occur.
  - NHRs can also consult an external psychologist. If so, the consultation reimbursement depends on whether the psychologist is contracted by the national health insurance or not. If yes, the out-of-pocket cost for the consultation is 11 euros. If not, the reimbursement depends on the mandatory insurance company the NHR adheres to but is overall low (around 20€ per session).
  - Some associations/organisms do provide free psychologist consultations to NHRs.
- Pharmacy and multidisciplinary approaches:
  - National funding for medico-pharmaceutical concertations. These concertations consist of 2-hour meetings of physicians and pharmacists from the same geographic area to discuss topics related to medication use that requires improvement and better coordination. Improving BZRA use is one of the topics funded.

- Medication review activities from pharmacists in NHs are not currently funded.

- Additional strategies for medication optimisation in NHs in Flanders:

- In the Dutch-speaking part of Belgium, the psychofarmaca project, supported by the Flemish government, is being implemented in NHs. This project encompasses HCPs training on psychotropics and non-pharmacological approaches, MR, and transition towards person-centred care. This intervention has been evaluated in a sample of 5 NHs, and showed effectiveness in reducing hypnosedative use, and concomitant psychotropics use (120, 121). Within this project, a practical guide on how to implement a psychotropic policy at the NH level is available in Dutch (122). It goes along with a monitoring tool, that includes indicators on psychotropics use.

- A cluster randomized controlled trial conducted among 481 NHRs in 23 Flemish NHs evaluated the impact of need-based care and non-pharmacological approaches on NHRs with dementia and behavioural and psychological symptoms. Non-pharmacological approaches included, among others, massage, music moments, creative moments, or moments of movements. Need-based care decreased behavioural and psychological symptoms of dementia, and decreased HCPs distress (123).

- The KULeuven has launched a training of coordinating pharmacists for NHs. This training, which lasts a semester, encompasses (i) an e-learning on medications, infection controls, NHs structure, communication,… (ii) an internship, and (iii) the conduction of a quality assessment, medication process related talks with NHRs, and medication review. Despite the existence of this training, the function of the coordinating pharmacist is not yet recognized and funded. The upcoming POOMAH trial will, among other thing, evaluate the intervention of these coordinating pharmacists (124).

Table 3: Examples of Interventions aiming at BZRA or psychotropics deprescribing evaluated in nursing homes							
Study name, Author, year	**Setting**	**Participants No; Average age**	**Study design, and duration**	**Intervention**	**Stakeholders involved in intervention**	**Main outcome measures**	**Results of the intervention on BZRA**
RedUSe, Westbury, 2010 (117, 118)	25 NHs, Australia	N=1591; no report	Non-randomized controlled trial, 26 we (+18mo follow-up)	- two medication **audit and feedback** cycles - **Training** sessions for staff - **interdisciplinary sedative review**	GP, Nurses, Pharmacist	- Psychotropics prevalence rate and dosage variation	- Statistically significant decrease in the mean proportion of BZRA used in intervention NHs from baseline (M=31.8, SD=8.6) to 26 weeks (M=26.9, SD=8.6), p<0.005 - Significant impact of the intervention on dosage variation - Sustained decline in prevalence of use and dosage at 18mo
IQUARE: de Souto Barreto, 2016 (97)	159 NHs, France	N=629; 87.0 yrs	cCT, 18mo	- **Audit and feedback on quality indicators** for both IG and CG - Two half-day **meetings with geriatrician** and NH staff to discuss results and decide strategies for improvement	GP, Nurses, Hospital geriatrician, Coordinating physician	- Benzodiazepines use, new-use, discontinuation	- Higher reductions in benzodiazepine use (-2.8% vs. -1.5%) and long-acting benzodiazepine (-3.7% vs. -3.5%) in the IG, but not statistically significant

Weeks, 2018 (119)	45 NHs, Spain	N=1653 dementia NHRs; 86.5 yrs	Retrospective, PSM, control--led, 1mo	Comparison of 3 interventions: - Interdisciplinary **MR** - Use of **STOPP/START** criteria - Use of a **Patient decision aid**	Not reported	- change in specific milligram-equivalent daily dose for 3 **psychotropic drug** classes (antipsychotic, antidepressant, anxiolytic) - patient falls and restraint use at 2 weeks	- Significant reduction in daily doses for all 3 classes and for every intervention - Most effective intervention: STOPP/ START criteria: 39.5% reduction for anxiolytics - Patient decision aid: 31.8% reduction in anxiolytics - Interdisciplinary MR: 23.1% reduction in anxiolytics - No higher rates of patient falls or physical restraints
Wauters, 2019 (120)	5 NHs, Belgium	N=677 dementia and non-dementia NHRs; 85.6 yrs	BAS, 12mo	**- Training**: educational session for GPs and nurses on **psychotropic drugs** (evidence-based practice, reduction in use, non-pharmacological alternatives) - **MR** - transition towards **person-centred care**	Coordinating physicians, GPs, Nurses, Pharmacist	- prevalence of psychotropics use and long-term use - concomitant psychotropic drug use	- Significant decrease in hypnosedative prevalence of use, from 35.3% to 28.7% - Significant decrease from 31.5% to 24.0% (p=0.001)
Legend: BAS: Before-After Study; **CG**: Control Group; **CGIC:** Clinical Global Impressions of Change; **CI:** Confidence Interval; **CT:** Controlled Trial; **DRP**: Drug-related problems; **GP**: General Practitioner; **IG:** Intervention Group; **MR:** Medication Review; **mo:** months; **N:** nurse; **NH:** Nursing Home; **NHR:** Nursing Home Resident; **OR:** Odds Ratio; **PIP:** Potentially Inappropriate Prescription; **QoL**: Quality of Life; **RCT:** Randomized Controlled Trial; **cRCT:** cluster-RCT; **START/STOPP**: Screening Tool to Alert Doctors to Right Treatment/ Screening Tool of Older Persons' Prescriptions							

3. Intervention development and implementation science

Implementation science is defined as "the study of methods to promote the adoption and integration of evidence-based practices, interventions, and policies into routine health care and public health settings to improve the impact on population health" (125). De-implementation, on the other side, refers to "abandonment of medical practices or interventions that have been found to be ineffective and harmful" (126). As stated before, the current large use of BZRA in NHs is not recommended and could therefore be seen as a low-value care needing to be de-implemented.

The Choosing Wisely initiative developed a framework for de-implementing low-value care (See Figure 2) (127). According to this, de-implementing could be achieved through the following phases:

- phase 0: identification of potential areas of low-value healthcare
- phase 1: identification of local priorities for implementation of recommendations
- phase 2: identification of barriers and enablers to implementing recommendations and potential interventions to overcome these
- phase 3: evaluation of implementation programs
- phase 4: spread of effective implementation programs

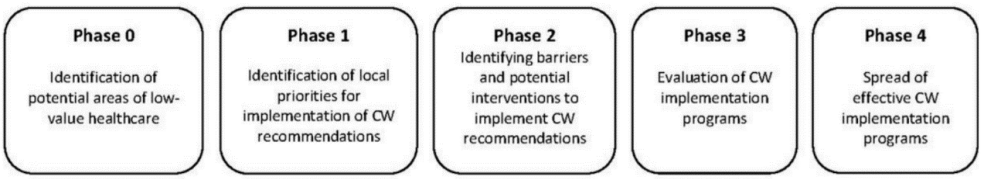


Figure 2: Choosing Wisely (CW) de-implementing framework, reproduced from Grimshaw JM, et al. (127), with kind authorization

This de-implementation process is based on behaviour-change theories and on the French 4-step model for the theory-informed development of interventions (128). These steps encompass: (i) identifying who needs to do what differently, (ii) identifying barriers and enablers for the needed change, (iii) identifying intervention components that would overcome these barriers and enablers, and (iv) evaluating the identified intervention. Behavioural theories explicit the structural and psychological processes of behaviour regulation and

change (129). Therefore, they can help investigate implementation (or de-implementation) issues and intervention development. More precisely, behavioural theories can inform methods for identifying behavioural determinants, selection of techniques to address the identified barriers and change behaviour, or evaluation of the behaviour change interventions (127). There have been calls for more use of theories in intervention development (129), and for making theory and tool use more explicit (130). In 2023, the World Health Organisation adopted the first Behavioural Sciences for Better Health resolution. This acknowledges behavioural sciences as an important approach and urges the development of its use in public health (131). Using theory is also in line with recommendations from the United Kingdom Medical Research Council (MRC) for the development and evaluation of complex interventions (132).

Multiple theories and frameworks on behaviour change exist, and sometimes overlap. However, there is currently no evidence on which theory to choose upon (128). Several behaviour science tools useful for (de-)implementation have been developed, mapping constructs from various theories. The tools we chose to use in the present thesis are described below.

3.1. The Theoretical Domains Framework

The Theoretical Domains Framework (TDF) has been developed through an expert consensus approach, to make behaviour change psychological theories more accessible and useful for researchers working on evidence-based practice implementation (133). Its primary aim is the identification of influences on healthcare providers behaviour related to the implementation of evidence-based practices or recommendations (129). The TDF is a framework of theoretical domains that should be considered as potential behavioural determinants. The constructs encompassed in the identified domains come from 33 different psychological theories (133). Therefore, the TDF is an extensive framework, with greater coverage of potential barriers and enablers for behaviour-change and intervention components than previously used models (128). After validation of the TDF by behavioural experts, the TDF version 2 (which we used), is a list of 14 domains, and 84 component constructs (134) (See table 4).

Table 4: Domains of the TDF version 2 and their descriptions, taken from Cheung et al. (135)	
Knowledge	Existing procedural knowledge, knowledge about guidelines, knowledge about evidence and how that influences what participants do
Skills	Competence and ability about procedural techniques required to perform the behaviour
Social/Professional role and identity	Boundaries between professional groups (i.e., is the behaviour something the participant is supposed to do or someone else's role?)
Beliefs about capabilities	Perception about competence and confidence in performing the behaviour
Optimism	Whether participants' optimism or pessimism influences what they do
Beliefs about consequences	Perceptions about outcomes, advantages, and disadvantages of performing the behaviour
Reinforcement	Previous experiences that have influenced whether or not the behaviour is performed
Intention	A conscious decision to perform a behaviour or resolve to act in a certain way
Goals	Priorities, importance, commitment to a certain course of actions or behaviours
Memory, attention, and decision processes	Attention control, decision making, memory (i.e., is the target behaviour problematic because patients simply forget?)
Environmental context and resources	How factors related to the setting in which the behaviour is performed (e.g., people, organizational, cultural, political, physical, and financial factors) influence the behaviour
Social influences	External influence from people or groups to perform or not perform the behaviour; How the views of colleagues, other professions, patients and families, and doing what you are told influence the behaviour
Emotion	How feelings or affect (positive or negative) may influence the behaviour
Behavioural regulation	Ways of doing things that relate to pursuing and achieving desired goals, standards, or targets; Strategies that participants have in place to help them perform the behaviour; Strategies the participants would like to have in place to help them

The TDF can be used in various ways, both in qualitative and quantitative research. As examples, it can be used to develop data collection materials (e.g. questionnaires, semi-structured interview guides, structured observations…), to

guide data analysis, or to structure the report of findings (129). In published research, it has been used with various aims:

- Explore behavioural determinants of healthcare providers (e.g., antipsychotic prescribing behaviours for NHRs with dementia (136) hand-hygiene compliance in long-term care (137)), as well as behavioural determinants of patients and population (e.g.: children vaccination (138)).
- Systematically design interventions (as described in the French 4-step model) (128).
- Conduct process evaluation of implementation trials (e.g.: process evaluation of the CT head rule trial (139)).
- Synthesis of evidence (e.g.: qualitative systematic review of barriers to diabetes management in primary care (140)).

3.2. The behaviour change technique taxonomy v1

A behaviour change technique (BCT) is defined as "an observable, replicable, and irreducible component of an intervention designed to alter or redirect causal processes that regulate behaviour; that is, a technique is proposed to be an "active ingredient" (e.g., feedback, self-monitoring, and reinforcement)" (141). BCTs can be used individually or in various combinations to form a (de-)implementation strategy of an evidenced-based practice, such as benzodiazepines deprescribing. With the involvement of 54 different experts, the BCT taxonomy v1 was developed and encompasses 93 different BCTs (141). All these BCTs are clearly defined, but the way they are delivered, and their specific content can be adapted depending on the needed behaviour change and on the context. As an example, the BCT "Feedback on behaviour" is defined as follow "Monitor and provide informative or evaluative feedback on performance of the behaviour (e.g. form, frequency, duration, intensity)". It can be delivered in a written form, or in a face-to-face meeting, or in a group meeting, that is the method of delivery of the BCT. In the same way, the specific content of the feedback can be adapted.

The use of the BCT taxonomy v1 to develop and describe an intervention has several benefits. First, it can help promote accurate replication of interventions across settings and behaviours. Second, intervention description based on BCTs facilitates faithful implementation. Finally, it enables easier comparison of

interventions, and therefore can be used for systematic reviews of intervention contents, and identification of effective components (141).

3.3. The theory and techniques tool

To identify the BCTs to be included in an intervention, there is a need to understand their mechanisms of actions, and therefore the potential behavioural determinants they can impact (142). Understanding these links helps choosing BCTs more likely to be effective and investigating intervention effects. Based on intervention literature synthesis, 2636 BCTs-Mechanisms of action have been identified (142). The theory and techniques tool, available online, presents evidence of links (or non-links) between 74 BCTs and 26 mechanisms of action (143). The 14 TDF domains, presented earlier, are among the 26 Mechanisms of action investigated in the tool. Therefore, the tool can be used to select BCTs that can potentially impact the TDF domains identified as behavioural determinants, and to develop an intervention aiming at these behavioural determinants. As an example, the BCT demonstration of the behaviour could be used to target behavioural determinants in the TDF domain of Skills.

In the context of BZRA deprescribing in nursing homes, we used behaviour change theories and implementation science through this process. After identifying areas for improvement, we investigated behavioural determinants using the TDF, and mapped identified TDF domains with potential BCTs, using the theory and techniques tool. This led to a novel intervention, of which we tested the feasibility and conducted a theory-based process evaluation. These steps are described in detail in the chapters of this thesis.

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THESIS AIMS AND STRUCTURE

In a context of potential over- and mis-prescribing of BZRA in Belgian nursing homes, this thesis aims at:

1. Describing current practices in terms of BZRA prescribing and deprescribing in Belgian nursing homes
2. Developing an intervention towards BZRA deprescribing using a theory-based approach made of two main steps:
    a. Identification of the barriers and enablers for BZRA deprescribing in Belgian nursing homes
    b. Selection and design of strategies to promote BZRA deprescribing
3. Evaluating the feasibility of implementing and evaluating the designed intervention

The thesis is structured into three sections, each one addressing a specific research objective. These sections fit with the Choosing wisely de-implementation framework (See figure below). Each of the six chapters of this thesis relates to one article (published or in preparation).

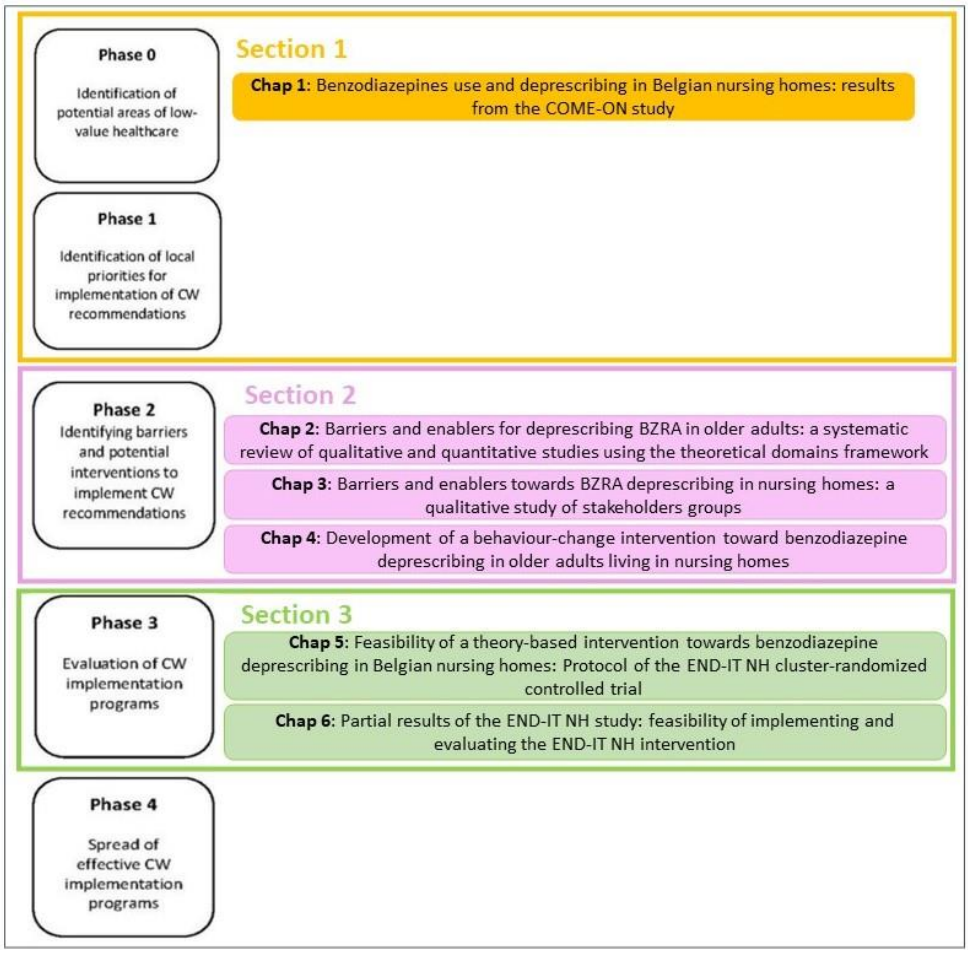
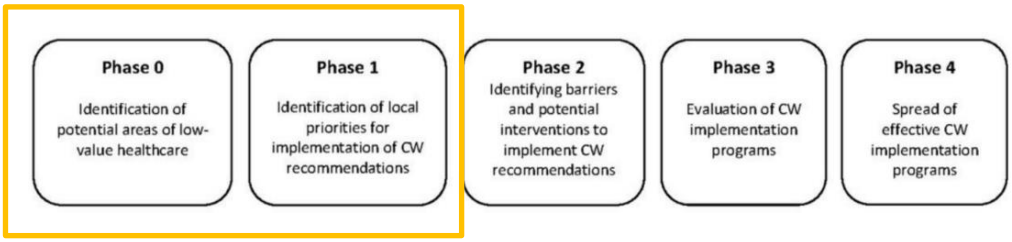


Figure: Structure of this thesis, embedded in the Choosing Wisely (CW) de-implementation framework, from Grimshaw et al., BMJ Quality and Safety, 2020

SECTION 1: Identification of potential areas of low-value healthcare and local priorities



Choosing Wisely framework for de-implementing low-value care (Grimshaw et al. 2020)

Chapter 1. Benzodiazepines use and deprescribing in Belgian nursing homes: results from the COME-ON study

Chapter 1. Benzodiazepines use and deprescribing in Belgian nursing homes: results from the COME-ON study

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Chapter adapted from the homonymous article published in *Journal of the American Geriatrics Society* (2020)

https://doi.org/10.1111/jgs.16751

Authors' contributions:

Conceptualized and designed the study: Evrard and Spinewine. Performed data cleaning and initial data analysis: Evrard. Performed statistical analyses: Henrard. Performed data analysis and interpretation: All authors. Wrote the initial draft of the manuscript: Evrard. Critically reviewed and edited the first and subsequent drafts of the manuscript: Spinewine. Critically revised the manuscript and read and approved the final manuscript: All authors.

Funding:

The COME-ON project was funded by the National Institute for Health and Disability Insurance (Belgium). The funding body had a limited role in the design of the COME-ON study, but it had no role in data collection, implementation, analysis, or the decision to publish the results.

ABSTRACT

BACKGROUND/OBJECTIVES. To describe the use and deprescribing of benzodiazepine receptor agonists (BZRAs) among nursing home residents (NHRs), to evaluate appropriateness of use and to identify factors associated with BZRA use and deprescribing.

DESIGN. Posthoc analysis of the Collaborative Approach to Optimize Medication Use for Older People in Nursing Homes (COME-ON) study, a cluster controlled trial that evaluated the impact of a complex intervention on potentially inappropriate prescriptions (PIPs) in nursing homes (NHs).

SETTING. A total of 54 NHs in Belgium.

PARTICIPANTS. A total of 797 NHRs included in the study who had complete medical, clinical, and medication information at baseline and at the end of the study (month 15).

MEASUREMENTS. Data were recorded by participating healthcare professionals. Reasons why BZRA use was considered as PIPs were assessed using the 2019 American Geriatrics Society Beers Criteria® and the Screening Tool of Older Persons' Prescriptions (STOPP) criteria, version 2. Deprescribing included complete cessation or decreased daily dose. We identified factors at the NHR, prescriber, and NH levels associated with BZRA use and BZRA deprescribing using multivariable binary and multinomial logistic regression, respectively.

RESULTS. At baseline, 418 (52.4%) NHRs were taking a BZRA. The use of BZRA for longer than 4 weeks, with two or more other central nervous system active drugs, and in patients with delirium, cognitive impairment, falls, or fractures was found in more than 67% of BZRA users. Eight NHR-related variables and two prescriber-related variables were associated with regular BZRA use. Deprescribing occurred in 28.1% of BZRA users (32.9% in the intervention group and 22.1% in the control group). In addition to four other factors, dementia (odds ratio [OR] = 2.35; 95% confidence interval [CI] = [1.45–3.83]) and intervention group (OR = 1.74; 95% CI = 1.07–2.87) were associated with deprescribing.

CONCLUSION. Use of BZRAs was highly prevalent, and reasons to consider it as PIP were frequent. Deprescribing occurred in one-fourth of NHRs, which is

encouraging. Future interventions should focus on specific aspects of PIPs (ie, indication, duration, drug-drug and drug-disease interactions) as well as on nondementia patients.

CHAPTER 1

INTRODUCTION

Benzodiazepine Receptor Agonists (BZRA) encompass benzodiazepines and Z-drugs (zopiclone, eszopiclone, zolpidem and zaleplon). These medications are widely prescribed for the management of insomnia and anxiety in older adults despite decades of evidence showing that long-term use in older adults is harmful and often not beneficial, resulting in an unfavorable benefit-risk ratio (1-7). As a result, BZRAs are on the lists of potentially inappropriate prescriptions (PIP) criteria (8, 9) and deprescribing (the process of withdrawal or dose reduction of an inappropriate medication (10)) is strongly recommended in chronic BZRA users (11, 12).

Deprescribing of BZRAs is highly relevant in nursing home residents (NHRs), who are particularly at risk, due to increased sensibility and vulnerability (13). Yet prevalence of BZRA use in NHRs in Europe and Northern America remains high, with rates between 14.6% and 54.4% (14-18). However, although the literature is replete with observational and experimental data on the use of antipsychotics in NHRs (12, 19-21), data about BZRA use and PIP in the nursing home (NH) setting remain limited (19). Only a few studies have analyzed the evolution of BZRA use through an intervention, and most of these were conducted in a limited number of countries, had limited sample size, or lacked long-term follow-up (17, 22-24).

Identifying those factors associated with both BZRA use and BZRA deprescribing is a key step in the process of medication optimization. Female sex, older age, depression, sleeping issues and anxiety are factors reported to be associated with BZRA use (14, 25-27). However, most of the data comes from the ambulatory setting (25-30), and only a few studies have explored these factors in the NH setting (14, 31). Factors associated with BZRA deprescribing in NHs remain unknown. It is likely that factors associated with BZRA prescribing and deprescribing differ between the NH setting and the ambulatory care setting, and between countries.

The Collaborative approach to Optimize Medication use for Older people in Nursing homes (COME-ON) study was a cluster controlled trial performed in 54 Belgian NHs over a period of 15 months (April 2015-June 2016) to evaluate the effect of a complex intervention on the appropriateness of medicines prescribed for NHRs (32). Overall, the intervention had a positive impact on the appropriateness

of prescribing (33). The COME-ON database offers a unique opportunity to explore further the appropriateness of use and deprescribing of BZRAs in NHRs.

The aim of the present study was to perform a posthoc analysis of the COME-ON study to (i) describe baseline BZRA use among Belgian NHRs, in terms of prevalence, medication use, dosage, regimen, duration, indications, and appropriateness and its associated factors, and (ii) to describe the BZRA deprescribing rate at the end of the follow-up among the Belgian NHRs and its associated factors.

METHODS

The COME-ON study

This work is a posthoc analysis of data from the COME-ON study, a cluster-controlled trial aimed at evaluating the impact of a complex intervention on PIPs in Belgian NHs. The protocol has been described elsewhere (32). In total, 54 NHs that applied to the study project and were eligible for randomization participated. Eligible NHRs were those aged 65 or older treated by a participating general practitioner (GP). Randomization was performed at the NH level. Allocation to study arms was stratified according to province, experience in case conferencing, and type of pharmacy (hospital or community pharmacy). Each GP only had patients either in the intervention or in the control group. 1804 residents were included. Participating healthcare professionals (HCPs) recorded data online at three study points: baseline, month 8 and month 15 (end of study). Medication data were recorded by pharmacists, administrative and clinical data by nurses and comorbidities were recorded by the GP. For the present work, we analyzed data collected at baseline and at the end of the study (month 15).

The intervention encompassed (1) education and training of HCPs, (2) local interdisciplinary meetings (LIMs), and (3) repeated interdisciplinary case conferences (Figure 1). The intervention was global and not focused on BZRA or psychotropic drugs. However, a few examples of BZRA-related PIPs and instructions on BZRA deprescribing were provided during the training. During case conferences, drug-related problems discussed could relate to any class of medication, including BZRAs, but there was no specific incentive to discuss BZRA deprescribing. The

intervention was implemented in 24 NHs over a 15-month period. The 30 control NHs operated as usual.

Selection of residents

For the present study, residents with medical, clinical, and medication data available at both baseline and end of study were included. Residents for whom BZRA deprescribing was not appropriate (i.e., residents entering palliative care, residents with ongoing alcohol withdrawal) and residents with ongoing BZRA withdrawal documented at baseline were excluded.

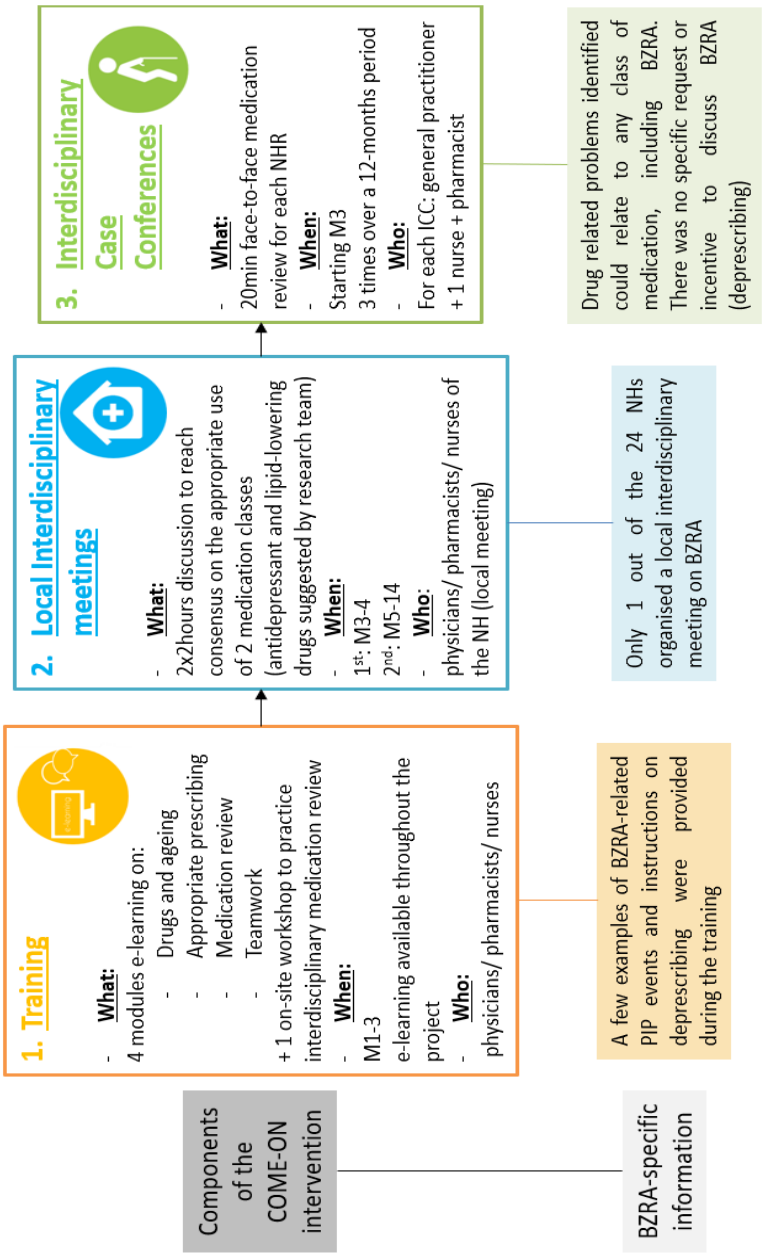


Figure 1: COME-ON intervention components and timeline, adapted from Anrys et al. (32)

Legend: BZRA= benzodiazepine receptor agonists (benzodiazepines and related Z-drugs); ICC= interdisciplinary case conference; M= month; NH= nursing home; NHR= nursing home resident; PIP= potentially inappropriate prescriptions.

Assessments

BZRA use

For descriptive purposes, we extracted data at baseline and end of study relative to drug name, dosage, dosage regimen, time and duration of use, and presumed indications, based on comorbidities recorded by the GP (i.e. insomnia and/or anxiety). Theses Anatomical Therapeutic Chemical classes were considered: N05BA, N05CD and N05CF. To enable dosage comparisons, every BZRA dosage was converted into lorazepam equivalent dose, using a national conversion table (34).

Factors associated with BZRA use at baseline

The selection of factors for which the association with either chronic or as-needed BZRA use was to be tested was based on literature data (14, 25-31) as well as on relevance as judged by the research team. These included factors at the level of the NHR (n=29), the GP (n=6) and the NH (n=6) (detailed list of factors in Supplementary Table S1).

Reasons to consider BZRA as PIPs

We evaluated BZRA appropriateness at baseline and end of study in control and intervention groups, based on the 2019 American Geriatrics Society (AGS) Beers Criteria® (use of any BZRA; use of BZRA in patient with delirium, dementia or cognitive impairment, history of falls or fractures; simultaneous use of BZRA and opioid; simultaneous use of three or more Central Nervous System (CNS) active drugs) (9), and on the Screening Tool of Older Persons' Prescriptions/ Screening Tool to Alert to Right Treatment (STOPP/START) criteria, version 2 (use of BZRA for >4 weeks; use of BZRA without "valid indication") (8). For the latter criterion, insomnia and anxiety were considered as the only valid indications for BZRA use, based on Belgian recommendations (12) and from the Canadian Deprescribing Network (11).

Deprescribing and associated factors

Deprescribing was defined as the achievement of any of these three situations: (1) complete cessation of BZRA, (2) decrease in overall chronic daily

BZRA dose, and (3) cessation of an "if needed" BZRA prescription, in addition to an unchanged chronic dose. Data collection on deprescribing was performed by the main researcher (PE) who was blinded to intervention status at the time of data collection.

Factors potentially associated with BZRA deprescribing were selected through literature review (14, 25-31) and discussion among research team members. These included factors at the level of the NHR (n=31), the GP (n=6), the NH (n=6), and the study group (intervention or control) (detailed list of factors in Supplementary Table S2).

Statistical analysis

Continuous variables are presented as medians [P_{25}; P_{75}]. Categorical variables are presented as number and proportions.

Variables associated with the type of BZRA use ('regular' or 'if needed') at baseline were assessed using a multinomial logistic regression. Variables associated with BZRA deprescribing were assessed using a logistic regression in people having a BZRA at baseline (N=418). All variables associated with the outcome in univariate analysis with a p-value <0.15 were candidate for the multivariable model. A stepwise selection based on the Akaike Information Criterion was then applied to select the final multivariable model.

All analyses were performed using R software version 3.3.1. (R Foundation for Statistical Computing, Vienna, Austria'); P<.05 was considered statistically significant.

RESULTS

BZRA use at baseline and associated factors

From the 1804 NHRs included in the COME-ON study, 511 left the study before the end (mainly because of death), 392 did not have complete data at baseline and/or end, and 104 were not eligible for BZRA deprescribing. In total, 797 NHRs were included in this analysis (Supplementary Figure S1). Comparison of included and excluded residents is available in Supplementary Table S3. The median age of the included NHRs was 87 years; 73.0% were women (Table 1). The number of medicines per NHR ranged from 0 to 25 with a median of 9.

Overall, 418 (52.4%) NHRs were prescribed a BZRA. Most users had been taking a BZRA for more than a year (n=323; 77.3%) and on a regular schedule (n=380; 90.9%). Of the 160 and 204 NHRs with reported anxiety and insomnia, respectively, 117 (73.1%) and 159 (77.9%) were taking a BZRA. Among BZRA users, 175 (41.9%) had no documentation of insomnia or anxiety by the GP. Baseline data are presented in Table 1.

Table 1: Study Population characteristics and BZRA prescribing patterns (N=797)	
Population Characteristics	
Age, y[a]	
Median [IQR]	87 [81.75 ; 91]
Sex, *n(%)*	
Male	215 (27.0)
Female	582 (73.0)
No. of medicines taken	
Median [IQR]	9 [6 ; 12]
No. of CNS-active medicines taken	
Median [IQR]	3 [1 ; 4]
Comorbidities (as reported by the GP), *n(%)*	
Insomnia	204 (25.6)
Anxiety (past or current)	235 (29.5)
History of falls in previous 3 months	107 (13.4)
Dementia	183 (23.0)
Delirium (current)	22 (2.8)
Depression (past or current)	148 (18.6)
History of fragility fracture	101 (12.7)

SECTION 1

BZRA prescribing patterns	
BZRA users, n(%)	418 (52.4)
BZRA multiple users, *n(%)*	76 (9.5)
Most prescribed BZRA, *n(%)*	
lorazepam	123 (15.4)
lormetazepam	108 (13.6)
alprazolam	87 (10.9)
zolpidem	71 (9.8)
Half-life of prescribed BZRA, *n(%)*	
Short- and Intermediate-acting BZRA	392 (49.2)
Long-acting BZRA	49 (6.1)
Regimen, *n(%)*	
Regular use	380 (47.7)
If needed use[b]	37 (4.6)
Duration of use, *n(%)*	
≤ 4 weeks	7 (0.88)
> 4 weeks and ≤ 6 months	41 (5.1)
> 6 months and ≤ 1 year	63 (7.9)
> 1 year	323 (40.5)
Daily chronic BZRA dose among BZRA users (lorazepam equivalent in milligrams)	
Median [IQR]	1 [1 ; 2]
(min ;max)	(0.25 ; 10.5)
Presumed indication,[c] *n(%)*	
BZRA user with documented insomnia	159 (19.9)
BZRA user with documented anxiety	154 (19.3)
BZRA user without documented insomnia or anxiety	175 (22.0)

Legend: BZRA= Benzodiazepines Receptors Agonists (ATC N05BA, N05CD and N05CF), **CNS**= Central Nervous System, **GP**= General Practitioner

Short- and Intermediate-acting BZRA: triazolam, midazolam, zolpidem, alprazolam, bromazepam, oxazepam, lorazepam, lormetazepam, brotizolam, loprazolam, zopiclone, clotiazepam.

Long-acting BZRA: diazepam, clorazepate, prazepam, flurazepam, nitrazepam, flunitrazepam

[a]**:** 5 missing data (0.63%)

[b]: A resident was considered as an "if needed" user of BZRA if when receiving an "if needed" BZRA without any chronic BZRA

[c] **:** According to comorbidities/health problems recorded by the GP

In multivariable analysis, eight NHR characteristics and two GP characteristics but no NH characteristics were associated with regular BZRA use versus no BZRA use (Table 2). History of fall in the past 3 months, anxiety, insomnia, chronic obstructive pulmonary disease, number of medicines without counting BZRA, use of antidepressant, and age of GP were associated with regular BZRA use. Conversely, dementia, use of trazodone, and being cared by the NH coordinating physician were associated with lower odds of regular BZRA use (Table 2 lists odds ratios (ORs) and 95% confidence intervals (CIs)). In the same model, three NHR characteristics and one GP characteristic but no NH characteristic were associated with *if needed* BZRA use vs no BZRA use (Table 2). Residents with insomnia, behavioral, and psychological symptoms of dementia and male residents were more likely to receive if needed BZRA than no BZRA. Anxiety was not associated with if needed prescriptions. Residents receiving care from the coordinating physician were less likely to receive if needed BZRA compared to no BZRA (Tabe 2 lists the ORs and 95% CIs, and Supplementary Table S4 describes the univariate model).

Potentially inappropriate prescriptions

All 418 BZRA users flagged the AGS Beers Criteria® "use of any BZRA" for potentially inappropriate medication. The STOPP criterion "duration of use over 4 weeks" was flagged for 98.3% of users. Many of these users had additional reasons for PIP: lack of indication (41.9% of users), drug-disease interaction (BZRA and dementia, delirium, history of falls and fractures; 67.2% of users), or drug-drug interaction (BZRA and opioids, or BZRA and two or more other CNS drugs, 21.1 and 67.2% of users, respectively) (Table 3).

In the intervention group, between baseline and end of study, we observed an absolute decrease in the prevalence of NHRs meeting each of these criteria, ranging from 1.3% to 5.3% of NHRs. In the control group, differences ranged from an absolute decrease of 2.4% to an absolute increase of 2.3% (Table 3).

Table 2: Factors associated with the type of use of BZRA at baseline in final multivariable multinomial logistic regression (N=754)				
	Multivariable model			
	BZRA regular vs no use		BZRA if needed vs no use	
Variable	OR (95%CI)	p-value	OR (95%CI)	p-value
Patient's baseline characteristics				
Male	0.83 (0.57; 1.21)	0.335	2.50 (1.14; 5.49)	0.023[a]
Clinical characteristics at baseline				
Fall history in the past 3 mo	1.59 (1.07; 2.38)	0.022[a]	0.80 (0.31; 2.11)	0.658
Comorbidities at baseline				
Dementia	0.66 (0.44; 0.99)	0.047[a]	0.67 (0.26; 1.78)	0.427
BPSD	1.05 (0.69; 1.61)	0.805	3.95 (1.47; 10.56)	0.006[a]
Anxiety	1.60 (1.09; 2.36)	0.017[a]	0.75 (0.31; 1.83)	0.525
Insomnia	3.19 (2.10; 4.84)	<0.001[a]	4.15 (1.76; 9.79)	0.001[a]
COPD	1.73 (1.02; 2.95)	0.042[a]	0.92 (0.24; 3.57)	0.900
Medications at baseline				
No. of medications without BZRA				
0-4	1.00		1.00	
5-9	2.90 (1.70; 4.96)	<0.001[a]	1.06 (0.31; 3.58)	0.926
10-13	2.79 (1.57; 4.95)	<0.001[a]	0.90 (0.23; 3.50)	0.876
≥14	4.00 (1.89; 8.47)	<0.001[a]	1.66 (0.36; 7.66)	0.517
Antidepressant	2.74 (1.59; 4.71)	<0.001[a]	1.74 (0.49; 6.13)	0.390
Trazodone	0.46 (0.26; 0.82)	0.008[a]	2.55 (0.91; 7.17)	0.076
SSRI	0.65 (0.37; 1.12)	0.118	1.53 (0.55; 4.21)	0.414
Nursing home characteristics				
Ratio NHR per nurse	0.95 (0.90; 1.01)	0.092	0.87 (0.72; 1.06)	0.180
GP characteristics				
Age, per 10 additional y	1.19 (1.01; 1.40)	0.036[a]	0.85 (0.61; 1.18)	0.324
Residents for which the GP is the CP	0.69 (0.48; 0.99)	0.042[a]	0.22 (0.07; 0.68)	0.009[a]

Legend: BZRA= Benzodiazepines Receptors Agonists (ATC N05BA, N05CD and N05CF), **BPSD=** Behavioral and Psychological Symptoms of Dementia, **CI=** Confidence Interval, **CIRS-G=** Cumulative Illness Rating Scale – Geriatric, **COPD=** Chronic Obstructive Pulmonary Disease, **CP=** Coordinating Physician, **GP=** General Practitioner, **NHR=** Nursing Home Resident, **OR=** Odds Ratio, **SSRI=** Selective Serotonin Reuptake Inhibitors
[a]Significant: P < .05.

Table 3: Evolution of BZRA-related PIPs prevalence between baseline and endpoint of the COME-ON study												
	Intervention group						Control group					
	Baseline			End			Baseline			End		
PIP criteria	n	% Total NHRs (N=453)	% BZRA users (N=237)	n	% Total NHRs (N=453)	% BZRA users (N=214)	n	% Total NHRs (N=344)	% BZRA users (N=181)	n	% Total NHRs (N=344)	% BZRA users (N=173)
Use of any BZRA	237	52.3	100.0	214	47.2	100.0	181	52.6	100.0	173	50.3	100.0
Duration of use												
Use of BZRA for > 4 weeks (STOPP D5)	235	51.9	99.2	211	46.6	98.6	176	51.2	97.2	168	48.8	97.1
Lack of indication reported by GP												
Use of BZRA without insomnia or anxiety (STOPP A1)	100	22.1	42.2	81	17.9	37.9	75	21.8	41.4	68	19.8	39.3
Drug-disease interaction												
Use of BZRA in patient with delirium, dementia or cognitive impairment or history of falls or fractures (AGS 2019)	167	36.9	70.5	154	34.0	72.0	114	33.1	63.0	114	33.1	65.9
Drug-drug interaction												
Simultaneous use of BZRA and opioid (AGS 2019)	55	12.1	23.2	49	10.8	22.9	33	9.6	18.2	38	11.0	22.0
Simultaneous use of BZRA and ≥ 2 other CNS active drugs (AGS 2019)	170	37.5	71.7	156	34.4	72.9	111	32.3	61.3	119	34.6	68.8

Legend = **AGS:** American Geriatrics Society, **BZRA**: Benzodiazepines Receptors Agonists (ATC N05BA, N05CD and N05CF), **CNS**: Central Nervous System, **GP**: General Practitioner, **NHRs**: Nursing Home Residents, **PIPs**: Potentially Inappropriate Prescriptions

SECTION 1

BZRA deprescribing and associated factors: effect of the intervention

Prevalence of BZRA use decreased from 52.3% (237/453) at baseline to 47.2% (214/453) at end of study in the intervention group (absolute decrease of 5.1%), and from 52.6% (181/344) to 50.3% (173/344) in the control group (absolute decrease of 2.3%).

Deprescribing at study end occurred in 32.9% of baseline users (78/237) in the intervention group and 22.1% (40/181) in the control group, with a combined deprescribing rate of 28.2% (118/418). A complete cessation of BZRA prescription was observed in 37 (47.4%) of the 78 NHRs with deprescribing in the intervention group and in 21 of 40 NHRs in the control group (52.5%) (combined study arms: 58/118, (49.2%)).

In the final multivariable model, the study arm, three NHR characteristics, two NH characteristics but no GP characteristic were associated with BZRA deprescribing (Table 4). The intervention group was associated with BZRA deprescribing. Dementia at baseline was highly associated with deprescribing. Parkinson's, extrapyramidal syndrome, and a history of hospitalization in the past 3 months were also associated with deprescribing. At the level of the NH, a higher number of beds was associated with deprescribing, whereas being institutionalized in a public NH was found to be associated with less deprescribing (Table 4 lists the ORs and 95%CIs). The complete analysis is available in Supplementary Table S5.

Table 4: Factors associated with BZRA deprescribing at the end of the study in univariate and multivariate logistic regression among NHRs with BZRA prescribed at baseline (N=418)				
Among the 418 people: 118 with BZRA deprescribing (28.2%)				
Variable	**Univariate model**		**Multivariable model**	
	OR (95%CI)	**p-value**	**OR (95%CI)**	**p-value**
Study arm				
Intervention vs control	1.73 (1.12; 2.71)	0.016[a]	1.74 (1.07; 2.87)	0.029[a]
Clinical characteristics at baseline				
Katz score	1.06 (1.01; 1.11)	0.018[a]		
Dependency				
O	1.00			
A	3.47 (1.19; 12.66)	0.034[a]		
B	5.23 (1.94; 18.28)	0.003[a]		
C	5.03 (1.69; 18.64)	0.007[a]		
C dementia	7.61 (2.84; 26.56)	<0.001[a]		
D	15.31 (3.02; 90.08)	0.001[a]		
Hospitalization in the past 3 months	1.79 (0.95; 3.32)	0.066	2.01 (1.02; 3.91)	0.039[a]
Incontinence	1.70 (1.09; 2.68)	0.022[a]	1.52 (0.92; 2.52)	0.103
Comorbidities at baseline				
Parkinson/extrapyramidal syndrome	2.03 (1.12; 3.63)	0.018[a]	2.26 (1.19; 4.25)	0.011[a]
Dementia	2.31 (1.50; 3.61)	<0.001[a]	2.35 (1.45; 3.83)	0.001[a]
BPSD	2.14 (1.39; 3316)	0.001[a]		
Delirium	2.22 (1.23; 3.96)	0.007[a]		
Nursing home characteristics				
Ownership status				
- Private non for profit	1.00		1.00	
- Private for commercial purposes	1.02 (0.42; 2.328)	0.969	2.05 (0.78; 5.18)	0.135
- Public	0.48 (0.27; 0.81)	0.008[a]	0.53 (0.29; 0.96)	0.040[a]
No. of beds, per 10 beds	1.07 (1.02; 1.12)	0.004[a]	1.06 (1.01; 1.12)	0.025[a]
GP characteristics				
Age, per 10 y	0.78 (0.64; 0.95)	0.015[a]	0.84 (0.68; 1.05)	0.133
No. of years of experience as a GP, per 10 y	0.78 (0.64; 0.95)	0.015[a]		

Legend: **BZRA**= Benzodiazepines Receptors Agonists (ATC N05BA, N05CD and N05CF), **BPSD**= Behavioral and Psychological Symptoms of Dementia, **CI**= Confidence Interval, **CIRS-G**= Cumulative Illness Rating Scale – Geriatric, **COPD**= Chronic Obstructive Pulmonary Disease, **CP**= Coordinating Physician, **GP**= General Practitioner, **NHR**= Nursing Home Resident, **OR**= Odds Ratio, **SSRI**= Selective Serotonin Reuptake Inhibitors
Dependency and number of years of experience as a GP per 10 years were not introduced as candidates for the final multivariable model as they presented a variance inflation factor > 5
Goodness-of-fit: Hosmer and Lemeshow test: p-value = 0.337
[a]Significant: P < .05.

DISCUSSION

This post hoc analysis of the COME-ON study data reveals a high prevalence of BZRA use and of PIP related to BZRA use in NHRs in Belgium. Deprescribing occurred in 28% of NHRs, and the intervention had a significant impact on BZRA deprescribing. Several factors were found to be associated with BZRA use and with deprescribing, which is important to prepare improvement initiatives in the future. In contrast to the considerable attention that has been given to the use of antipsychotic drugs in NHs over the last decades, this is one of the first studies that evaluated the appropriateness of BZRA use, evolution over time, and factors associated with use and with deprescribing.

Use of BZRA was highly prevalent. At baseline, 52% of NHRs were receiving a BZRA. This is similar to a previous report from 2005 in which 53% of the 1730 Belgian NHRs were BZRA users (14) and suggests no change over time in BZRA prescribing overall, despite rising awareness of their harms, strong international recommendations to avoid their use, and national campaigns (35). The prevalence of BZRA use in NHRs in the present study was similar to the prevalence reported in NHRs in France (54.5%) (18) but much higher than the prevalence as reported in other countries such as Australia (31.8%) and Canada (14.6%) (17, 22). Differences may be due to variations in terms of population, context, or culture. Indeed, in Belgium, we also observed a very high overall prevalence of BZRA use in the ambulatory setting (36). An in-depth evaluation of these differences and of the barriers and enablers of BZRA deprescribing in the NH setting in different countries would be highly valuable.

Beyond the high prevalence, our data show that BZRA use was often inappropriate in several aspects. Potential overuse is a major concern because 42% of BZRA users had no insomnia or anxiety reported by the GP, and 98% had been receiving a BZRA for longer than 4 weeks. In terms of potential misuse, approximately two-thirds of NHRs had a drug-disease interaction (i.e., use of BZRA in patients with delirium, cognitive impairment, history of falls or fractures), and a similar proportion had a drug-drug interaction (i.e., simultaneous use of BZRA and at least two other CNS drugs). These are, to the best of our knowledge, the first published data on several BZRA-related PIPs in NHRs. Together with the high prevalence rate, they call for urgent action towards more rational use of BZRA in NHRs. Further education of health care professionals (HCPs) around these PIP criteria and use as quality indicators may help achieve this objective. A project of this kind is currently ongoing in Flanders (37).

Eight patient-related and two GP-related factors were significantly associated with regular BZRA use. Identifying these factors could help prioritize populations to be targeted by future interventions and quality improvement initiatives. Comparison with other studies is difficult because very few studies have analyzed factors associated with BZRA use in the NH setting (14, 31), compared with the outpatient setting (25-30). First, dementia was significantly associated with less regular BZRA use but also with BZRA deprescribing. Current literature reports similar as well as conflicting findings (14, 29, 31). A potential explanation might be the fear of association between BZRA and cognitive impairment. There may also be fewer barriers towards the non-use or deprescribing of BZRA in patients with dementia (e.g. less pill request, less reluctance to stop) (14). Second, there were fewer regular BZRA use versus no use among trazodone users. Off-label use of trazodone for its sedative properties is frequent (38), and a switch from BZRA to trazodone has been described elsewhere (39-42), despite no strong evidence that low dose trazodone is safer than BZRAs among older adults (38). Third, the use of antidepressants was associated with regular BZRA use as compared to no use. This association might be of concern because the combination of psychotropic drugs is potentially harmful. Guidelines recommend that the association should be limited to 8 weeks, which is far from what we observed (43). Finally, less BZRA use occurred among NHRs treated by the coordinating physician of the NH. The coordinating physician is in charge of the medication policy of the NH. Given this positive

association, the role of the coordinating physician in the implementation of local strategies toward BZRA deprescribing seems promising.

Over the 15-month study period, the prevalence of BZRA use decreased from 52.4% to 48.6%, and deprescribing, a distinct and complementary concept, occurred in 28.2% of BZRA users. These data are encouraging. Our data also suggest that the intervention group did better than the control group. The intervention group was one of the few factors significantly associated with BZRA deprescribing in the multivariate analysis. These results confirm that reducing BZRA use in the NH setting is feasible, and it suggests that a global approach towards more appropriate prescribing to NHRs, such as the COME-ON intervention, can also specifically decrease BZRA overuse. However, BZRA use was high and could often be considered a PIP because of additional drug-drug or drug-disease interactions, placing NHRs at greater risk of harm. This calls for further wide-scale, dedicated, and long-term initiatives.

A 2016 study in French NHs produced conflicting results, showing that a global geriatric intervention did not improve benzodiazepine discontinuation (18). Possible explanations might be that the intervention did not target medications and could have been implemented with large variations between NHs. Moreover, this study used a control group that received an audit and feedback intervention. We may expect that higher rates of BZRA deprescribing could be achieved with an intervention targeting BZRA or psychotropic drugs. Indeed, in the COME-ON study, information on problems related to BZRA use was provided during training of HCPs, but among other messages on many other medication classes. Specific barriers to BZRA deprescribing (e.g., non-pharmacological approaches) were not addressed. Only one NH explicitly chose to focus a LIM on the use of BZRA. A retrospective propensity score-matched controlled study in 2019 among 1653 NHRs with dementia in Spain found that team rounds, use of START/STOPP criteria, and use of patient decision aids were associated with a BZRA daily dose reduction of 23.1%, 39.5% and 31.8%, respectively (24). However, follow-up was limited to 4 weeks. In the RedUSe controlled trial led in 25 NHs in Australia, a multifaceted program that was very similar to the COME-ON intervention but focused on benzodiazepines and antipsychotics was implemented. At 6 months, a significant reduction was found in the prevalence of use of benzodiazepines, from 31.8% to 26.9% (22). This decrease is similar to that observed in our intervention group, but

not larger. Interestingly, benzodiazepine use continued to decline in intervention NHs in the year following the trial (44). However, it is difficult to identify which part of the intervention had the greatest impact on BZRA, and the study highlighted a lack of participation of physicians, which we think are important to involve. More recently, in Belgium, the effect of a practice improvement initiative including education, professional support, and transition to person-centered care at the NH level was reported. In five NHs over 12 months, the prevalence of BZRA use significantly decreased, from 32.2% to 23.4% (45). The approach implemented, with an attention to psychotropic policy and non-pharmacological approaches at the NH level, is interesting, but the lack of a control group and the inclusion of only five NHs with baseline BZRA use lower than the national average limit the validity and generalizability of study findings. A detailed evaluation of barriers and enablers associated with BZRA deprescribing in our specific context could help the development of a theory-informed, transferable intervention.

This study has several strengths. First, we analyzed the data of a large sample of NHRs, covering the two largest regions in Belgium (Wallonia and Flanders). Second, in contrast with other published data, we examined prescribing patterns in detail, including with regard to dosages and comorbidities, and we analyzed prescribing evolution case by case. Third, the study took place in real-life conditions with the involvement of HCPs working in the included NHs.

This study also has limitations. Several were related to its post hoc design. Indications for BZRA use were estimated by the research team, based on GP-recorded comorbidities, and there was no confirmation by HCPs. Some factors possibly associated with BZRA use or with deprescribing were not available from the research database, such as the availability and use of non-pharmacological alternatives or the attitude of residents or relatives toward BZRA deprescribing. Evolution of use over time and comparison of data from the intervention and control group remained descriptive only. We based the evaluation of PIPs on AGS Beers Criteria® and START/STOPP criteria. These are not specifically designed for NH use and therefore may not be relevant for some NHRs. Finally, a high number of patients were excluded due to missing data on comorbidities. Age, number of medicines, and BZRA use did not differ significantly between the group of NHRs included and excluded, but a selection bias cannot be ruled out.

In conclusion, this posthoc analysis highlighted the substantial and often inappropriate use of BZRA among Belgian NHRs, the encouraging yet insufficient deprescribing, and their associated factors including the complex intervention implemented in the COME-ON study. Future interventions should focus on the indication, duration of use, drug-drug and drug-disease interactions, as well as pay attention to residents without dementia.

Supplemental materials (available online):

Supplementary Table S1: Factors analyzed for potential association with BZRA use in multinomial regression

Supplementary Table S2: Factors analyzed for potential association with BZRA deprescribing

Supplementary Table S3: Comparison of socio-demographic characteristics and baseline medication use between Nursing Home Residents included and excluded

Supplementary Table S4: Factors associated with the type of use of BZRA at baseline in univariate and multivariable multinomial logistic regression

Supplementary Table S5: Factors associated with BZRA deprescribing at the end of the study in univariate and multivariate logistic regression among NHRs with BZRA prescribed at baseline (N=418)

Supplementary figure S1: Flowchart of nursing home residents selection for inclusion in the analysis

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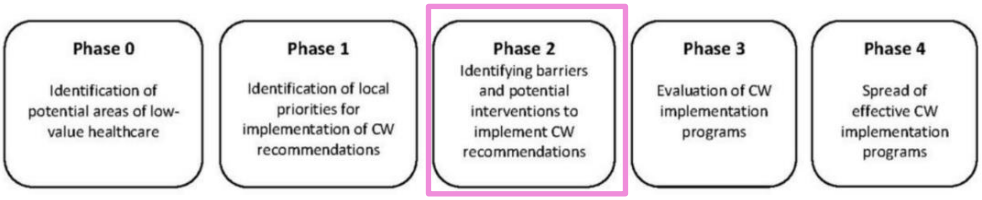
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SECTION 2: Identification of barriers and enablers and potential interventions to implement the needed change



Choosing Wisely framework for de-implementing low-value care (Grimshaw et al. 2020)

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. Barriers and enablers towards benzodiazepine-receptor agonists deprescribing in nursing homes: A qualitative study of stakeholder groups

Chapter 4. Development of a behaviour-change intervention toward benzodiazepine deprescribing in older adults living in nursing homes

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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Chapter adapted from the homonymous article published in *Implementation Science* (2022)

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

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.

Funding:

This research received no external funding.

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.

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).

SECTION 2

TRIAL REGISTRATION.

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

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 programs, 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, CINHAL 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 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 (Figure 1).

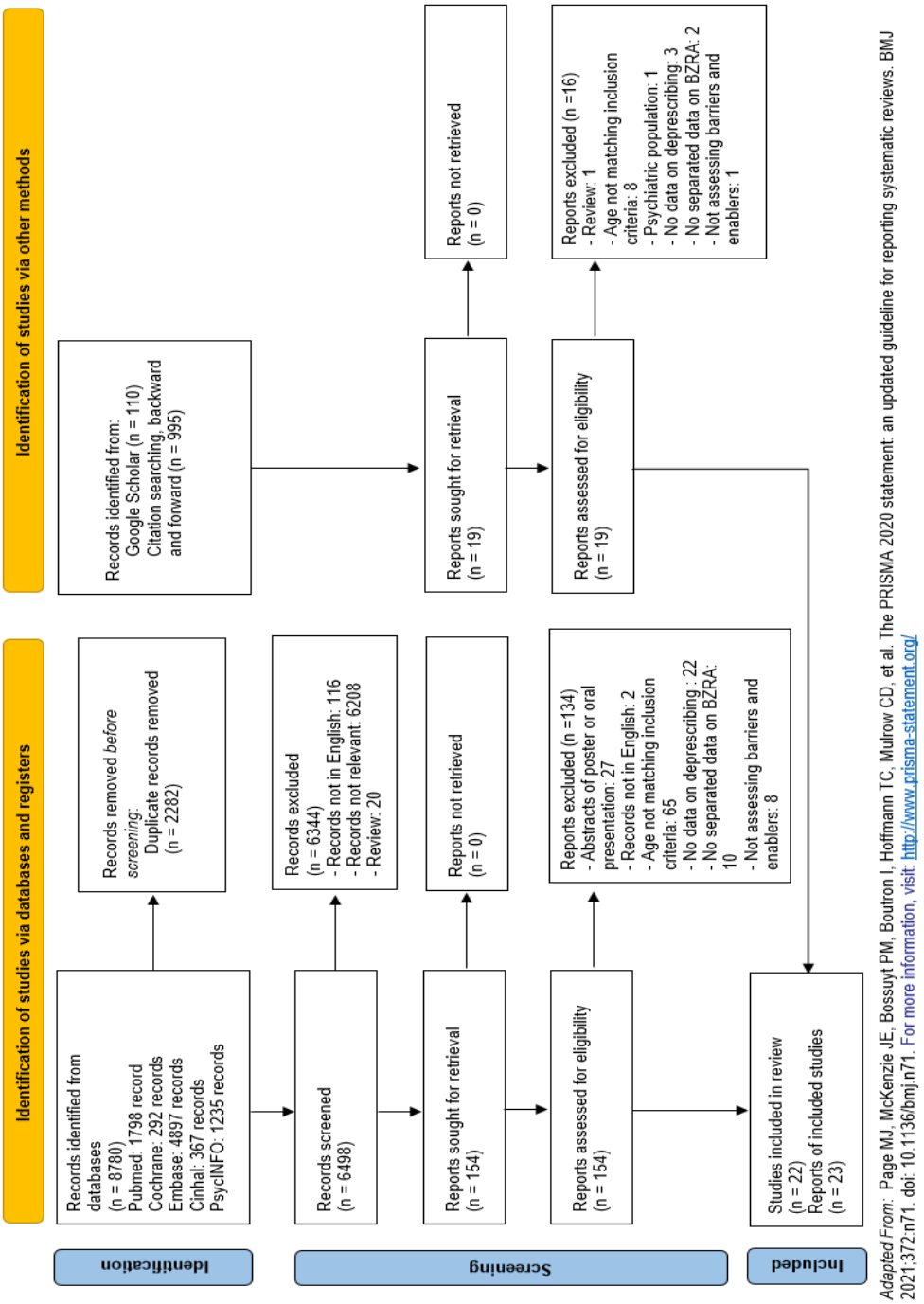


Figure 1: Flow chart of studies screening and selection

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, data were missing to assess the quality of at least one of the MMAT criteria, and for 2 of these studies 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).

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 deprescribe Feasibility of deprescribing	BZRA discontinuation	<u>Willingness for discontinuation:</u> 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 <u>Feasibility of discontinuation:</u> 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	Previous attempts 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 Willingness to stop GPs and nurses indicated willingness to stop chronic BZRA use in respectively 33 and 21% of NHRs Resident-specific barriers 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. General attitudes 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 when stopping BZDs and that there is little scientific information available for stopping.

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	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
Evrard, 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/extrapyramidal 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 Questionnaire: BZRA perceptions and concerns	Not reported	<u>Patient interviews:</u> - 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 <u>GP questionnaire:</u> - 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. - 67% felt they were bothered by endless requests for benzodiazepine prescriptions

							Nursing staff questionnaire: - 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.
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		In general Barriers: - Female gender - Low income - Aggregated Diagnosis group (more comorbidities) Enablers: - Older age - Higher aggressive behaviour scale score Among men Enablers: - Older age - Widowed - Higher aggressive behaviour scale score Among women Barriers: - Low income - Aggregated Diagnosis group (more comorbidities) Enablers: - Older age - Higher aggressive behaviour scale score
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) Differences between followers and non-followers	Following the clinical rule meant that the GP started BZRA deprescribing		27 out of 161 (16.8%) of the alerts actioned were followed Reasons for not following: - Already tried (n=10, 6.2%) - Patient/family resistance (n=37, 23.0%) - No need (non-continuous BZRA use) (n=32, 19.9%) - Indication still present (n=27, 16.8%) The alert-following group had a shorter median-time of BZRA, compared to the alert non-following group 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	Major themes: - 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	One enabler: - 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= loosing 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)	<u>In one of the two models used:</u> 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 benzodiazepines; thoughts about discontinuation;	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

				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.
			83 practice staff: 72 GPs, 5 managers, 4 nurses, 2 counsellors	Group interview on main problems, advantages and disadvantages they anticipated in withdrawing their elderly patients from 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% 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"

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	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 educative intervention	10 older adults, Z-drug users 7 GPs	Interview about: - Past and current Z-drug use - Prior education about sedative - Educational needs - Reactions to the intervention material 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	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) 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) Qualitative interviews	261 adults over 65, receiving at least 5 medicines and chronic BZRA prescription 21 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 Interviews on: - Initial reactions to the intervention - Reasons underlying the decision to taper - Experience with the tapering process	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 - 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)

				- Personal interactions with HCPs		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 practioner, **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 Figure 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.

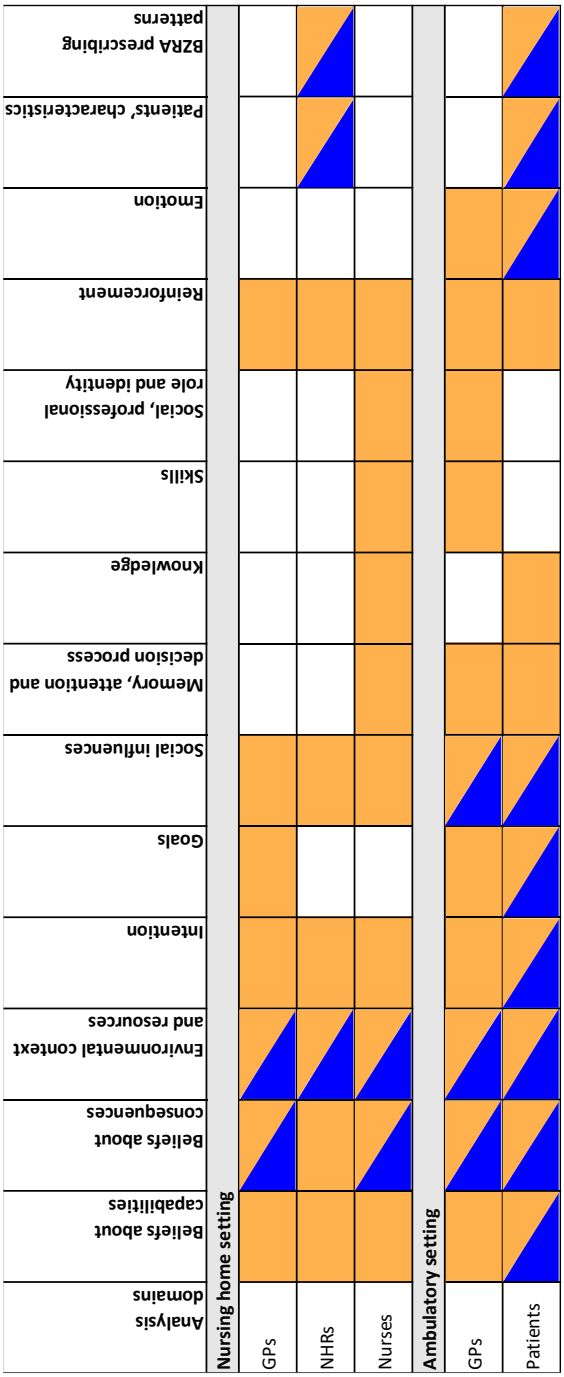


Figure 2: Reported relevant analysis domain, identified as barrier and/or enabler per setting and per stakeholders.

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	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)
Beliefs about capabilities																										
Perceived capability of stakeholders to perform BZRA deprescribing and the problems they face																										
Patients' self-efficacy											E												E			
Deprescribing is challenging				B								B				B		B	B		B	B				
Perceived efficacy or lack of efficacy				B			B		B			B;E				B		B	B;E		B			B		
Beliefs about consequences																										
What stakeholders think could happen from performing BZRA deprescribing																										
No perceived benefit				B			B		B			B		B		B		B	B		B		B	B		
Return of primary condition			B	B			B									B			B		B		B	B		
Withdrawal symptoms				B			B							B				B	B			B				
Increase in care burden				B															B		B					
Avoiding adverse effects of long-term BZRA				E			E					E		E		E			E		E		E			
Environmental context and resources																										
Influence of the environment on stakeholders' behaviour																										
Tool implementation						E								E				B			B		E			
Favourable/ Unfavourable moment			B	B								B									B;E		B;E			
Lack of resources																						B	B			
Difficulty of alternatives				B														B			B	B				

Heavy workload		B															B			B					
Inheritance of prescribing culture																				B					
BZRA deprescribing not prioritised by the healthcare system		B																		B					
NH specific requirements		B		B			B																		
NH characteristics					B;E	B;E														B					
BZRA cost												E													
Intention *How inclined stakeholders are to perform BZRA deprescribing*																									
Level of willingness			B	B			B		B			B		E		B		B	B	E	B			E		
No intention to use non-pharmacological approaches				B												B		B								
Goals *How important is BZRA deprescribing for stakeholders*																									
Competing goals				B												B		B			B		B			
Patients' attachment to these medicines				B								B		B		B		B			B	B	B	B		
Perceived need of sleep		B										E											E	B		
Having a more natural sleep												E		E												
Social influences *How others influence stakeholders' behaviour*																									
Expected patient resistance			B	B			B		B									B	B		B	B				
Pressure for continuous prescribing							B															B				
Belief that GP's prescription equals safety and approval for continuous use							B					B				B							B	B		
Patient's trust in GP												B											B;E	E		
Memory, attention and decision process *Habits factors and decision process regarding BZRA deprescribing*																									
BZRA as an easy solution							B											B								
Routine approach		B		B			B					B				B					B			B		

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

Low orientation score																										E
Parkinson or extrapyramidal symptoms						E																				
Comorbidities								B							B											
Hospitalisation in past 3 months						E																				
Higher number of medications					B																					
Antidepressant use					E																					E
Medical cause of sleeplessness			B																							
Poorer quality of sleep											E															
Low income								B																		
Widowed men								E																		
BZRA prescribing patterns																										
Lower dose											E				E											
Lower frequency of intake																	E			E						
Shorter duration of treatment									E																	
Indication other than sleeping issues			B																							

Legend: BZRA= Benzodiazepines receptor agonists, **GP**= General practitioner, **NH**= nursing home, **TDF**= Theoretical domains framework
[B] stands for an identified barrier and [E] for an identified enabler.

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 behavior 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 behavior, were reported in 13 of the studies, mainly as a barrier. In 11 studies, stakeholders did not perceive any adverse effects of BRZA and therefore did not believe stopping them would have any benefit. As patients aged, HCPs 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.

> *"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.

> *"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).
>
> "*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 re-evaluation.

> *"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).

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 three 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. Use of the TDF is also valuable with regards to 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 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, we excluded studies conducted in older adults receiving palliative care or mentioned at end of life. However, an important percentage of nursing home residents could be considered at end of life. In a prospective study conducted among 690 residents in Norway, the median survival in NHs was 2.2 years (65). Belgian data reported a rate of death at 1 year ranging from 10.5% to 35.0% depending on the resident level of dependency (66). In the specific context of this thesis, we therefore might have missed relevant publications. Fourthly, 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.

Supplemental materials (available online):

Appendix 1: PRISMA 2020 Checklis

Appendix 2: Research equations

Appendix 3: Data extraction form

Appendix 4: Quality of studies included in the review

Appendix 5: TDF domains, analysis subthemes and matching citations. (Contains additional citations for each analysis subtheme).

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Chapter 3. Barriers and enablers towards benzodiazepine-receptor agonists deprescribing in nursing homes: A qualitative study of stakeholder groups

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Adapted from the homonymous article published in *Exploratory Research in Clinical and Social Pharmacy* (2023)

https://doi.org/10.1016/j.rcsop.2023.100258

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Funding:

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

ABSTRACT

BACKGROUND. Despite recommendations to deprescribe chronic benzodiazepine receptor agonists (BZRA) among older adults, the prevalence of their use in Belgian nursing homes (NHs) remains above 50%. The use of a behavioral science approach, starting with the evaluation of barriers and enablers for BZRA deprescribing, has the potential to decrease BZRA prescribing.

OBJECTIVES. To identify barriers and enablers for BZRA deprescribing perceived by the different stakeholders involved in nursing home care in Belgium.

METHODS. In a purposive sample of 6 NHs, we conducted face-to-face interviews with general practitioners (GPs), and focus groups with other healthcare providers (HCPs), including nurses, pharmacists, occupational therapists, physical therapists, and with NH residents and relatives. All interviews with HCPs were analyzed through deductive thematic analysis, using the theoretical domains framework (TDF) as the coding framework. Residents' and relatives' interviews were analyzed using an inductive thematic approach.

RESULTS. We interviewed 13 GPs, 35 other HCPs, 22 nursing home residents, and 5 relatives. Overall, 9 TDF domains were identified as most relevant among HCPs interviewed: Skills, Beliefs about capabilities, Goals, Memory attention and decision processes, Environmental context and resources, Social influences, Knowledge, Social/professional role and identity, and Beliefs about consequences. Five additional themes emerged from residents' and relatives' interviews: knowledge on medications used, communication with NH staff and GPs, perceived efficacy and necessity of BZRA, influence of the environment, and reluctance towards BZRA deprescribing. Some domains and themes differ between stakeholders (e.g., knowledge), while others match between groups (e.g., environmental aspects).

CONCLUSION. BZRA deprescribing is influenced by knowledge and skills gaps, automatic BZRA refilling, competing priorities, social challenges, environmental factors and poor nursing home residents involvement. Targeting these barriers will be a key step for implementation of BZRA deprescribing.

SECTION 2

INTRODUCTION

Benzodiazepine Receptor Agonists (BZRA, namely benzodiazepines and Z-drugs) are mainly used in the treatment of anxiety and insomnia (1). In most cases, BZRAs have only modest benefits (2) but can trigger severe side effects in older adults including falls and fractures, delirium, cognitive impairment, and dependence (1, 3-5). Consequently, the benefit-risk profile is unfavorable and international recommendations advise against the use of BZRAs in older adults (6, 7). Yet BZRAs are widely used among Belgian nursing home residents (NHRs), with a reported prevalence of 52.4% (8).

Deprescribing is the action of discontinuing or reducing the use of a medication that is no longer needed or which may put the patient at risk, under the supervision of Health Care Providers (HCPs), to manage polypharmacy and improve outcomes (9). Many interventions promoting BZRA deprescribing have already been studied (mainly in the outpatient settings) and achieve deprescribing rates ranging from 27 to 80% (10). However, it remains unclear how to best implement BZRA deprescribing in nursing homes (NHs).

Implementation science recommendations highlight the need and benefit to build theory-driven approaches, starting with the identification of barriers and enablers, when designing implementation strategies (11-13). Two recent systematic reviews analyzed barriers and enablers of BZRA deprescribing in older adults, and reported more barriers than enablers, including a lack of knowledge, expected patients' resistance and interprofessional conflicts (14, 15). However, the majority of studies were undertaken in outpatient settings and their results may not be applicable to other contexts (for example nursing homes). In addition, these studies did not involve the full range of HCPs involved in prescribing BZRAs. In Belgian NHs, only nurses' perceptions were evaluated in previously conducted studies (8, 16-18), and no study was based on psychological theories.

The objective of the present study was to use a behavioral science approach to identify barriers and enablers to BZRA deprescribing in Belgian NHs perceived by i) physicians, ii) HCPs directly involved in nursing home care and iii) NHRs and their close relatives, and to map them into the theoretical domains framework v2 (TDF), a comprehensive commonly used framework to assess barriers

and enablers. Ultimately, we aim to inform the development of a future intervention toward BZRA deprescribing.

METHODS

We reported this study following the COREQ consolidated criteria for reporting qualitative research (19).

Study design

We conducted a qualitative study involving focus groups and face-to-face interviews with all relevant stakeholders in NH settings. The core behavior of interest was the initiation of BZRA deprescribing by general practitioners (GPs), when appropriate and in collaboration with other stakeholders. We explored GPs' perspectives in face-to-face semi-structured interviews. In addition, focus groups were used to explore the perspectives and potential influences of other stakeholders (other HCPs, and NHRs or relatives) in relation to the GP. We chose to separate GPs from other HCPs because of the difference in the behavior of interest (deprescribing vs supporting deprescribing), and to avoid social desirability bias, induced by hierarchical relationships.

Setting

This study was conducted in Belgian NHs. We conducted interviews in a purposive sample of NHs, to identify a wide range of views. Included NHs differed regarding the following variables: location (country regions, rural or urban area), type of ownership, and previous/ongoing experience of medication optimization approaches. We contacted the senior manager of each chosen NH for a participation agreement. NHs were identified based on previous collaborations, references from other collaborators, or personal contacts with one of the research team members. In case of refusal to participate, another NH with similar characteristics was asked for participation. We intended to perform interviews in a minimum number of 5 NHs and to continue recruitment until data saturation.

In Belgium, each NH must appoint a coordinating physician (CP), who is in charge of the NH medical policy, and acts as a contact person for NH staff. However, each NHR can freely choose his/her GP, meaning that the number of GPs visiting any NH is unrestricted. These GPs have complete freedom regarding diagnostic and therapeutic strategies. Medication delivery is performed by a single

pharmacy (either a community or a hospital pharmacy) for all NHRs. Currently, medication review activities are not funded, and the role of the pharmacist is often limited to medication delivery.

Participants

In each participating NH, we conducted face-to-face interviews with 2 GPs, and 2 focus groups, one with other HCPs involved in NH care, and one with NHRs and relatives. First, we interviewed the CP and at least one other GP for whom we received contact information either from the CP or from the NH senior manager. Second, in the focus group with other HCPs, we aimed to have 5 to 8 participants including at least one pharmacist, one chief nurse, and one nurse. NH staff were free to invite any other HCPs who might be involved in deprescribing. Finally, we included 4 to 8 NHRs and close relatives of NHRs from each NH. To be eligible, NHRs had to have lived in the NH for at least 6 months, regularly used BZRA or have had BZRA prescriptions for at least 4 weeks in the past 12 months, be aged 65 and older, and be able to participate in a focus group discussion (as judged by the staff). Close relatives of NHRs, identified by NH staff, were defined as someone who regularly visited the NHR and with knowledge/interest in medicines management for the resident. NH staff recruited NHRs and close relatives. They provided an information letter from the research team and written consent for participation was requested. Participants had no prior contact or collaboration with interviewers.

Data collection

All interviews were conducted using semi-structured, pilot-tested, interview guides (Appendix 1). Interview guides were developed in collaboration with researchers specialized in health behavior change and implementation science (AMP,JMG). We used behavioral theories as they help to better understand the behavior change process inherent in implementation of evidence-based practices (20, 21). GPs' and HCPs' interview guides were developed based on the TDF. The TDF maps 128 constructs from 33 behavior change theories into 12 domains (14 for TDF version 2) that are possible determinants of a behavior (22). It has often been used to evaluate barriers and enablers for behavior changes (23-25). To ensure a detailed investigation of the determinants of behavior, interview guides contained at least one question per TDF domain. The NHRs' and relatives' interview guide was based on the revised Patients' attitudes towards deprescribing questionnaire (rPATD) (26). The rPATD is a validated questionnaire that explores older adults' and

their carers' attitudes and willingness towards deprescribing. We chose not to use the TDF for NHRs and relatives as we were not specifically studying NHRs behaviors but considered them as a potential influence on HCPs' behavior. In addition, the TDF has primarily been developed to investigate HCP's perspectives, and we believed that the rPATD approach would be easier to use with NHRs and relatives. When appropriate, additional open-ended questions were asked to further clarify the respondents' point-of-view.

Face-to-face interviews with GPs were conducted at the GP practice, at the NH, or by phone. Focus groups with HCPs, NHRs and close relatives were conducted at the NH by a moderator and a second researcher, in charge of field notes. Only participants and research team members were present in the room. French-speaking interviews and focus groups were conducted by PE and Dutch ones by AD. All interviews were audiotaped, transcribed, and anonymized before data analysis. Transcripts were not returned to participants. However, to ensure correct comprehension of participants' ideas, frequent summaries were made and discussions with the research team were held during data collection and analysis.

Data analysis

All transcripts were entered into QSR Nvivo 11 for data analysis. Two researchers (PE and AD), who both are pharmacists and researchers trained in qualitative data analysis and TDF coding, independently coded data. Discrepancies were resolved through discussion and, when needed, help from a third coder (AMP - an expert in TDF), was requested.

For HCPs and GPs interviews, we conducted a deductive thematic analysis, using the TDF version 2 as coding framework (13). One researcher (PE) then generated belief statements, which represented the specific themes from responses within each domain, and identified the most relevant TDF domains based on the frequency of the belief statements, the presence of conflicting beliefs, and evidence of strong beliefs that may affect the target behavior (13). A second researcher (AD) reviewed domain selection and the generated statements for relevance and appropriateness. Finally, the most relevant TDF domains were mapped into integrative themes, to ease presentation of the results. The identification of these themes was performed through discussions with all research team members.

For NHRs and relatives' interviews, we conducted an inductive thematic analysis (27). The coding tree was developed by two researchers (PE and AD)

working together on the first two focus groups and was then used for the other transcripts. The coding tree evolved until the end of the analysis, to ensure the inclusion of all meaningful answers.

Ethical considerations

This study was approved by the ethical committee of CHU UCL Namur on the 19th of May, 2020. (NUB: B0392020000019). All participants gave informed written consent before interviews.

RESULTS

Interviews were conducted in 6 NHs between September 2020 and January 2022. Initially, interviews were planned in 5 NHs. Because of the COVID-19 pandemic, one NH withdrew from the study before focus groups. GPs' interviews had already been conducted and were kept in the analysis. This NH was replaced with a 6th NH with similar characteristics. Two HCPs (both pharmacists) could not participate in the focus group discussions and were interviewed separately. In total, we interviewed 13 GPs and conducted 5 focus groups with other HCPs (35 HCPs: 18 nurses (including 5 chief-nurses), 4 pharmacists, 4 occupational therapists, 3 care aids, 3 physical therapists, 3 speech therapists), and 5 focus groups with 22 NHRs and 5 relatives. Participants' and NHs' characteristics are presented in Table 1. The mean duration of interviews was 50 minutes (range 36-67) for GPs, 67 (54-84) for other HCPs, and 59 (44-75) for NHRs and relatives. Data saturation was reached after interviews in these 6 NHs.

Table 1: Characteristics of nursing homes and participants included.	
Nursing home characteristics (N=6)	
Location *(n)*	
Brussels	1
Flanders	1
Wallonia	4
Ownership type *(n)*	
Private, non for profit	3
Public	3
General practitioners' characteristics (N=13)	
Female gender *n(%)*	4 (30)
Years of experience as a GP	
Median	27
Range	1.5 - 47
Years of experience in NHs	
Median	27
Range	1.5-47
Number of nursing home where the GP has patients to visit	
Median	4
Range	2-8
GPs being coordinating physician of any NH *n(%)*	7 (53.8)
Other HCPs' characteristics (N=35)	
Female gender *n(%)*	31 (88.6)
Occupation *n(%)*	
Nurses	18 (51.4)
Pharmacists	4 (11.4)
Occupational therapist	4 (11.4)
Physical therapist	3 (8.6)
Speech therapist	3 (8.6)
Care aid	3 (8.6)
Number of HCPs per NH in the focus group	
Median	7
Range	6-8
NHRs and relatives characteristics (N=27)	
Number of participants per NH	
Median	5
Range	4-7
Female gender, NHRs *n(%)* (N=22)	16 (72.7)
Female gender, relatives *n(%)* (N=5)	2 (40)
Legend: GP= General Practitioner; **HCP=** Health Care Provider; **NH=** Nursing Home; **NHR=** Nursing Home Resident	

SECTION 2

Barriers and enablers from the perspective of physicians and other HCPs

Overall, all HCPs, including GPs, perceived BZRA deprescribing to be very challenging *(Beliefs about capabilities)* and identified many barriers. Enablers were also identified, mainly by participants with recent experience with deprescribing or medication review interventions.

Six TDF domains were identified as most relevant for both GPs and other HCPs: Skills, Beliefs about capabilities, Goals, Memory attention and decision processes, Environmental context and resources, and Social influences. Additionally, Knowledge, Social/professional role and identity and Beliefs about consequences were most relevant for other HCPs only. A summary of key themes identified in each of these 9 domains is presented in table 2. Quotes are presented per TDF domain and stakeholders' group in table 3 (including quotes for TDF domains identified as not relevant).

Table 2: Summary of the most relevant TDF domains and key themes for BZRA deprescribing in Belgian nursing homes, per stakeholders' group.			
Relevant TDF domains	**Key Themes**	**GPs**	**Other HCPs**
TDF domains relevant for both GPs and other HCPs			
Skills	Lack of practical training on how to deprescribe BZRAs	B	B
	Lack of training on non-pharmacological alternatives		B
	Good communication skills (with other health care providers and with NHRs)	E	E
Beliefs about capabilities	Low self-efficacy	B	B
	Difficulties to convince other stakeholders (including the resident)	B	
Goals	BZRA deprescribing should be a long-term goal	E	E
	Competing goals (including NHR well-being, acute conditions, keeping a smooth NH environment).	B	B
Memory, Attention and Decision process	BZRA refilling happens automatically	B	B
	BZRA prescribing is seen as an easy solution	B	
	Triggers for BZRA deprescribing: Other stakeholders' suggestions, balance issues, over sedation, confusion…	E	E
Environmental context and resources	Collective living, with strict time schedule, noise, and disturbances	B	B
	Lack of time and NH staff (nurses, care aids…)	B	B
	Difficulties to implement non-pharmacological alternative (limited access, low practicability for NHRs or interest from them)	B	B
	High number of visiting GPs	B	
	Multidisciplinary work	E	E
	Need for a pharmacological alternative	B	
	Use of non-pharmacological alternatives, including phytotherapy, daytime activities	E	E

	Patient characteristic/ context: Long-term BZRA use (years)		B
	Use of a brochure to raise NHRs' awareness		E
	Automated medication delivery system reduces the opportunity to review medications		B
Social influence	Perceived NHRs' reluctance to deprescribe BZRA/ NHRs' pressure to have BZRA	B	B
	Other HCPs' pressure on GPs to prescribe BZRA	B	
	HCPs triggering GPs to deprescribe	E	
	Relatives' influence	B/E	B/E
TDF domains most relevant for HCPs except GPs			
Knowledge	Lack of familiarity with BZRA, BZRA side-effects and BZRA deprescribing		B
	Non-pharmacological alternatives unknown or not well known		B
Social/professional role and identity	Difficulties for GPs to accept remarks and advices from colleagues		B
	Feeling of depending on GPs' decision		B
	Perceived role of nurses or other HCPs (e.g. physical therapist) to report NHRs' behaviour/status to the GP or nurses		E
Beliefs about consequences	Increased workload at the NH level		B
	Easier management of NHRs on the long-term		E
	Potential negative outcomes for NHRS (Withdrawal symptoms, insomnia, anxiety, anger, …)		B
	Potential positive outcomes for NHRs (reduction of falls, cognitive and mobility improvement, …)		E
Legend: B= Barrier, **BZRA**= Benzodiazepine receptor agonists, **E**= Enabler, **GP**= General practitioner**, HCP**= Health care provider, **TDF**= Theoretical domains framework			

Table 3: Barriers and enablers to BZRA deprescribing for NH HCPs according to relevant TDF domains.					
Relevant TDF domains	**Belief statements**	**Barrier (B) or Enabler (E)?**		**Quotes**	
		GPs	**Other HCPs**	**GPs**	**Other HCPs**
TDF domains relevant for both GPs and other HCPs					
Skills	Lack of practical training on how to deprescribe BZRAs	B	B	*"We are told that they [BZRAs] are bad, that we must avoid them, but I have never attended a workshop on BZRA deprescribing. That would be interesting."* 1106 *"But I think that what we need above all is to be guided by plans or detailed protocols that explain properly how to do it."* 1104	"[Have you been trained in BZRA deprescribing?] *Me? Certainly not, 40 years ago. Those were things we didn't talk about. - We were trained in… techniques but none that related to deprescribing benzos."* 1412 and 1451 (nurse and occupational therapist)
	Lack of training on non-pharmacological alternatives		B		*"Perhaps if we were better informed [about non-pharmacological alternatives] ourselves, we could say "Hey Doctor, I heard that…"."* 1411 (nurse)
	Good communication skills (with other health care providers and with NHRs)	E	E	*"You have to discuss things with the patient, you have to make arguments in favour."* 1106	*"Communication in general is the only thing that helps a lot."* 1312 (nurse)
Beliefs about capabilities	Low self-efficacy	B	B	*"I am not very confident. I am not very confident because I know that it's a lot of work."* 1202	*"Indeed, I don't feel very comfortable either, I should argue"*1141 (physical therapist)
	Difficulties to convince other stakeholders (including the resident)	B		*"The most difficult part is starting the deprescription and the withdrawal, because sometimes you are faced with a patient who just refuses, who is categorical and says, "No, I've been taking this [BZRA] for 20 years, you cannot take it away from me, … I categorically refuse to*	*"You will never be able to persuade those people that they need to give it up [the BZRA]. As long as they are convinced that it is doing them some good, we will never be able to deprescribe it. It's not possible."* 1211 (nurse)

				have it taken away or reduced". And that's what sometimes causes the most difficulty." 1104	
Goals	BZRA deprescribing should be a long-term goal	E	E	"*It is clear that it is very important to reduce these medicines so that they can get the best possible results and really take proper care of themselves there."* 1104	*"What I think would be helpful is if you really saw sleep medication and anxiety medication as something temporary, just when a resident needs it."* 1531 (pharmacist)
	Competing goals (including NHR well-being, acute conditions, keeping a smooth NH environment).	B	B	*"If there is something else, more serious, well, it [BZRA deprescribing] will come later."* 1104 "*It is important, but not important enough to completely destabilise the existing overall [NHR] balance."* 1205	"*Because we need them to sleep. When you have 138 [NHRs] who aren't sleeping … the button, as I call it [the call bell], goes constantly when they aren't sleeping*." 1412 (night shift nurse) "*As long as it has a positive effect on the person, I am for continuing it."* 1211 (nurse)
Memory, Attention and Decision process	BZRA refilling is part of an automatism of GPs	B	B	"*No, on a normal visit, I ask him [the resident] how he is, I measure his blood pressure, and I renew his BZRA prescription."* 1202	*"We don't even think about it [deprescribing]."* 1211 (nurse)
	BZRA are seen as an easy solution	B		*"Unfortunately, I think that doctors sometimes prescribe a BZRA out of convenience, because it is easy to say "Having a panic attack? Take a Temesta®, take one every day to be sure not to have one."* 1104	
	Triggers for BZRA deprescribing: Other stakeholders' suggestions, balance issues, over sedation, confusion…	E	E	"*Systematically, if they tell me that they are confused, that they have experienced falls, well, the side effects of medication come to mind, starting with BZRAs. It's automatic*." 1105	"*For example, we have residents who take that and we see that they are always very quiet, so we try to stop or reduce it."* 1515 (nurse)

Environmental context and resources	Collective living, with strict time schedule, noise and disturbances	B	B	*"The problem is that we are in a place that is not their normal environment. There are more people passing by, nurses, noises. They might also be less comfortable sleeping there than at home."* 1105	*"In shared accommodation, of course, it is complicated. There is a lot of noise, even at night, there are patients walking around, people shouting, bells sounding frequently. … It is difficult for residents to get quality sleep."* 1121 (head nurse)
	Lack of time and NH staff	B	B	*"We don't have the time, and you need to sit with them, and explain things and review their treatments."* 1202 *"I think there is a severe shortage of staff and patients suffer because of that shortage."* 1105	"For us, *at night, it is even worse. Three [care staff] for 138 [NHRs]."* 1412 (night shift nurse)
	Difficulties to implement non-pharmacological alternative (limited access, low practicability for NHRs or interest from them)	B	B	*"For minor anxiety, I don't push too hard for a psychologist, because I know that, unfortunately, it is really difficult to access that kind of care."* 1104	*"We don't have the time [for non-pharmacological approaches]. It's not possible, it's not feasible."* 1411-1421 (nurses) *"It's also generational. I think that if I spoke to today's residents about Snoezelen, essential oils, lights… I think they would be more reassured by a drug than by our new techniques."* 1252 (occupational therapist)
	High number of visiting GPs	B		*"Creating a NH policy is very difficult, for benzodiazepines, for the use of antibiotics, for anything. It is difficult to reach a consensus or unanimity or even to get a large majority of doctors to follow it."* 1203	
	Multidisciplinary work	E	E	*"Team decisions. Having the collaboration and support of the care staff. Because they are truly on the front line and they are the ones who can tell us how the residents feel."* 1203	*"We always consult with colleagues. Yes, colleagues first. Because it's multidisciplinary, the care staff, the cleaners – yes, they will be there too – and we go on from there. To the team head, then meetings, and then we go to the doctor."* 1513 (nurse)

	Need for an alternative/substitute	B		*"At that point, we try to find alternatives, because patients do not want to go from taking something to taking nothing."* 1105	
	Use of non-pharmacological alternatives, including phytotherapy, daytime activities	E	E	*"I think that any activity during the day will make them [NHRs] think about something else, so it is beneficial."* 1202	*"Going on trips, going out, they expend energy so they get a good sleep. If, however, you don't change anything in their lives and you take away the sleeping pills, then..."* 1112 (nurse)
	Patient characteristic/ context: Long-term BZRA use (years)		B		"*Sometimes they arrive with them, they have used the medication for years and, when they arrive here, we continue it.*" 1211 (nurse)
	Use of a brochure to raise NHRs' awareness		E		*"We have a brochure, an information brochure and we go around the residents. So we explain the disadvantages and consequences of using psychotropic drugs. And yes, some people have taken it on board because we have good results here with stopping sleep medication."* 1513 (nurse)
	Automated medication delivery system reduces the opportunity to review medications		B		*"When we prepare the drugs, well, we look at the drugs that we need to prepare. The others are in the automated dispensing system. We don't look at them as closely as when we prepare them."* 1421 head nurse
Social influence	Perceived NHRs' reluctance to deprescribe BZRA/ NHRs' pressure to have BZRA	B	B	"*We often hit a wall with patients: "No, not that one". We can stop anything we want, we can stop their anti-arrythmia medicine, we can stop their anti-cholesterol medicine, but not their Zolpidem or their Alprazolam.*" 1202	*"People who are lucid sometimes cling to their medication. What time is my Temesta®? What time is my Zolpidem®? What time will it come at?"* 1211 (nurse)
	Other HCPs' pressure on GPs to prescribe BZRA	B		"*There is sometimes intense pressure from the care staff to calm these patients.*" 1105	

	HCPs triggering GPs to deprescribe	E		*"When the care staff speak up and say, 'everything is going very well, do they really need this medicine?', it makes the doctor's job easier to be aware of that."* 1101	
	Residents relatives' influence	B/E	B/E	*"There are people who will say to you, 'don't you think that Dad or Mum is taking a bit too many kinds of medication?'* 1205	*"Ask the doctor to come by, my mother is not sleeping, perhaps he can prescribe something to help her sleep."* 1211 (nurse reporting on a conversation with a relative)
TDF domains relevant for HCPs other than GPs only					
Knowledge	Lack of familiarity with BZRA, BZRA side-effects and BZRA deprescribing		B		*"There are lots of drugs [names] there that I know …, and I am shocked to discover that they are in fact benzos. So, that just goes to show that it's really not my field at all."* 1141 (physiotherapist)
	Non-pharmacological alternatives unknown or not well known		B		*"You see, there may be things we could do to help some people that we don't know about."* 1451 (occupational therapist)
	Lack of familiarity with deprescribing guidelines and tools	B		*"We perhaps lack information on how to do it. How to do it so that it works properly. We know that we need to deprescribe them [BZRAs], but how, that's where it gets complicated."* 1103	
Social/professional role and identity	Difficulties for GPs to accept remarks and advices from colleagues	B	B	*"Doctors are very touchy. Doctors, I'm generalising of course, are quite sensitive and not very open to criticism regarding their practice. Myself included."* 1101	*"They [GPs] should start listening to us, to everything we have to say, and agree to review their diagnoses. But for every ten doctors, there may be one who will do that."* 1131 (pharmacist)
	Feeling of depending on GPs' decision		B		*"We are dependent on the doctor's prescription."* 1121 (head nurse)
	Perceived role of nurses or other HCPs (e.g. physical therapist) to		E		*"We observe and report back to the doctor. We will say he is quieter now… but, on the other*

	report NHRs' behaviour/status to the GP or nurses				*hand, there are issues because he is sleeping a lot."* 1411 (nurse)
Beliefs about consequences	Increased workload at the NH level	B	B	*"I think that could be difficult for the nursing home to manage, er… If there were withdrawal symptoms, recurring anxiety, or recurring insomnia… I think all that would be complicated."* 1103	*"Caring for someone who hasn't had a good night's sleep, you can take a beating! Anxiety sets in, agitation sets in. It's harder to treat the person during the day too. - It's not easy."* 1211 and 1212 nurses
	Easier management of NHRs on the long-term	E	E	*"If a patient has fewer falls, less care is required for that patient. If the patient is less confused, it may be easier for the nurses to care for them. Yes, it's positive."* 1105	*"It is not in our interest to give people that kind of medicine: anything that calms them down, anything that inhibits them. […] Because anything like that will also complicate our care."* 1411 (nurse)
	Potential negative outcomes for NHRS (Withdrawal symptoms, insomnia, anxiety, anger, …)	B	B	*"Well, we will have angry and grumpy people and there will still be insomniacs and anxious people too…"* 1202	*"You are obliged to give it to the person so that they can rest. Otherwise, they are tired during the day and at risk of falls and so on."* 1212 (nurse)
	Potential positive outcomes for NHRs (reduction of falls, cognitive and mobility improvement, …)	E	E	*"The recovery of certain cognitive functions and a reduction in falls in particular."* 1102	*"If we have someone who falls frequently, it would be a good idea to reduce them [BZRAs]."* 1321 (head nurse)
Other TDF domains (beyond most relevant domains)					
Optimism	Varying views	B/E	B/E	*"Long-term, it [BZRA deprescribing] certainly appears to be beneficial." 1101* *"I don't believe that BZRAs destroy patients."* 1205	*"No, it [BZRA deprescribing] would be a disaster."* 1211 (nurse) *"That [BZRA deprescribing] would be nice. It would be great."* 1131 (pharmacist)
Reinforcement	Bad perception of policies and incentives	B		*"Doctors are a bit… Well, they don't like constraints, sometimes they can react badly."* 1106	

	Influence of past experiences	B/E		*"When you get a little bit of positive feedback, you tell yourself that things can go well and it encourages you to try to repeat the experience." 1101* *"I had a lot of bad experiences, well failures, so maybe I'm a bit more reluctant to try. Because I tell myself that it's a losing battle."* 1103	
Intention	Intention to review medication and to prescribe the less possible	E		*"The intention is always there, but I try with the patients."* 1105	
Emotion	Satisfaction	E		*"It's always gratifying to say that we did things well."* 1102	
Behavioural regulation	Visual reminder	E		*"I think that even just one poster in the medical office would help a lot. Even just a good visual reminder."* 1104	
Legend: B= Barrier, **BZRA**= Benzodiazepine receptor agonists, **E**= Enabler, **GP**= General practitioner, **HCP**= Health care provider, **NH**= nursing home **TDF**= Theoretical domains framework					

SECTION 2

The main barriers and enablers participants encountered are described in the following 5 integrative themes:

Knowledge and Skills gaps

We found various levels of knowledge regarding BZRAs, their side effects, and deprescribing. In particular, HCPs (other than GPs, nurses and pharmacists) admitted to lack of knowledge of BZRAs and their use. Knowledge of non-pharmacological alternatives also differed between HCPs and a lack of training for their implementation was highlighted *(Knowledge)*. GPs reported not having received practical training on how to deprescribe and were not always familiar with available tools and withdrawal schedules *(Skills)*. It appeared that younger GPs had more training regarding deprescribing than older GPs. The most cited necessary skills were communication (between HCPs and with NHRs and relatives) and management of withdrawal symptoms.

Automatic BZRA refilling

Most GPs and HCPs indicated that BZRA prescription and refilling happens automatically and that they do not routinely think about deprescribing *(Memory attention and decision processes)*. Refilling was perceived as a quick and easy way to address insomnia or anxiety. Nevertheless, respondents identified multiple triggers for considering BZRA deprescribing: other stakeholders' suggestions, occurrence of adverse effects (e.g. over-sedation, balance issue, confusion, lack of appetite, agitation), becoming GP of a new patient, implementation of deprescribing or medication review interventions at the NH level, and NH entry. Nurses specifically reported that having an automated medication delivery system, in which nurses do no longer have to prepare medications before administration, reduced the probability of having them review medications *(Environmental context and resources)*.

Competing priorities

Although GPs agreed that BZRA deprescribing was clinically relevant and should be a long-term goal for all NHRs, it was often considered not to be a top priority *(Goals)*. Higher priorities included treating acute conditions, maintaining a balance in the NHR's well-being, and maintaining a smooth NH environment. In

particular, BZRA deprescribing was not a top priority when NHRs did not experience BZRA side effects.

Social challenges and opportunities enhanced by perceived consequences

GPs reported finding it difficult to deprescribe (*Beliefs about capabilities*) due to feeling pushed to prescribe or refill BZRA, both by other HCPs and NHRs themselves *(Social influences)*. They perceived that NHRs were reluctant to reduce or stop BZRAs out of fear to not be able to sleep. NH staff also played an important role, as GPs reported sometimes prescribing BZRA to please HCPs. This reluctance from some HCPs to deprescribe BZRA might be explained by the beliefs they had that it would lead to increased staff workload and adverse consequences for NHRs, such as frustration, anxiety, and anger *(Beliefs about consequences)*. Still, some HCPs also perceived positive consequences such as improving NHRs' balance and awareness. HCPs who were willing to support BZRA deprescribing perceived that their role was to report on NHRs' behaviour and status to the GP, yet they did not always feel listened to by GPs *(Social/professional role and identity)*. GPs indeed admitted feeling irritated when receiving colleagues' suggestions, but recognized that other HCPs could act as triggers for BZRA deprescribing.

Environmental factors

Many barriers and enablers for BZRA deprescribing are related to environmental factors. This was highlighted by all stakeholders' groups and substantially influenced beliefs about capabilities. First, communal living imposes some difficulties such as noise, strict bedtime schedules and potential disturbance by other NHRs, that could lead to increased anxiety and sleep issues (*Environmental context and resources)*. Second, the lack of staff was highlighted, directly leading to lack of time for all HCPs, and a lack of human contact for NHRs. The implementation of non-pharmacological alternatives to BZRA was described as difficult (*Beliefs about capabilities*), because of this lack of staff and time, and because of poor training on how to implement them (*Environmental context and Resources, Skills).* In particular, lack of access to psychological support was highlighted by GPs. The implementation of multidisciplinary care and medication reviews was seen as an important enabler for all HCPs. Still, time constraints were an important barrier to the implementation of such meetings.

Barriers and enablers from the perspective of NHRs and relatives

Five themes emerged from focus groups with residents and relatives: knowledge on medications used, communication with NH staff and GP, perceived efficacy and necessity of BZRA, influence of the environment and reluctance towards BZRA deprescribing. Overall, NHRs and relatives had similar views on these themes. Themes are described hereafter, and quotes are available in Table 4.

Poor knowledge on medications used

Despite having overall poor knowledge about their medication, including BZRA and their side-effects, most NHRs were able to recognize their sleep medication based on the tablets' colour and shape. NHRs were interested in knowing more about their medication, and seemed to hold themselves responsible to collect the information they desire. Nevertheless, residents indicated to lack the opportunity to ask questions.

Lack of communication with NH staff and GP

NHRs were generally unhappy with communication inside the NH and their relationship with their GP. Some NHRs believed that they should follow GPs prescriptions, without further discussion.

Perceived efficacy and necessity of BZRA

NHRs were using BZRA for various reasons, sometimes for many years. Perceived BZRA effectiveness differed between residents, but most NHRs thought they were effective. Almost all NHRs believed that BZRA were a necessity and suggested they would not be able to sleep without them. The perception of BZRA efficacy and necessity was enhanced by the fact that they were prescribed by their GP, whom they trust largely, and by experiencing sleeping issues when they did not use the BZRA.

Sleep-hindering and anxiety-enhancing environment

NHRs reported that the NH environment did not favour sleep (e.g., noise issues, uncomfortable sleeping accommodations). NHRs also reported a lack of human contact and told they were bored, which could lead to overthinking and anxiety. Only a few residents were interested in the activities organized in the NH.

Moreover, not all of them were aware of relaxation opportunities available in the NH. Finally, NHRs reported being impacted by the ambient stress in NHs, and nurses' stress.

Reluctance towards BZRA deprescribing

NHRs were generally reluctant to have BZRA deprescribed, even if suggested by the GP. Still, some NHRs would be interested in trying, sometimes only with an alternative. The two main difficulties anticipated were the lack of sleep and the lack of supervision of the deprescribing process.

Table 4: Quotes per themes and sub-themes identified in focus groups with nursing home residents and relatives.

Theme	Sub-theme	Quotes
Knowledge on medications taken	Poor knowledge of their overall medication (barrier)	"*But I don't know what I'm taking*" 2115
	Ability to recognize the shape and colour of their BZRA (barrier)	*"In the evening, I take a little yellow one."* 2312 *"I know that one. It is a white pill"* 2115
	No knowledge on BZRA and their potential side-effects (barrier)	*"Thanks to that meeting [the focus group]. Because, otherwise, I would not even have realised that she was taking that kind of medicine. I have heard the name Temesta® since I was young. It's a medicine like Dafalgan® to me."* 2221 (NHR's daughter)
	Lack of time and opportunity to ask their questions regarding BZRA, or other medications (barrier)	*"When you ask for something, they [the nursing staff] are already gone."* 2113
Communication with NH staff and GPs	Communication issues inside the NH (barrier)	*"What I mean is that communication here, at every level, sucks …"* 2212
	Lack of relationship and time spent with GP (barrier)	"*I haven't seen my doctor since… When he comes, it takes two minutes, so I don't need to pay €40 for that. He*

		writes the prescriptions; I don't need to see him." 2413
	Feeling that they should just follow GPs' instructions (barrier)	*"Me, I just do what he says and that's that*." 2313 "*We are never given an explanation. Only that you have to follow what the doctor says. And [take] whatever [medications] they bring you."* 2115
Perceived efficacy and necessity of BZRA	Perception that BZRA are effective or not effective (barrier and enabler)	"*I was given this sleeping pill, which is going very well by the way. […] It's perfect.*" 2313 "*I take it but, despite that, we are woken up by each other, so it's not of much use in the end."* 2412
	Perception that BZRA are necessary, enhanced by sleeping issues when BZRA are forgotten (barrier)	"*But I can't do without them*." 2511 "*I don't know if they do anything, but I think it would be even worse not to take them."* 2115 *"Yes, I need them. I don't think they would be given to me otherwise.*" 2315 *"If by chance I forget it, I toss and turn in my bed. … That means that, usually, it works."* 2411
	High importance of sleep for NHRs (barrier)	"*There is no other solution yet because, if you have not slept, you are nothing. You're a rag, as the expression goes*." 2515
Sleep-hindering and anxiety-enhancing environment	Unfavorable environment: noises, uncomfortable accommodations (barrier)	*"We can't sleep in peace here in the nursing home. There are people passing by, shouting at night… People who are lost."* 2115 "*Because we have no air, we can't open the windows. It is 25-26 degrees [Celsius] in the rooms. We don't have access to the thermostatic valves, the mattress is plastic." 2413*
	Lack of human contact and activities (barrier)	*"[The day] seems long, eh? Oh yes, it seems long.*" Conversation between 2311 and 2312
	Environmental stress	"*Sometimes I get stressed when I see*

	(barrier)	*things that I don't like in the home [NH]. Which upset me. I get very stressed then, because I would like to do something, I would like to help other people …, so I need Lysanxia® from time to time, ten drops during the day."* 2413
Reluctance towards deprescribing	Agreement to stop if GP said so (enabler)	*"If the doctor says I don't need to take it anymore, I won't take it anymore. I think he knows what I do and do not need to take."* 2315
	Expected difficulties: lack of sleep, need for an alternative and for support during deprescribing (barrier)	*"No matter who advised it [BZRA deprescribing], I wouldn't stop taking it [BZRA]. If I stop taking it, I won't sleep, so it's not worth it."* 2113 *"I think I would say, 'We can try, of course, but by giving her another drug that can also help her sleep."* 2221 (NHRs' daughter) *"But then I have to be 100% sure that the patient's observation is in direct proportion to the reduction of medication"* 2521 (NHR's son)
Legend: BZRA= Benzodiazepine receptor agonists, **GP=** general practitioner, **NHR=** nursing home resident		

SECTION 2

DISCUSSION

This qualitative study of barriers and enablers for BZRA deprescribing in Belgian NHs reveals that 6 TDF domains are highly relevant for all HCPs (*Skills, Beliefs about capabilities, Goals, Memory attention and decision process, environmental context and resources, Social influences*). Additionally, 3 domains were relevant for HCPs other than physicians (*Knowledge, Beliefs about consequences, and Social/professional role and identity*). NHRs and relatives expressed strong barriers related to a lack of knowledge and environmental context. They also reported a lack of communication with GPs and NH staff, variation in perceived efficacy and necessity of BZRA, and reluctance towards deprescribing.

Comparison with existing literature

Two recent systematic reviews reported barriers and enablers for BZRA deprescribing among older adults, with most studies included coming from the ambulatory setting, and fewer studies from the NH setting (14, 15). One of these systematic reviews, also used the TDF (15), and found common relevant TDF domains: *Beliefs about capabilities, Beliefs about consequences, Environmental context and resources, Goals, Social influences*, and *Memory attention and decision process*. *Intention* was also highlighted as relevant. In our study, we found various levels of intention, but it did not seem to be a major behavioral factor. Additionally, our qualitative study reported *Knowledge, Skills* and *Social/professional role and identity* as most relevant. These domains were identified but not classified as most relevant in the systematic review. The difference might be due to the inclusion of a wider diversity of stakeholders in the present study. Still, the lack of knowledge and skills we report seems to be present worldwide (28-30). The other systematic review also had findings similar to our qualitative study, highlighting the lack of knowledge, the perceived efficacy of BZRA and the importance of multidisciplinary concertation (14).

Heinrich et al. recently performed a 'best-fit' framework synthesis of the qualitative evidence of barriers and enablers for deprescribing in long-term care (28). We evaluated how their framework of 17 barriers and 16 enablers (that mapped to 11 of the 14 TDF domains), fits with our results in the specific context of BZRA deprescribing in Belgian NHs. Their framework remains overall applicable but

we identified additional barriers (e.g. the automatic refilling, the competing goals and the difficulties to implement non-pharmacological approaches) that were absent from their framework. In Figure 1, we present a conceptual model of the barriers and enablers reported by HCPs, based on the results from the present study.

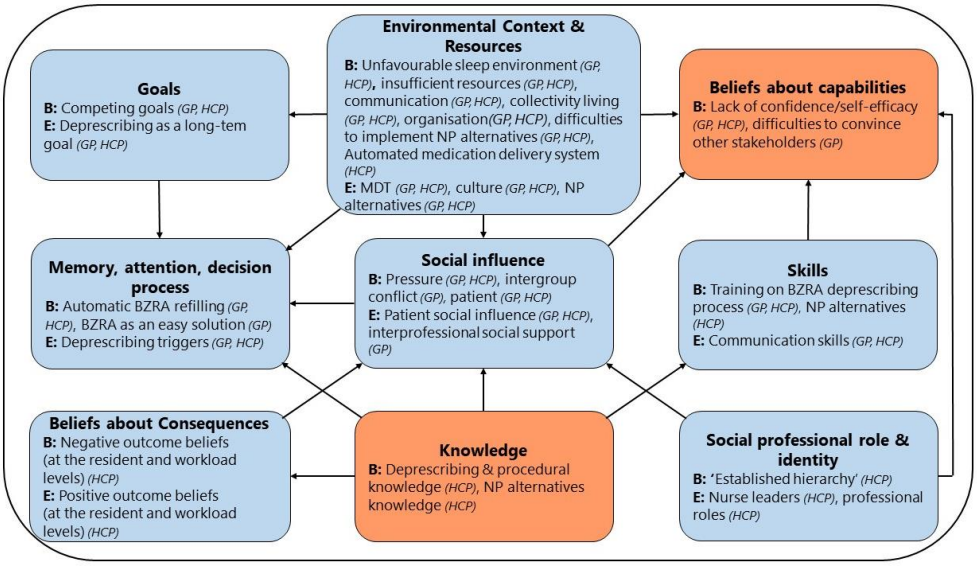


Figure 1: Conceptual model of healthcare providers perceived deprescribing barriers and enablers in the specific context of BZRA deprescribing in Belgian Nursing homes.

Legend: B= Barrier, E= Enabler, BZRA= benzodiazepine receptor agonists, LTCF= long-term care facilities, MDT= multidisciplinary team, NP= non-pharmacological. Barriers/enablers were reported by either GPs *(GP)*, other HCPs *(HCP)*, or both *(GP, HCP)*. In blue are domains containing both barriers and enablers. In orange are domains containing only barriers. Black arrows indicate potential influences between domains. Potential influences were determined by the research team, based on the conceptual model by Heinrich et al., (28) and adapted from the data collected and analyzed.

SECTION 2

Moving from barriers and enablers to potential intervention components

Unsurprisingly, our data suggest that a complex intervention made of several components targeting important barriers is essential. Previous interventions such as the COME-ON and the RedUse interventions included components such as HCP training, multidisciplinary meetings and audit and feedback (for RedUse intervention). The authors reported a reduction on benzodiazepines use at both 6 and 12 months (31, 32) and increase rates of BZRA deprescribing (8). Our findings suggest a number of potential strategies to promote BZRA deprescribing.

First, providing education and training to HCPs will be essential to address some of the barriers. Indeed, we reported a lack of skills for all HCPs, and HCPs other than GPs also had knowledge gaps regarding BZRAs and their use. Training could also enhance HCPs' perceived beliefs about capabilities regarding deprescribing. HCPs' training should cover shared decision-making, BZRA side-effects, health consequences of deprescribing, the tapering process, and non-pharmacological alternatives. Specific tools such as a tapering schedule and deprescribing algorithm should also be presented to HCPs. While some parts of training should be tailored to the HCPs' profile (e.g tapering schedule for GPs, non-pharmacological alternatives for nurses), interdisciplinary training should also be explored as it may then facilitate multidisciplinary work.

Second, HCP level interventions should go beyond education and training so as to better impact the decision process. For example, action planning or goals setting could help to tackle the current situation of automatic refilling of BZRA and the issue of competing priorities. Such strategies could be organised at the NH level. As an example, defining a common vision and strategic approach towards BZRA deprescribing at the NH level might enhance HCPs' perceived capability and targets the identified barrier of competing goals. This should be done with all stakeholders' involvement, including NH management, and should guarantee a supportive organizational culture, which is of major impact (33, 34). Providing audit and feedback on BZRA use and deprescribing might also ensure that BZRA deprescribing remains an institutional priority.

Third, clarifying and strengthening the role of each stakeholder and enhancing interdisciplinarity collaboration needs to be part of the defined approach and process. It is also in line with recommendations for interventions

towards prescribing optimization in NHs (35, 36), and with reported enablers of medication reviews (37). If time constraints do not allow multidisciplinary team meetings, other approaches can be considered, such as the use of a dedicated communication tool, which can improve communication between HCPs (38).

Fourth, change in the physical NH environment, such as reduction of noises, soft lightnings, or comfortable sleeping accommodations, may also be necessary to target environmental barriers. However, evidence is still lacking on the feasibility and medication-related impact of such physical environment changes.

Fifth, engaging NHRs and their families in deprescribing also appears essential to address the many barriers identified on their side such as poor knowledge of BZRA and their side-effects, and the report of not feeling heard and poor communication. A previous Belgian study reported that NHRs' involvement was currently unstructured, and occurred mainly at NHRs' initiative. HCPs believed that NHRs' involvement would prevent potential disagreements and increase NHRs' autonomy, but could also decrease the quality and safety of medication use (34). A recent qualitative study analysed barriers and enablers of older adults initiating deprescribing conversation (39). They mainly reported barriers and enablers similar to our results such as a low self-efficacy, lack of knowledge and communication, and poor resources access. Strategies to promote conversation initiatives included the use of information tools, telemedicine to increase discussion opportunities, and multidisciplinary team environments (39). Previous trials reported that patient brochures aimed at increasing knowledge and concerns about BZRA's long-term use and at raising patients' self-efficacy led to significant increases in deprescribing of BZRAs (40, 41). No published data on the effectiveness of such brochures exist in the NH setting, but it is worth exploring. In person interactions are also required, and highlighting the risk of adverse effects is an important aspect, although conversations should ideally be individualised to what matters most to patients (42).

Strengths and Limitations

This study has several strengths. First, we used the TDF, which is a validated psychological framework to evaluate barriers and enablers for health professional and health-related behaviour. This enhances the validity of our findings and enables linking identified TDF domains to behaviour change techniques (BCTs) (43)

in the purpose of developing an intervention. Second, we interviewed a large sample of respondents, representing all stakeholders' groups, and with various points of view. This is particularly important, as a previous systematic review reported the views of some healthcare providers', including pharmacists, had not been elicited (15). Importantly, data saturation was reached for all interview groups. Finally, the trustworthiness of our results was also strengthened by investigator and data source triangulation. We did not return transcripts to respondents to check on accuracy, but we ensured a correct interpretation of their perspectives through frequent reformulation during interviews.

This study also has limitations. Interviews were performed over a long period (approximately one year and a half) and during the COVID-19 pandemic, which might have triggered anxiety and sleep issues in nursing homes. We raised this question in each FG, and respondents reported no perceived change in BZRA use related to the pandemic, which is consistent with a published analysis from Spanish NHs (44), suggesting that the pandemic may have had limited to no impact on our findings. Additionally, we did not explore the interactions between GPs and other HCPs, as they were not mixed in focus groups. However, we felt that keeping them separate was needed to have all participants talking freely.

CONCLUSION

In this large qualitative study with participation of many stakeholders, we identified that BZRA deprescribing is influenced by knowledge and skills gaps, automatic BZRA refilling, competing priorities, social challenges, environmental factors and poor NHRs involvement.

The next step in the present theory-driven approach is now to select BCTs related to the TDF domains, using the theory and techniques tools (45). To ensure the acceptability and practicability of the intervention, various stakeholders will be involved. Finally, we will evaluate the designed intervention in a pilot cluster-randomized controlled trial.

Supplemental materials (available online):

Appendix 1: Interview guides

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Chapter 4. Development of a behaviour-change intervention toward benzodiazepine deprescribing in older adults living in nursing homes

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Chapter adapted from the homonymous article published in *Journal of the American Medical Directors Association* (2024)

https://doi.org/10.1016/j.jamda.2024.105053

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- Drafting of the manuscript: Perrine Evrard
- Critical revision of the manuscript for important intellectual content: Perrine Evrard, Séverine Henrard, Anne Spinewine

Funding:

The present work is supported by EBPracticenet (Projet d'implémentation EBPracticenet 2023) and by a research credit from the Fond National de la Recherche Scientifique (FNRS) (CDR40013898).

Acknowledgments:

The authors would like to thank all stakeholders that participated in the intervention development.
The sponsors had no role in the design, methods, subject recruitment, data collections, analysis and preparation of paper.
During the preparation of this work the authors used Chat GPT 3.5 in order to provide assistance in last manuscript draft language editing. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

ABSTRACT

OBJECTIVE. We aimed to develop a context-specific intervention toward benzodiazepine deprescribing in nursing homes (NHs), with insights from behavior-change theories and involvement of stakeholders.

DESIGN. Selection of behavior change techniques (BCTs), though online survey and group discussion, followed by operationalization of these BCTs into intervention components.

SETTING AND PARTICIPANTS. The intervention was developed for Belgian NHs, involving various stakeholders: healthcare professionals (HCPs), NH administrators, and policymakers.

METHODS. Using the Theory and Techniques Tool, we pre-selected the BCTs linked to one of the 9 Theoretical Domain Framework domains identified as being the main barriers for benzodiazepines deprescribing in Belgian NHs. These were then presented to stakeholders. Based on the APEASE (Acceptability, Practicability, Effectiveness, Affordability, Side-effects, and Ethics) criteria, participants ranked BCTs through an online survey, and then performed final selection during a group discussion. Selected BCTs were operationalized into intervention components, with specific contents and methods of delivery validated by stakeholders.

RESULTS. Thirty-seven potential BCTs were identified. Eighteen stakeholders participated in the survey, and 7 in the group discussion. This led to the final inclusion of 9 BCTs: Instruction on how to perform the behavior, information about health consequences, pros and cons, problem solving, goal setting (behavior), social comparison, restructuring physical environment, restructuring social environment, and graded tasks. These BCTs were operationalized into a 6-component intervention: process and goal setting, HCP education, physical environment adaptations, audit and feedback, NH residents' and relatives' increased awareness, and multidisciplinary work.

CONCLUSION AND IMPLICATIONS. Use of a theory-based approach toward intervention development has the potential to improve the probability of its feasibility and effectiveness in tackling barriers to benzodiazepine deprescribing. By doing so, we have developed a multi-faceted approach with actions taken at the

patient, HCPs, and NH levels. Our novel 6-component intervention will be evaluated in a pilot cluster-randomized controlled trial to assess its feasibility.

INTRODUCTION

Benzodiazepine Receptor Agonists (BZRAs, namely benzodiazepines and Z-drugs), are commonly prescribed for anxiety and insomnia among older adults, despite an unfavorable benefit-risk ratio (1-5). Current guidelines advise against BZRA use and recommend limiting treatment to 4 weeks when necessary (6, 7). Furthermore, guidelines suggest deprescribing long-term BZRAs (8), deprescribing being the action to discontinue or reduce the use of a medication that is no longer needed or that may put the patient at risk, under the supervision of Health Care Professionals (HCPs), with the goal of managing polypharmacy and improving outcomes (9). BZRAs are considered priority medicines to deprescribe in older adults (10). BZRAs can be safely deprescribed in nursing homes (NHs), via slow tapering and dose reduction (11). Still, according to a study conducted in 2015, BZRA use among Belgian nursing home residents (NHRs) remains higher than 50%, with 98% of users having a prescription for more than 4 weeks (12).

Numerous interventions targeting BZRA deprescribing in older adults have been studied, primarily in outpatient settings, with deprescribing rates ranging from 27 to 80% (13). These interventions involve various components such as medication review, medication substitution, educational program, and multifaceted approaches (13, 14). However, there is still no consensus on which components are most effective, and data from the NH setting are limited. Context plays a crucial role and can significantly impact the intervention's effectiveness. The NH setting differs from outpatient settings and can also vary between countries. Intervention development must consider these differences, and a one-size-fits-all approach is therefore unlikely to be effective.

Previously studied interventions often lacked theory-based development (15). Theory-based development allows for the identification of behavior determinants, understanding intervention mechanisms of change, the condition of its success, and implementation issues. It is also helpful in future intervention assessment and refinement (16, 17). In recent years, interest in theory-based intervention increased in the field of deprescribing (18). A theory-based intervention can be developed through the 4-step process proposed by French et al (19):

Step 1. Specification of the needed behavior change.

Step 2. Evaluation of the barriers and enablers of the targeted behavior in a specific context

Step 3. Choice of intervention components targeting the identified barriers and enablers

Step 4. Intervention evaluation, with measurable and predefined outcomes

In the context of BZRA deprescribing in Belgian NHs, preliminary work covered the first 2 steps (20, 21). This paper focuses on step 3 with the aim of developing a comprehensive intervention for BZRA deprescribing in older adults in NHs.

METHODS

Targeted Behavior and Context of Intervention Development

The intervention aims to enhance BZRA deprescribing in NHs. Specifically, the behaviors targeted are, for (i) general practitioners (GPs), to initiate BZRA deprescribing discussion with NHRs/relatives, and initiate deprescribing when indicated, as part of patient care, and in collaboration with other HCPs, and for (ii) other HCPs, to support GPs and NHRs in BZRA deprescribing.

The intervention aims to enhance BZRA deprescribing in NHs. Specifically, the behaviors targeted are, for (1) general practitioners (GPs), to initiate BZRA deprescribing discussion with NHRs and relatives, and initiate deprescribing when indicated, as part of patient care, and in collaboration with other HCPs, and for (2) other HCPs, to support GPs and NHRs in BZRA deprescribing.

The intervention was developed for the context of NHs in the French-speaking part of Belgium. In Belgium, approximately 40% of NHs are public, 40% private nonprofit, and 20% private for-profit (22). NH governance is fragmented between the federal level (in charge of healthcare and medication reimbursement) and the federated entities (regions and communities, in charge of programming, supervision, financing, price regulation). Each NH must appoint a coordinating physician (CP) who oversees the NH medical policy, and acts as a contact person for NH staff. However, each NHR can freely choose his or her GP, and the number of GPs visiting any NH is unrestricted. GPs have complete freedom regarding therapeutic strategies. Medication delivery is performed by a single pharmacy for

all NHRs. Currently, in French-speaking NHs, there is no regionwide strategy or initiative focusing on psychotropic medications, medication review activities are not funded, and the pharmacist's role is often limited to medication delivery. Regarding BZRAs, prescriptions are neither restricted nor monitored. As BZRA are not reimbursed, there is no routinely collected data on their use.

Preliminary Work Exploring Barriers and Enablers for BZRA Deprescribing

In previous work, we explored barriers and enablers for BZRA deprescribing (Step 2 of the 4-step model), using behavior change theories (23). We used the Theoretical Domains Framework (TDF), a map of 128 constructs of 33 behavior change theories, categorized in 12 domains (or 14 for version 2). Each domain is a potential behavior determinant (24). We first conducted a systematic review of barriers and enablers for BZRA deprescribing in older adults and mapped our results within the TDF (20). We then performed a qualitative study in Belgian NHs, evaluating the perspective of GPs, other HCPs, and residents and relatives (21). This study highlighted key TDF domains for BZRA deprescribing in Belgian NHs: knowledge, skills, social professional role and identity, beliefs about capability, beliefs about consequences, goals, memory attention and decision process, environmental context and resources, and social influences.

Intervention Development: Overall Approach

We followed international recommendations on intervention development (17, 25, 26). Former examples on the development of complex interventions also informed our approach (27-33). Our description follows the GUIDED (GUIDance for the rEporting if intervention Development) recommendations for intervention development reporting (34). Intervention development used the Behavior Change Wheel approach (19, 35) and was divided into 2 main parts: the identification and selection of behavior change techniques (BCTs) and the operationalization of these BCTs into intervention components.

Identification and selection of BCTs

A BCT is defined as an observable, replicable, and irreducible component of an intervention designed to change behavior, and a postulated active ingredient within the intervention (36). As BZRA deprescribing appears to be

a complex phenomenon with many behavior determinants, our future intervention should encompass a suite of BCTs, addressing all identified determinants (18).

The identification and selection of BCTs was performed through a 4-step process, with stakeholder's involvement (see Figure 1).

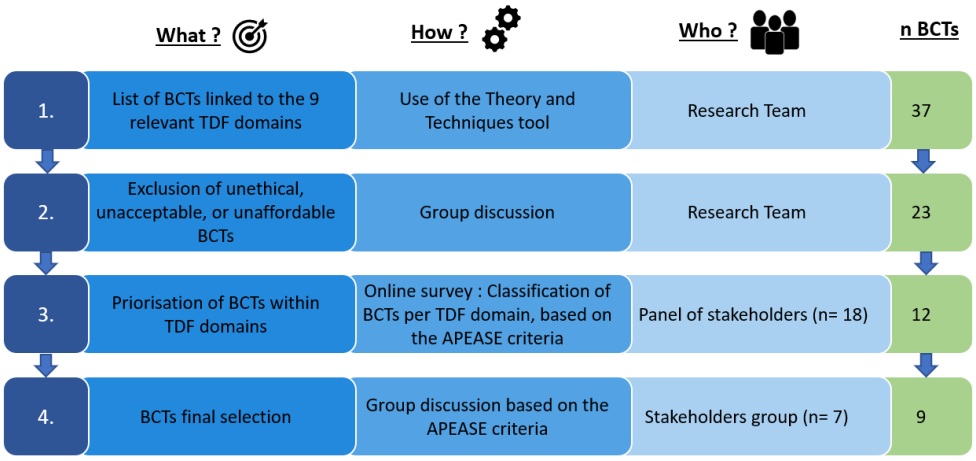


Figure 1: The four steps of the selection process of behavior change techniques. Legend: BCT= Behavior change technique; TDF= Theoretical domains framework; Research team included 2 pharmacists, and one pharmacoepidemiologist; Stakeholders included nursing home healthcare providers and direction, and policymakers

First, using the Theory and Techniques tool (37), we identified BCTs with evidence of link to one of the 9 TDF domains we identified as most relevant for BZRA deprescribing in Belgian NHs (21).

Second, the research team (with expertise in medication optimization and implementation science) excluded BCTs considered to be unethical, unacceptable, or unaffordable in the Belgian NH context. These criteria are part of the APEASE criteria: Acceptability, Practicability, Effectiveness, Affordability, Side-effects, and Ethics (35). Results of the qualitative study (21) were also considered.

Third, the list of BCTs was presented to a panel of stakeholders, through an online questionnaire. The questionnaire started with explanations about study's aims, and the APEASE criteria, on which stakeholders should base their choices. For each TDF

domain identified, we presented a summary of the main barriers and enablers, and asked stakeholders to rank BCTs in preference order. For each BCT, we provided the definition as stated in the BCT taxonomy version 1 (38), and a practical example of how it could be implemented for BZRA deprescribing in Belgian NHs. Stakeholders invited to participate were HCPs involved in NH care, NH direction staff, and policy makers (eg, member of national health insurance, and of a regional agency in charge of NH care). We aimed at having a minimum of 15 responses. For each survey completed, in each TDF domain, we gave 1 point to the BCT ranked first, 2 points to the BCT ranked second, and so on. Summed scores were computed to establish a final ranking per TDF domain. Participants also had the possibility to write open comments.

Finally, we organized an online group meeting of stakeholders, including previous panel members interested in participating further. We planned on having 6 to 8 participants, representing each of the following groups: HCPs working in NH, NH direction staff, and policy makers. In case we did not have one representative of a targeted group with previous panel members, we identified new stakeholders' representatives through previous collaborations. The discussion focused on the BCTs that had been ranked higher in the online survey, with the intention to reach consensus on the final list of BCTs. Based on the APEASE criteria, we asked participants to select at least 1 BCT per TDF domain. Participants did not receive any financial compensation for participation.

Operationalization of BCTs into Intervention components

The list of BCTs was operationalized into a set of intervention components, and the content and methods of delivery for each component was then defined. A first proposal was prepared by the research team and then discussed and refined with the group of stakeholders. For intervention components that required tools or communication materials to be developed, this was also done in collaboration with relevant stakeholders (either HCPs or NHRs, depending on the target of the tool) during informal meetings, or face-to-face interviews. For this purpose, in addition to our previous stakeholder panel, we recruited 1 NHR and 1 relative for face-to-face interviews. Developed tools were refined based on stakeholders' input, following an iterative process that ended when all comments had been taken into account.

Ethical considerations

The protocol for intervention development was approved by the CHU UCL Namur ethical committee (NUB B0392022000064). Online survey participants had to indicate consent before accessing the survey. Participants of all group meetings and interviews signed an informed consent before discussion.

RESULTS

Identification and selection of BCTs

Using the Theory and Techniques tool (37), we identified 37 BCTs with evidence of link with at least 1 of the 9 TDF domains targeted. No BCT was linked to social, professional role and identity. The research team first excluded 14 BCTs (See Appendix 1 for justification).

The 23 remaining BCTs were presented in the online survey. As only 1 preselected BCT was linked to Memory, attention and decision process, no ranking was asked for this TDF domain. Still, this BCT was also linked to the domain of environmental context and resources and was proposed for ranking in this domain. Eighteen stakeholders participated in the online survey (GPs=2; pharmacists=3; nurses=3; occupational therapist=1; physical therapist=1; NH direction staff=3; nursing care coordinator=2; quality coordinator=1; policy makers=2). A summary of findings is available in Table 1. Appendix 2 presents detailed data on the BCTs proposed for ranking per TDF domain, with their definitions and examples, and online survey results.

Table 1: Results of the online survey, per TDF domain.					
BCT name (and number*)	Global ranking**	Individual participants ranking			Selection for future step?
		Mean	Median	Range	
Knowledge					
Instruction on how to perform the behavior (4.1)	2	2.56	3	1-4	Yes
Information about antecedents (4.2)	4	3.06	3	1-4	
Information about health consequences (5.1)	1	1.56	1	1-4	Yes
Information about social and environmental consequences (5.3)	3	2.83	3	1-4	
Skills					
Instruction on how to perform the behavior (4.1)	1	1.83	2	1-3	Yes
Behavioral practice/rehearsal (8.1.)	3	2.27	2	1-3	Yes
Graded tasks (8.7)	2	1.89	2	1-3	Yes
Beliefs about capabilities					
Problem solving (1.2)	1	2.61	2	1-7	Yes
Instruction on how to perform the behavior (4.1)	2	2.78	2	1-6	Yes
Demonstration of the behavior (6.1)	3	3.11	3	1-5	Yes
Behavioral practice/rehearsal (8.1.)	5	4.39	4.5	2-7	
Graded tasks (8.7)	4	3.44	4	1-6	Yes
Verbal persuasion about capability (15.1)	6	4.83	6	1-6	
Self-talk (15.4)	7	6.83	7	5-7	
Beliefs about consequences					
Information about health consequences (5.1)	1	2.06	2	1-4	Yes
Salience of consequences (5.2)	3	2.61	3	1-4	
Information about social and environmental consequences (5.3)	4	2.94	3	1-4	
Pros and cons (9.2)	2	2.39	2.5	1-4	Yes
Goals					
Goal setting (behavior) (1.1)	1	1.22	1	1-2	Yes
Review behavior goal(s) (1.5)	3	2.56	3	1-3	
Discrepancy between current	2	2.22	2	1-3	

behavior and goal (1.6)					
Environmental context and resources					
Social support (practical) (3.2)	3	3	3	1-5	Yes
Prompts/Cues (7.1)	4	3.17	3.5	1-5	
Restructuring the physical environment (12.1)	2	2.94	3	1-5	Yes
Restructuring the social environment (12.2)	1	2.61	2.5	1-5	Yes
Adding objects to the environment (12.5)	5	3.28	3	1-5	
Social influences					
Social support (practical) (3.2)	2	2.39	2	1-4	Yes
Social comparison (6.2)	1	2.06	1	1-4	Yes
Information about others' approval (6.3)	3 (ex-aequo)	2.78	3	1-4	
Social reward (10.4)	3 (ex-aequo)	2.78	3	1-4	
Legend: BCT= behavior change technique, **GP**= General Practitioner, **TDF=** Theoretical domains Framework *Numbers between brackets refer to the BCT number, following the BCT taxonomy v1 by Michie et al. (38) **Score ranging from 1 to x, depending on the number of BCTs per TDF domain, 1 indicating higher priority					

Twelve BCTs, with higher ranking in the survey, were discussed during the online meeting. Seven stakeholders participated in the group discussion (coordinating physician=1; GP=1, pharmacist=1, nurse=1, psychologist=1, NH direction staff=1, policy maker=1). Per TDF domain, they discussed on the proposed BCTs, and unanimously agreed on which BCTs to include or exclude. At the end of this selection process (summarized in Figure 1), 9 BCTs were selected for inclusion in our complex intervention: instructions on how to perform the behavior, information about health consequences, pros and cons, problem solving, goals setting (behavior), graded tasks, social comparison, restructuring the physical environment, and restructuring the social environment. Detailed results of group discussion and reasons for BCTs exclusion are presented in Appendix 3.

Operationalization of BCTs: Intervention Components and Modes of Delivery

The research team designed a 6-component intervention encompassing the 9 selected BCTs (See Figure 2). The 6 components were as follows: process and

goals setting, HCP education, physical environment adaptation, audit and feedback, NHRs and relatives' increased awareness, and multidisciplinary work. These components were approved by the panel of stakeholders (N=5, coordinating physician=1; GP=1, nurse=1, NH direction=1, policy maker=1). Content for each component and methods of delivery were also discussed with the panel. Based on their remarks and suggestions, content was further adapted. Intervention components and tools were developed to be as flexible as possible, so that each NH can adapt it to its specific context.

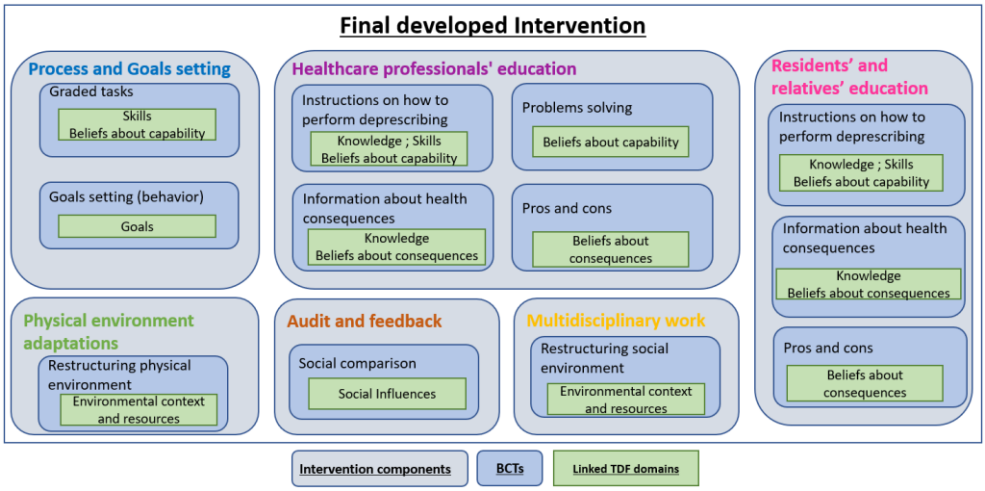


Figure 2: Final developed intervention, with intervention components, encompassed behavior-change techniques, and linked theoretical domains framework.
Legend: BCT= Behavior-change technique; TDF= Theoretical domains framework

Intervention Description

Each component of the intervention is further described in Table 2, following the Template for Intervention Description and Replication (TIDieR) checklist (39). Apart from the audit and feedback provided by the research team, actors of usual care will be responsible for their implementation. Intervention implementation will take place directly in the NH.

Table 2: Description of the developed intervention components				
Intervention component	**Objective(s)**	**Description**	**Involved stakeholders**	**Tools available to support implementation**
Process and Goal setting	- Prioritization of BZRA deprescribing - Definition of graded tasks towards BZRA deprescribing	Definition of steps for implementing a BZRA deprescribing process at the NH level, and of achievable goals for implementation timeline	NH direction staff HCPs	Tool 1: List of potential steps and goals, encompassing the 5 subsequent components of the intervention. The tool is flexible: each NH can adapt or add steps, designate a responsible person, and determine a timeline.
HCP education	-Increase knowledge and skills of HCPs regarding BZRA, BZRA deprescribing and non-pharmacological approaches	Training session organized at the level of the NH	All HCPs, including GPs. Educator free of choice, preferably CP	Tool 2: PowerPoint presentation (editable format). Encompasses: - Information on BZRA and their side effects - Information on alternatives to manage sleep and anxiety - Prompts to waive pros and cons of deprescribing - Practical information on how to taper BZRA - Practical tips on how to address BZRA deprescribing with NHRs and relatives - Clinical cases for problem solving
Physical environment adaptation	- Promoting better sleep and relaxation environment at the NH level	Restructuration of the NH physical environment to promote relaxation and better sleep	NH direction staff and HCPs	Tool 3: List of potential environmental adaptations. The tool is flexible: each NH can select the feasible adaptations depending on its context, designate a responsible person, and fix a due date. Adaptations beyond the list are also possible

Audit and Feedback	- Allowing comparison with BZRA use in other NHs - Tracking progress at the NH level	At the beginning of the intervention and every 3 mo, the research team provide NHs with feedback data on BZRA use of their residents. Feedback will be based on the percentage of residents taking at least 1 BZRA (ATC codes N05CD, N05CF, N05BA or N03AE01), as reported by the NH pharmacist.	Pharmacist	Tool 4: Audit and Feedback document - Comparison of BZRA use rate in the NH to the percentage of NHR taking at least one BZRA in the COME-ON study [12,42] (a multicentric study performed in 54 NHs in Belgium, 52.4% of BZRA use) - Recommendations regarding BZRA use, alternatives, and how to deprescribe (as advised in a systematic review on how to best construct an effective audit and feedback [46]).
NHRs' and relatives' awareness	-Increase awareness and self-efficacy of NHRs and relatives regarding BZRA deprescribing - Decrease NHRs' reluctance to stop BZRA - Favor communication with HCPs	HCPs (including GPs) will distribute an educational brochure to NHRs and/or relatives (when discussing deprescribing, or to all NHRs they think might benefit from it.) In situations involving residents with dementia, it is expected that relatives will be engaged.	NHRs and relatives HCPs	Tool 5: Educational leaflet for NHRs and relatives Leaflet adapted from the EMPOWER brochure to the NH context*.

Multidisciplinary work	- Enhancing interdisciplinary collaboration towards BZRA deprescribing	Organization of multidisciplinary meetings, to which GPs will be invited, to jointly review BZRA indications and opportunities for deprescribing	All HCPs	Tool 6: Multidisciplinary opinion document** This tool enables NH staff to communicate potential BZRA side-effects to the GP (in case the GP doesn't attend multidisciplinary meetings), and propositions of changes in prescriptions and nonpharmacological approaches. The GP can respond on the same document.

Legend: BZRA= Benzodiazepine Receptor Agonists, **CP**= Coordinating physician, **GP**= General practitioner, **HCP**= Healthcare professional, **NH**= Nursing home, **NHR**= Nursing home resident, **TDF**= Theoretical domains framework

*: *The EMPOWER brochure, which has already shown substantial effectiveness in BZRA deprescribing for ambulatory patients (47,48), has recently been adapted to the Belgian context (49). With agreement from original authors, we further adapted the brochure to the Belgian NH context. Mainly, we revised brochure images, to better represent NHRs, and adjust the nonpharmacological approaches presented. We also adapted the list of professionals to support patients in the process. We presented the adapted brochure to different stakeholders in group discussions or face-to-face interviews (GP=1, nurse/quality coordinator =1, NH direction=1, policy maker=1, NHR=1, relative= 1), and incorporated their feedback to our adapted brochure.*

**: *The Multidisciplinary opinion document has been adapted from the pharmaceutical proposal document used in the D-PRESCRIBE study (50) and adapted to the Belgian setting (49). Adaptations for the NH setting aimed at better fitting the context of a multidisciplinary team. Adaptations were proposed by the research team, and refined by the stakeholders' panel at the stage of BCT operationalization.*

DISCUSSION

Using behavior change theories and stakeholders' insights, we developed a novel intervention toward BZRA deprescribing, with 9 BCTs operationalized into a 6-component intervention: process and goals setting, HCPs' education, physical environment adaptations, audit and feedback, NHRs' and relatives' awareness, and multidisciplinary work.

In comparison to other interventions implemented in NHs, our intervention represents a novel combination of strategies (15). As an example, in Australia, the RedUSE intervention, aiming at sedative reduction, included audit and feedback cycles, HCPs educational session, and interdisciplinary sedative review. However, NHRs and relatives' education and physical environment adaptation were not included. RedUSE led to a reduction in prevalence of BZRA use, from 31.8% to 26.9% (40). In Denmark, an intervention aiming at antidepressants deprescribing in residents with dementia is being evaluated (41). It gathers 3 tools: an educational tool for NH staff on behavioral and psychological symptoms of dementia and antidepressant, a previsit checklist to ensure staff's and relatives' presence during visit, and a dialog tool to enhance shared decision making. The intervention involves NHRs and relatives, but does not include audit and feedback, or possible environmental adaptations. In the same context as ours, Belgian NHs, the COME-ON intervention aimed to reduce potentially inappropriate prescriptions (42, 43). It encompassed HCPs education, local multidisciplinary meetings, and interdisciplinary medication review but no audit and feedback, environmental changes, or raising NHRs' awareness. Although not focused on BZRA, the COME-ON intervention was associated with BZRA deprescribing (32.9% of NHRs, versus 22.1% in the control group) (21). Our intervention was codesigned with stakeholders and specifically targets BZRA deprescribing behavior determinants. Therefore, we believe that it could lead to higher rates of deprescribing.

Recently, Scott et al. used a similar theory-based approach for developing an intervention toward deprescribing (CHARMER) in acute geriatric care (18). They selected 5 BCTs (a*ction planning, environmental restructuring, social comparison, pros and cons*, and *salience of consequences)* and operationalized them in a 5-component intervention *(hospital action plan, regular geriatrician and pharmacist briefing, videos of geriatricians successfully navigating deprescribing consultations, workshop for pharmacists including videos of fictional patient case studies, and a*

deprescribing dashboard). Although the settings and focuses differ, these 2 interventions share several similarities in BCTs and components. Both involve social environment restructuring, social comparison, and pros and cons. It is noteworthy that one of their components, namely, videos of geriatricians navigating deprescribing consultations, was rejected by our stakeholders' panel. They believed it would be too simplistic and ineffective. Our intervention introduces 2 additional components: adapting physical environment, which is particularly relevant given that NHs are the NHRs' living place; and directly targeting NHRs and relatives, which is crucial for the long-term effectiveness of deprescribing interventions (44). Recent studies have shown a lack of NHRs' knowledge and involvement in medication review processes (21, 45).

We are now moving on to our intervention evaluation (fourth step of the model proposed by French et al (19)). Before an effectiveness trial, we are conducting a pilot study in a limited number of NHs (clinicaltrials.gov registration number: NCT05929443), as recommended by the Medical research council guidance (17). Using a mixed-method approach, we will evaluate participants' responsiveness and adherence to the intervention, intervention's mechanisms of impact, as well as the role of contextual factors.

This study has several strengths. We used a rigorous methodology, which included context-specific data on barriers to BZRA deprescribing and a theory-based approach. We also involved a wide range of stakeholders. This aligns with international recommendations for developing complex interventions (17, 34). Moreover, our intervention allows for potential adjustments in the tool's implementation and use to fit the specific context of each NH. We will assess these potential adaptations in our upcoming pilot study. These strengths increase the likelihood of the intervention uptake and success.

This study also has limitations. First, BCTs' ranking in the online survey varied significantly between respondents, even between respondents with similar background and function. However, variations disappeared during the panel discussion, where all BCTs were chosen unanimously. There are limited data and guidance on how best to involve stakeholders in selecting BCTs. A survey facilitates participation of a larger group of stakeholders but has its own limitation. Following with a group discussion can help mitigate these limitations. This method has also been used in other studies (32, 33). Second, survey respondents were presented

with a summary of main barriers and enablers per TDF domains, but did not access a complete list of detailed barriers and enablers. We believe a detailed list would have make the questionnaire too long and would have reduce study participation. However, it is possible that respondents would have chosen different BCTs with more information on the barriers and enablers. Third, the sample sizes of respondents to both the online survey and panel discussions were rather small. Using multiple focus groups at each phase and involving a greater number of stakeholders in the panel discussions overall may have yielded different and/or more robust results. Involving implementation or behavioral scientists may have also led to inclusion/exclusion of different BCTs. Fourth, NHRs and relatives were solely involved in the development of the NHR brochure. Involving NHRs and relatives for BCT selection and intervention components design could have been considered. Walsh et al included NHRs carers in BCTs selection for antipsychotics reduction, but reported difficulties for them with BCT language (32). As NHRs and relatives are not direct actors of the targeted behavior, we opted not to include them in these steps. Fifth, there is no evidence of a BCT linked to the TDF domain of social professional role and identity. However, our intervention might impact this domain through the inclusion of all NH staff in educational session and multidisciplinary meetings, and through the designation of a person responsible at each step. Finally, we did not collect sociodemographic data from the participants, so we cannot tell if they are representative of their respective groups. Our goal was to involve a variety of stakeholders with various roles in NH care, and we believe we achieved that.

CONCLUSIONS AND IMPLICATIONS

Using a meticulous theory-based approach for intervention development has the potential to improve the probability of intervention feasibility and effectiveness. By doing so, we developed a novel 6-component intervention toward BZRA deprescribing in NHR. It encompasses actions taken at the resident, HCP, and NH levels. The intervention implementation and evaluation feasibility will now be pilot-tested in a cluster-randomized controlled trial. If the intervention is proven to be feasible, and later effective, its dissemination to Belgian NHs should be encouraged. Policy actions should also be explored to see how they could enable or strengthen intervention components implementation. The intervention, or its components, could also be implemented in other countries after cultural and

contextual adaptations. Sharing the development process of this behavior-change intervention could help both future adaptations, and using a similar process for other quality improvement initiatives, in Belgian NHs or elsewhere.

Supplemental materials:

Appendix 1: BCT linked to the TDF domains identified as most relevant in our qualitative study (according to the theory and techniques tool), and results of the research team preselection, with exclusion justification.

Appendix 2: Results of the online survey, per TDF domain.

Appendix 3: Results of the group discussion.

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Appendix 1: BCT linked to the TDF domains identified as most relevant in our qualitative study (according to the theory and techniques tool), **and results of the research team preselection, with exclusion justification.**				
BCT name (and number*)	BCT definition	Other TDF domain linked?	Preselection Yes/no	If applicable, reason for exclusion
Knowledge				
Biofeedback (2.6)	Provide feedback about the body (eg, physiological or biochemical state) using an external monitoring device as part of a behavior change strategy		No	No body measure can be used in daily practice to support BZRA deprescribing
Instruction on how to perform the behavior (4.1)	Advise or agree on how to perform the behavior (includes "Skills training")	Skills Beliefs about capabilities	Yes	
Information about antecedents (4.2)	Provide information about antecedents (eg, social and environmental situations and events, emotions, cognitions) that reliably predict performance of the behavior	Behavioral regulation	Yes	
Information about health consequences (5.1)	Provide information (eg, written, verbal, visual) about health consequences of performing the behavior	Beliefs about consequences Intention	Yes	
Information about social and environmental consequences (5.3)	Provide information (eg, written, verbal, visual) about social and environmental consequences of performing the behavior	Beliefs about consequences	Yes	

Skills				
Instruction on how to perform the behavior (4.1)	Advise or agree on how to perform the behavior (includes "Skills training")	Knowledge Beliefs about capabilities	Yes	
Behavioral practice/rehearsal (8.1.)	Prompt practice or rehearsal of the performance of the behavior 1 or more times in a context or at a time when the performance may not be necessary, in order to increase habit and skill	Beliefs about capabilities	Yes	
Graded tasks (8.7)	Set easy-to-perform tasks, making them increasingly difficult, but achievable, until behavior is performed	Beliefs about capabilities	Yes	
Social professional role and identity				
No BCT with proved links				
Beliefs about capabilities				
Problem solving (1.2)	Analyze, or prompt the person to analyze, factors influencing the behavior and generate or select strategies that include overcoming barriers and/or increasing facilitators (includes 'Relapse Prevention' and 'Coping Planning')	Behavioral regulation	Yes	
Instruction on how to perform the behavior (4.1)	Advise or agree on how to perform the behavior (includes "Skills training")	Knowledge Skills	Yes	
Demonstration of the behavior (6.1)	Provide an observable sample of the performance of the behavior, directly in person or indirectly eg, via film, pictures, for the person to aspire to or imitate (includes 'Modelling')		Yes	

Behavioral practice/rehearsal (8.1.)	Prompt practice or rehearsal of the performance of the behavior 1 or more times in a context or at a time when the performance may not be necessary, in order to increase habit and skill	Skills	Yes	
Graded tasks (8.7)	Set easy-to-perform tasks, making them increasingly difficult, but achievable, until behavior is performed	Skills	Yes	
Verbal persuasion about capability (15.1)	Tell the person that they can successfully perform the wanted behavior, arguing against self-doubts and asserting that they can and will succeed		Yes	
Focus on past success (15.3)	Advise to think about or list previous successes in performing the behavior (or parts of it)		No	Not all stakeholders do have past successes to focus on.
Self-talk (15.4)	Prompt positive self-talk (aloud or silently) before and during the behavior		Yes	
Beliefs about consequences				
Information about health consequences (5.1)	Provide information (eg, written, verbal, visual) about health consequences of performing the behavior	Knowledge Intention	Yes	
Salience of consequences (5.2)	Use methods specifically designed to emphasize the consequences of performing the behavior with the aim of making them more memorable (goes beyond informing about consequences)		Yes	
Information about social and environmental consequences (5.3)	Provide information (eg, written, verbal, visual) about social and environmental consequences of performing the behavior	Knowledge	Yes	

Anticipated regret (5.5)	Induce or raise awareness of expectations of future regret about performance of the unwanted behavior		No	Stakeholders currently do not perceive failure to deprescribe BZRA as an unwanted behavior and therefore will not have anticipated regrets.
Information about emotional consequences (5.6)	Provide information (eg, written, verbal, visual) about emotional consequences of performing the behavior		No	Some stakeholders anticipate that patients will be frustrated and more aggressive when BZRA deprescribing begins. Therefore, using this BCTs does not guarantee to enhance deprescribing.
Pros and cons (9.2)	Advise the person to identify and compare reasons for wanting (pros) and not wanting to (cons) change the behavior (includes 'Decisional balance')		Yes	
Comparative imaging of future outcomes (9.3)	Prompt or advise the imagining and comparing of future outcomes of changed versus unchanged behavior		No	Some stakeholders currently think that the risks of BZRA deprescribing outweigh the benefits; therefore, this BCT could lead to less deprescribing.
Material incentive (behavior) (10.1)	Inform that money, vouchers or other valued objects will be delivered if and only if there has been effort and/or progress in performing the behavior (includes 'Positive reinforcement')	Reinforcement	No	BZRA deprescribing should only occur when appropriate. Material incentive could lead to inappropriate deprescribing.
Incentive (outcome) (10.8)	Inform that a reward will be delivered if and only if there has been effort and/or progress in achieving the behavioral outcome (includes 'Positive reinforcement')	Reinforcement Intention	No	BZRA deprescribing should only occur when appropriate. Incentives could lead to inappropriate deprescribing.

Reward (outcome) (10.10)	Arrange for the delivery of a reward if and only if there has been effort and/or progress in achieving the behavioral outcome (includes 'Positive reinforcement')	Reinforcement	No	BZRA deprescribing should only occur when appropriate. Reward could lead to inappropriate deprescribing.
Goals				
Goal setting (behavior) (1.1)	Set or agree on a goal defined in terms of the behavior to be achieved	Intention	Yes	
Goal setting (outcome) (1.3)	Set or agree on a goal defined in terms of positive outcome of wanted behavior		No	BZRA deprescribing should only occur when appropriate; it is not appropriate to set a target of the number of BZRA deprescribed as this is dependent on several factors external to the prescriber, and could lead to inappropriate deprescribing.
Review behavior goal(s) (1.5)	Review behavior goal(s) jointly with the person and consider modifying goal(s) or behavior change strategy in light of achievement. This may lead to resetting the same goal, a small change in that goal or setting a new goal instead of (or in addition to) the first, or no change		Yes	

Discrepancy between current behavior and goal (1.6)	Draw attention to discrepancies between a person's current behavior (in terms of the form, frequency, duration, or intensity of that behavior) and the person's previously set outcome goals, behavioral goals, or action plans (goes beyond self-monitoring of behavior)		Yes	
Review outcome goal(s) (1.7)	Review outcome goal(s) jointly with the person and consider modifying goal(s) in light of achievement. This may lead to re-setting the same goal, a small change in that goal or setting a new goal instead or, or in addition to the first		No	BZRA deprescribing should only occur when appropriate; it is not appropriate to set a target of the number of BZRA deprescribed as this is dependent on several factors external to the prescriber, and could lead to inappropriate deprescribing.
Memory, attention and decision process				
Prompts/Cues (7.1)	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 place of performance	Environmental context and resources	Yes	
Conserving mental resources (11.3)	Advise on ways of minimizing demands on mental resources to facilitate behavior change	Behavioral regulation	No	There is no application to this BCT in the context of BZRA deprescribing.

Environmental context and resources				
Social support (practical) (3.2)	Advise on, arrange, or provide practical help (eg, from friends, relatives, colleagues, buddies or staff) for performance of the behavior	Social influences	Yes	
Prompts/Cues (7.1)	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 place of performance	Memory, attention and decision resources	Yes	
Remove aversive stimulus (7.5)	Advise or arrange for the removal of an aversive stimulus to facilitate behavior change (includes 'Escape learning')		No	There is currently no aversive stimulus.
Restructuring the physical environment (12.1)	Change or advise to change the physical environment in order to facilitate performance of the wanted behavior or create barriers to the unwanted behavior (other than prompts/cues, rewards and punishments)		Yes	
Restructuring the social environment (12.2)	Change or advise to change the social environment in order to facilitate performance of the wanted behavior or create barriers to the unwanted behavior (other than prompts/cues, rewards and punishments)		Yes	
Avoidance/reducing exposure to cues for the behavior (12.3)	Advise on how to avoid exposure to specific social and contextual/physical cues for the behavior, including changing daily or weekly routines.		No	There is no aversive stimulus that would lead to BZRA prescribing, as this has been reported to be part of an automatism.
Adding objects to the environment (12.5)	Add objects to the environment in order to facilitate performance of the behavior		Yes	

Social influences				
Social support (unspecified) (3.1)	Advise on, arrange, or provide social support (eg, from friends, relatives, colleagues, buddies, or staff) or non-contingent praise or reward for performance of the behavior. It includes encouragement and counselling, but only when it is directed at the behavior		No	Already covered by social support (practical).
Social support (practical) (3.2)	Advise on, arrange, or provide practical help (eg, from friends, relatives, colleagues, buddies, or staff) for performance of the behavior	Environmental context and resources	Yes	
Social comparison (6.2)	Draw attention to others' performance to allow comparison with the person's own performance		Yes	
Information about others' approval (6.3)	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		Yes	
Social reward (10.4)	Arrange verbal or non-verbal reward if and only if there has been effort and/or progress in performing the behavior (includes 'Positive reinforcement')	Reinforcement	Yes	

Legend: BCT= behavior change technique, **BZRA=** Benzodiazepine receptor agonists, **TDF=** Theoretical domains Framework
*Numbers between brackets refer to the BCT number, following the BCT taxonomy v1 by Michie et al. (Michie S, Richardson M, Johnston M, et al.; The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. *Ann Behav Med* 2013;**46**(1):81-95. doi: 10.1007/s12160-013-9486-6.)

Appendix 2: Results of the online survey, per TDF domain.							
BCT name (and number)*	BCT definition	Example provided for online questionnaire	Global rankings	Sum of individual rankings	Individual participants ranking		
					Mean	Median	Range
Knowledge							
Instruction on how to perform the behavior (4.1)**	Advise or agree on how to perform the behavior (includes "Skills training")	Organization of online course, or workshops on how to deprescribe BZRA	2	46	2.56	3	1-4
Information about antecedents (4.2)	Provide information about antecedents (eg, social and environmental situations and events, emotions, cognitions) that reliably predict performance of the behavior	Organization of online course, or workshops explaining in which situations you should or not deprescribe	4	55	3.06	3	1-4
Information about health consequences (5.1)**	Provide information (eg, written, verbal, visual) about health consequences of performing the behavior	Provide information (brochure or online course), on potential health consequences of BZRA and BZRA deprescribing	1	28	1.56	1	1-4
Information about social and environmental consequences (5.3)	Provide information (eg ,written, verbal, visual) about social and environmental consequences of performing the behavior	Provide information (brochure or online course), on potential social or environmental consequences of BZRA and BZRA deprescribing	3	51	2.83	3	1-4

Skills							
Instruction on how to perform the behavior (4.1)**	Advise or agree on how to perform the behavior (includes "Skills training")	Organization of online course, or workshops on how to deprescribe BZRA	1	33	1.83	2	1-3
Behavioral practice/rehearsal (8.1.)**	Prompt practice or rehearsal of the performance of the behavior 1 or more times in a context or at a time when the performance may not be necessary, in order to increase habit and skill	Organizing role play to practice shared-decision making or non-pharmacological approach implementation	3	41	2.27	2	1-3
Graded tasks (8.7)**	Set easy-to-perform tasks, making them increasingly difficult, but achievable, until behavior is performed	Set the objective to review the indication of use for each patient, then, if applicable, to discuss BZRA use with each patient	2	34	1.89	2	1-3
Beliefs about capabilities							
Problem solving (1.2)**	Analyze, or prompt the person to analyze, factors influencing the behavior and generate or select strategies that include overcoming barriers and/or increasing facilitators (includes 'Relapse Prevention' and 'Coping Planning')	Present potential issues stakeholders might be thinking and generate ideas on how to solve these issues in a group discussion	1	47	2.61	2	1-7
Instruction on how to perform the behavior (4.1)**	Advise or agree on how to perform the behavior (includes "Skills training")	Organization of online course, or workshops on how to deprescribe BZRA	2	50	2.78	2	1-6

Demonstration of the behavior (6.1)**	Provide an observable sample of the performance of the behavior, directly in person or indirectly (eg, via film, pictures), for the person to aspire to or imitate (includes 'Modelling')	Showing videos of shared-decision making, or non-pharmacological approaches implementation.	3	56	3.11	3	1-5
Behavioral practice/rehearsal (8.1.)	Prompt practice or rehearsal of the performance of the behavior 1 or more times in a context or at a time when the performance may not be necessary, in order to increase habit and skill	Organizing role play to practice shared-decision making or non-pharmacological approach implementation	5	79	4.39	4.5	2-7
Graded tasks (8.7)**	Set easy-to-perform tasks, making them increasingly difficult, but achievable, until behavior is performed	Set the objective to review the indication of use for each patient, then, if applicable, to discuss BZRA use with each patient	4	62	3.44	4	1-6
Verbal persuasion about capability (15.1)	Tell the person that they can successfully perform the wanted behavior, arguing against self-doubts and asserting that they can and will succeed	Tell stakeholders that they can successfully initiate BZRA deprescribing	6	87	4.83	6	1-6
Self-talk (15.4)	Prompt positive self-talk (aloud or silently) before and during the behavior	Prompt stakeholders to tell themselves that they can successfully initiate BZRA deprescribing	7	123	6.83	7	5-7

Beliefs about consequences							
Information about health consequences (5.1)**	Provide information (eg, written, verbal, visual) about health consequences of performing the behavior	Provide information (brochure or online course) on potential health consequences of BZRA and BZRA deprescribing	1	37	2.06	2	1-4
Salience of consequences (5.2)	Use methods specifically designed to emphasize the consequences of performing the behavior with the aim of making them more memorable (goes beyond informing about consequences)	Use of didactic material emphasizing in direct, memorable ways risks associated with not deprescribing BZRA.	3	47	2.61	3	1-4
Information about social and environmental consequences (5.3)	Provide information (eg, written, verbal, visual) about social and environmental consequences of performing the behavior	Provide information (brochure or online course) on potential social or environmental consequences of BZRA and BZRA deprescribing	4	53	2.94	3	1-4
Pros and cons (9.2)**	Advise the person to identify and compare reasons for wanting (pros) and not wanting to (cons) change the behavior (includes 'Decisional balance')	Encourage all stakeholders to write and discuss a list of pros and cons for BZRA deprescribing	2	43	2.39	2.5	1-4

Goals							
Goal setting (behavior) (1.1)**	Set or agree on a goal defined in terms of the behavior to be achieved	Setting the objective to discuss about deprescribing with half of the patients in a define time period, or to propose nonpharmacological approaches to all patients	1	22	1.22	1	1-2
Review behavior goal(s) (1.5)	Review behavior goal(s) jointly with the person and consider modifying goal(s) or behavior change strategy in light of achievement. This may lead to resetting the same goal, a small change in that goal or setting a new goal instead of (or in addition to) the first, or no change	Organize regular meetings to rediscuss objectives and, if necessary adapt them	3	46	2.56	3	1-3
Discrepancy between current behavior and goal (1.6)	Draw attention to discrepancies between a person's current behavior (in terms of the form, frequency, duration, or intensity of that behavior) and the person's previously set outcome goals, behavioral goals, or action plans (goes beyond self-monitoring of behavior)	Elaborate on how GPs mainly perceive BZRA deprescribing as important and as a long-term goal but do not actually do it	2	40	2.22	2	1-3

Environmental context and resources							
Social support (practical) (3.2)**	Advise on, arrange, or provide practical help (eg, from friends, relatives, colleagues, buddies or staff) for performance of the behavior	Creation of an online platform between NHs to share their experiences and working solutions	3	54	3	3	1-5
Prompts/Cues (7.1)	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 place of performance	Putting posters in medical room in NH, prompting to think about BZRA deprescribing	4	57	3.17	3.5	1-5
Restructuring the physical environment (12.1)**	Change or advise to change the physical environment in order to facilitate performance of the wanted behavior or create barriers to the unwanted behavior (other than prompts/cues, rewards and punishments)	Adapt lights in bedroom, having relaxation activities in a more accessible, visible, place	2	53	2.94	3	1-5

Restructuring the social environment (12.2)**	Change or advise to change the social environment in order to facilitate performance of the wanted behavior or create barriers to the unwanted behavior (other than prompts/cues, rewards and punishments)	Creation of multidisciplinary meetings to promote BZRA deprescribing	1	47	2.61	2.5	1-5
Adding objects to the environment (12.5)	Add objects to the environment in order to facilitate performance of the behavior	Addition of a specific document in each NHRs' chart to monitor the use of BZRA, and to allow each stakeholder to leave comments	5	59	3.28	3	1-5
Social influences							
Social support (practical) (3.2)**	Advise on, arrange, or provide practical help (eg, from friends, relatives, colleagues, buddies, or staff) for performance of the behavior	Creation of an online platform between NH to share on their experiences and working solutions.	2	43	2.39	2	1-4
Social comparison (6.2)**	Draw attention to others' performance to allow comparison with the person's own performance	Provide feedback either at the GP level or at the NH level on BZRA deprescribing data with comparison	1	37	2.06	1	1-4

Information about others' approval (6.3)	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	Informe GPs on other HCPs' point of view on BZRA deprescribing	3 (ex-aequo)	50	2.78	3	1-4
Social reward (10.4)	Arrange verbal or nonverbal reward if and only if there has been effort and/or progress in performing the behavior (includes 'Positive reinforcement')	Congratulate teams in case of improvement in rate of use, or effort towards this	3 (ex-aequo)	50	2.78	3	1-4
Legend: BCT= behavior change technique, **GP**= General Practitioner, **TDF=** Theoretical domains Framework *Numbers between brackets refer to the BCT number, following the BCT taxonomy v1 by Michie et al. (Michie S, Richardson M, Johnston M, et al.; The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. *Ann Behav Med* 2013;**46**(1):81-95. doi: 10.1007/s12160-013-9486-6.) **: BCTs selected for the further step of selection							

Appendix 3: Results of the Group discussion				
BCT name (and number)*	BCT definition	Example provided	Final selection (Yes/No)	Reason for exclusion
Knowledge				
Instruction on how to perform the behavior (4.1)	Advise or agree on how to perform the behavior (includes "Skills training")	Organization of online course, or workshops on how to deprescribe BZRA	Yes	
Information about health consequences (5.1)	Provide information (eg, written, verbal, visual) about health consequences of performing the behavior	Provide information (brochure or online course) on potential health consequences of BZRA and BZRA deprescribing	Yes	
Skills				
Instruction on how to perform the behavior (4.1)	Advise or agree on how to perform the behavior (includes "Skills training")	Organization of online course, or workshops on how to deprescribe BZRA	Yes	
Behavioral practice/rehearsal (8.1.)	Prompt practice or rehearsal of the performance of the behavior 1 or more times in a context or at a time when the performance may not be necessary, in order to increase habit and skill	Organizing role-play to practice shared decision making or non-pharmacological approach implementation	No	Stakeholders believed this BCT to be inappropriate, they thought repetitions to be time-consuming, unnecessary, and unfeasible.
Graded tasks (8.7)	Set easy-to-perform tasks, making them increasingly difficult, but achievable, until behavior is performed	Set the objective to review the indication of use for each patient, then, if applicable, to discuss BZRA use with each patient	Yes	

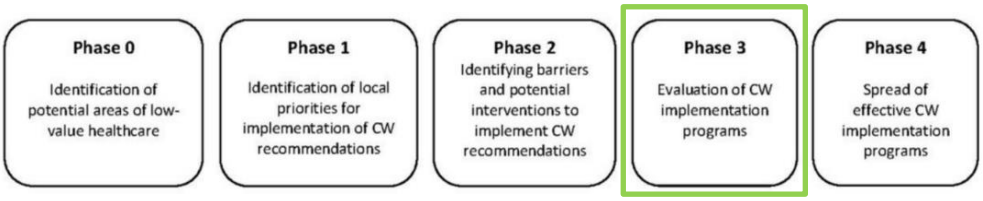
Beliefs about capabilities				
Problem solving (1.2)	Analyze, or prompt the person to analyze, factors influencing the behavior and generate or select strategies that include overcoming barriers and/or increasing facilitators (includes 'Relapse Prevention' and 'Coping Planning')	Present potential issues stakeholders might be thinking and generate ideas on how to solve these issues in a group discussion.	Yes	
Instruction on how to perform the behavior (4.1)	Advise or agree on how to perform the behavior (includes "Skills training")	Organization of online course, or workshops on how to deprescribe BZRA	Yes	
Demonstration of the behavior (6.1)	Provide an observable sample of the performance of the behavior, directly in person or indirectly (eg, via film, pictures), for the person to aspire to or imitate (includes 'Modelling')	Showing videos of shared-decision making, or implementation of nonpharmacological approaches	No	Stakeholders thought this BCT too simplet, childish.
Graded tasks (8.7)	Set easy-to-perform tasks, making them increasingly difficult, but achievable, until behavior is performed	Set the objective to review the indication of use for each patient, then, if applicable, to discuss BZRA use with each patient	Yes	
Beliefs about consequences				
Information about health consequences (5.1)	Provide information (eg, written, verbal, visual) about health consequences of performing the behavior	Provide information (brochure or online course) on potential health consequences of BZRA and BZRA deprescribing	Yes	
Pros and cons (9.2)	Advise the person to identify and compare reasons for wanting (pros) and not wanting to (cons) change the behavior (includes 'Decisional balance')	Encourage all stakeholders to write and discuss a list of pros and cons for BZRA deprescribing	Yes	

Goals				
Goal setting (behavior) (1.1)	Set or agree on a goal defined in terms of the behavior to be achieved	Setting the objective to discuss about deprescribing with half of the patients in a define time period, or to propose nonpharmacological approaches to all patients.	Yes	
Environmental context and resources				
Social support (practical) (3.2)	Advise on, arrange, or provide practical help (eg, from friends, relatives, colleagues, buddies or staff) for performance of the behavior	Creation of an online platform between NHs to share on their experiences and working solutions	No	Unrealist and complicated implementation according to stakeholders
Restructuring the physical environment (12.1)	Change or advise to change the physical environment in order to facilitate performance of the wanted behavior or create barriers to the unwanted behavior (other than prompts/cues, rewards and punishments)	Adapt lights in bedroom, having relaxation activities in a more accessible, visible, place	Yes	
Restructuring the social environment (12.2)	Change or advise to change the social environment in order to facilitate performance of the wanted behavior or create barriers to the unwanted behavior (other than prompts/cues, rewards and punishments)	Creation of multidisciplinary meetings to promote BZRA deprescribing	Yes	

Social influences				
Social support (practical) (3.2)	Advise on, arrange, or provide practical help (eg, from friends, relatives, colleagues, buddies or staff) for performance of the behavior	Creation of an online platform between NH to share on their experiences and working solutions.	No	Unrealist and complicated implementation according to stakeholders
Social comparison (6.2)	Draw attention to others' performance to allow comparison with the person's own performance	Provide feedback either at the GP level or at the NH level on BZRA deprescribing stats with comparison.	Yes	

Legend: BCT= behavior change technique, **GP**= General Practitioner, **TDF=** Theoretical domains Framework
*Numbers between brackets refer to the BCT number, following the BCT taxonomy v1 by Michie et al. (Michie S, Richardson M, Johnston M, et al.; The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. *Ann Behav Med* 2013;**46**(1):81-95. doi: 10.1007/s12160-013-9486-6.)

SECTION 3: Evaluation of the developed implementation strategies



Choosing Wisely framework for de-implementing low-value care (Grimshaw et al. 2020)

Chapter 5. Feasibility of a theory-based intervention towards benzodiazepine deprescribing in Belgian nursing homes: Protocol of the END-IT NH cluster-randomized controlled trial

Chapter 6. Partial Results of the END-IT NH study: feasibility of implementing and evaluating the END-IT NH intervention

Chapter 5. Feasibility of a theory-based intervention towards benzodiazepine deprescribing in Belgian nursing homes: Protocol of the END-IT NH cluster-randomized controlled trial

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Submitted manuscript (2024)

Authors' contributions:

PE, TC, CP, SH, and AS conceived the original study. JA and ST conceived the cost-effectiveness element of this protocol. PE wrote the first manuscript draft, which was then reviewed and amended by all authors. SH and AS supervised the study. They contributed equally and share the last authorship.

Funding:

The present work is supported by EBPpracticenet (Projet d'implémentation EBPpracticenet 2023); by a research credit from the fond national de recherche scientifique (FNRS) (CDR40013898); 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.

Acknowledgments:

The authors would like to thank all nursing homes, healthcare professionals and nursing home residents that participated in the study. We would also like to thank Prof. Catherine Legrand for her statistical expertise; Mrs. Anne-Gaëlle Peters for her great help with legal aspects; and Dr. Marine Jaeken for the revision of qualitative parts of this protocol.

ABSTRACT

INTRODUCTION. Despite several calls to deprescribe benzodiazepine receptor agonists (BZRA) in older adults, their use among nursing home residents (NHRs) remains high. Therefore, we developed an intervention targeting general practitioners' and healthcare professionals' behaviours regarding BZRA deprescribing in nursing homes (NHs): The END-IT NH 6-component intervention. Before moving on to a large-scale effectiveness and cost-effectiveness evaluation, this feasibility study aims at: (i) assessing the feasibility of the intervention implementation in NHs, (ii) assessing the feasibility of conducting a larger-scale evaluation, in terms of recruitment and data collection, and (iii) conducting an exploratory cost-effectiveness evaluation.

METHODS AND ANALYSIS. We will conduct a cluster-randomized controlled trial in a sample of 6 NHs, with 10 to 15 NHRs included per NHs. 4 NHs will be randomized into the intervention group, and 2 NHs will deliver usual care (control group). Data collection will occur at baseline, 3, and 6 months (study end). We will collect information to explore implementation fidelity, mechanisms of impact and contextual factors at patient-level, NH-level and healthcare professional-level, using both quantitative and qualitative measures. The feasibility of the study conduction will be assessed by measuring recruitment and attrition rates and completeness of data collection. An exploratory cost-effectiveness evaluation will be conducted based on quality of life and healthcare use and cost data.

ETHICS AND DISSEMINATION. This study protocol received approval from the ethical committee of the CHU UCL Namur on the 20th of June 2023. All data are confidential and will be anonymized prior to analysis. De-identified data will be shared on a data depository with a 2-year embargo. Results of the study will be disseminated through a scientific paper and will be communicated to local stakeholders and policy makers through a local symposium.

REGISTRATION. The END-IT NH feasibility study has been registered on clinicaltrial.gov (identifier: NCT05929443).

SECTION 3

INTRODUCTION

Benzodiazepine Receptor Agonists (BZRA, namely benzodiazepines and Z-drugs) are authorized medicines in the treatment of severe anxiety or short-term treatment of insomnia. BZRA are commonly used among Belgian nursing home residents (NHRs), with a prevalence of use of 52.4% (1, 2). However, these medicines have an unfavorable benefits-risk profile in the older population (3). Indeed, BZRA only have modest benefits (4) while they can trigger severe side effects including inappropriate sedation, increased risk of falls and fractures, cognitive impairment, and dependence (3, 5-7). Consequently, BZRA use should be avoided in older people or limited to 4 weeks (2 weeks for insomnia) (8-10). Alternatives exist, such as non-pharmacological approaches or utilization of antidepressant in the case of severe anxiety (11).

Deprescribing is the action to discontinue or reduce the use of a medication that is no longer needed or that may put the patient at risk, under the supervision of Health Care Professionals (HCPs), with the goal of managing polypharmacy and improving outcomes (12). In terms of deprescribing in older adults, BZRA are considered priority medicines (13). BZRA can be safely deprescribed in nursing homes (NHs), via slow tapering and dose reduction (14). Still, current deprescribing rates are low (1), and many barriers to deprescribing remain. Data from two systematic reviews (15, 16) indicate that some barriers are specific to the context and setting of care, while others are more generic, such as lack of knowledge and skills among HCPs and patients, perceptions of BZRA effectiveness, and fear of withdrawal symptoms. An intervention targeting identified barriers is expected to enhance BZRA deprescribing.

Many BZRA deprescribing interventions have already been studied – mainly in the outpatient setting (17). These interventions encompass medication review, substitution, educational programs, or mixed interventions. They achieved BZRA deprescribing rates ranging from 27 to 80% (17, 18). However, it is unclear which components of interventions are the most effective, and data from the NH setting remain scarce. Context is a key component that can influence the effect of the intervention and is significantly different between the NH and the ambulatory setting (15, 19). Additionally, previously developed interventions for medication optimization in NHs often lacked theoretical background (20), which is in contradiction with intervention development recommendations (21). Within this

state of knowledge, the present research program aims at developing and evaluating a theory-based intervention that would target general practitioners (GPs) and HCPs behavioural determinants and promote BZRA deprescribing, in the specific context of Belgian NHs.

The present study is part of an overall research program which follows the French 4-step model of theory-based intervention development (22), and recommendations of the Medical Research Council (MRC) on developing and evaluating complex interventions (21).

We developed an intervention towards BZRA deprescribing in NHs, using a theory-based process, and with involvement of appropriate stakeholders (HCPs involved in NH care, NH direction, policy makers, and residents or relatives). The behaviours targeted are, for (1) GPs, to initiate BZRA deprescribing discussion with NHRs and relatives, and initiate deprescribing when indicated, as part of patient care, and in collaboration with other HCPs, and for (2) other HCPs, to support GPs and NHRs in BZRA deprescribing. Briefly, we first identified barriers and enablers for BZRA deprescribing by performing a systematic review followed by a qualitative study, and mapping barriers and enablers with the Theoretical Domains Framework (TDF) (15, 23, 24). Using theory in intervention development is recommended by the MRC, as theory may help understanding the factors influencing the targeted behaviour, identifying possible techniques to promote the behaviour change (25) or developing the programme theory of the intervention (how the intervention is supposed to have its effect, and under which conditions (21)). The TDF was chosen as a theoretical framework, as it specifically aims at identifying influences on HCPs' behaviour related to the implementation of evidence-based practices or intervention (26). The intervention was then developed to target the 9 TDF domains that we identified as BZRA deprescribing determinants in Belgian NHs: Knowledge, Skills, Social Professional Role and Identity, Beliefs about capabilities, Beliefs about consequences, Goals, Memory attention and decision process, Environmental context and resources, and Social influences. We worked with stakeholders to select acceptable, practicable, effective, affordable, safe, and equitable behaviour change techniques (BCTs) from the BCT taxonomy v1 (27), with evidence of links to these TDF domains (28). Selected BCTs were then operationalized in a 6-component intervention. Intervention development and content have been described in detail elsewhere (29), and a summary of the intervention is available in

the methods section. The programme theory is available in Appendix 1 and summarizes the targeted behaviour, TDF domains, intervention components, potential mechanisms of impact, and expected behavioural and long-term outcomes.

The present study now aims at evaluating the feasibility of the END-IT NH intervention. Feasibility testing is recommended by the MRC and aims to evaluate the feasibility and acceptability of both the intervention and its evaluation design. Based on the feasibility study results, a decision should be made on whether to go on with the evaluation or not. The intervention can also be refined before the evaluation, and the programme theory adapted (21). Feasibility studies increase the chance of success of the following main studies, and they provide useful preliminary data that can be used by other researchers when developing future study designs (30).

The objectives of the present feasibility study are three-fold:

1. To evaluate the feasibility of implementing the END-IT intervention in Belgian nursing homes.
2. To assess the feasibility of conducting a larger cluster RCT to evaluate effectiveness and cost-effectiveness of the END-IT intervention, considering the many challenges of conducting a deprescribing trial in the NH setting.
3. Provided that the feasibility of the needed data collection is validated, to explore the potential cost-effectiveness of the intervention.

METHODS

The protocol of the END-IT NH feasibility study (version 1, in date of 25th of May 2023) has been registered on clinicaltrial.gov under the following identifier: NCT05929443. The SPIRIT checklist recommendations for interventional trials (31) and the CONSORT checklist extension to randomized pilot and feasibility trials (32) guided the reporting of this protocol. See Appendix 1 for the SPIRIT Checklist.

Study design, setting and participants

We will conduct a cluster-randomized, parallel-group, open-label controlled trial, with NHs being the clusters. As this feasibility study does not aim at

evaluating the effectiveness of the END-IT NH intervention for BZRA deprescribing, sample size calculation was not computed. Six NHs will be included. In each of these NHs, 10 to 15 NHRs will be included. The study will take place between July 2023 and March 2024.

Four of the 6 NHs will be randomised to the intervention group, and 2 to the control group. The higher number of NHs in the intervention group will help inform our primary research objective, which is evaluating the feasibility of implementing the END-IT NH intervention. Randomization of NHs will be performed after the recruitment of NHRs and baseline data collection. Because of the small number of clusters, randomization will not be stratified. The randomization will be computerized and done through REDCap. This step will be performed by a member of the research team involved neither in the recruitment nor in the data collection. Because of the nature of the intervention, blinding will not be feasible.

An overview of the study design and timeline is available in Appendix 3.

Recruitment process and eligibility criteria

Nursing homes

NHs were recruited through previous collaborations and mailing of the official list of existing NHs in Wallonia (French-speaking part of the country). Interested NHs were invited to an online meeting during which the research project was presented, and NHs were asked to confirm interest. Six NHs were then selected, with the aim of maximizing diversity in regards with the type of ownership, localization (rural vs urban) and presence of a specific Alzheimer unit.

Participating NHs will sign a convention with UCLouvain, defining the responsibilities of the NHs, modalities of compensation, recruitment, and data collection. Each NH will receive a financial compensation for their time participating in the study: 40€ per NHR for recruitment and data collection. Intervention group NHs will additionally receive 1500€ for implementing the intervention. The repartition of this compensation will be left to the NH's discretion.

Nursing home residents

To be eligible, NHRs must be aged 65 years and older and be taking at least one benzodiazepine or Z-drug for 4 weeks or longer. Exclusion criteria are: inability to communicate in French, palliative care, ongoing BZRA or alcohol withdrawal, severe anxiety, and severe depression (as clinically judged by GPs and/or nurses). These exclusion criteria were selected to avoid including NHRs for which BZRA deprescribing would not be recommended. The NH staff will establish a list of eligible residents and will approach eligible NHRs using an information letter. Written informed consent will be asked by physicians ((GP) or coordinating physician (CP)) or nurses to each resident or to a resident's representative if the resident is not mentally competent (e.g. in case of severe dementia). For residents who are not able to read or write in French, an impartial witness will assist to the recruitment process. The resident will give consent orally, and the witness will sign the informed consent. No financial compensation will be granted to NHRs for their participation.

Intervention

NH allocated to the intervention group will implement the END-IT NH intervention. The 6 intervention components are summarized in figure 1 and described below. A more detailed description is available elsewhere (29).

1. Process and goals setting: NHs direction and HCPs will be asked to define steps in BZRA deprescribing, and to set goals reachable at the level of their NH. For this purpose, we developed a list of possible steps and goals. This tool has been developed to be operationalized at the level of the NH, meaning that each NH can adapt the steps, add steps, appoint a person responsible for them, and a timeline.
2. Healthcare professionals education: We will provide material for HCPs training in a power point format. This training encompasses information about BZRA side-effects and deprescribing process. Additionally, it prompts HCPs to reflect on pros and cons of deprescribing, and on case vignettes. The training session will be organized at the level of each NH, preferably by the CP, whose role includes staff training.
3. Physical environment adaptation: We will provide NHs with a list of possible adaptations to promote relaxation and sleep, and each NH will be able to choose what adaptations are feasible in their specific context. This tool allows NHs

to appoint responsible staff for adaptations and due date. Adaptations beyond those listed in the document are also possible.

4. Audit and feedback: At the beginning of the intervention and every three months, we will provide NHs with feedback data on BZRA use in their NH. This feedback will be based on the percentage of residents taking at least one BZRA (ATC codes N05CD, N05CF, N05BA or N03AE01), as reported by the NH pharmacist. This percentage will be compared to the percentage of NHRs taking at least one BZRA in a previous study conducted in 54 Belgian NHs (1, 2).

5. NHRs and their relatives' awareness: We will provide an educational leaflet, adapted from the EMPOWER brochure, which has already shown to be effective in BZRA deprescribing (33, 34). The adaptation for the Belgian and NH context was performed with involvement of appropriate stakeholders (HCPs, older adults, NHR) (29, 35). This leaflet encompasses information about BZRA side effects, non-pharmacological alternatives for sleep issues and anxiety, a testimony of a NHR, and an example of an 18-week tapering scheme. NH staff and/or GPs will be in charge of distributing the leaflet to NHRs and/or relatives. NH staff may choose how and when to use this brochure depending on their specific context. For example, the brochure may be used to introduce deprescribing with the NHR, or HCPs may choose to distribute the brochure to all NHRs they think might benefit from it. In the context of residents with dementia, it is expected that relatives will be more involved.

6. Multidisciplinary work: Our intervention will promote multidisciplinary review of BZRA indications and opportunities for deprescribing. We developed a multidisciplinary opinion document to enable communication between NH staff and GPs, if GPs do not attend multidisciplinary meetings. This tool enables NH staff to report potential BZRA side-effects to the GP, and to suggest changes in prescriptions or non-pharmacological approaches. The GP can respond on the same document. As for other intervention components, the NH will have flexibility in how they organize the multidisciplinary meetings and use the multidisciplinary opinion document.

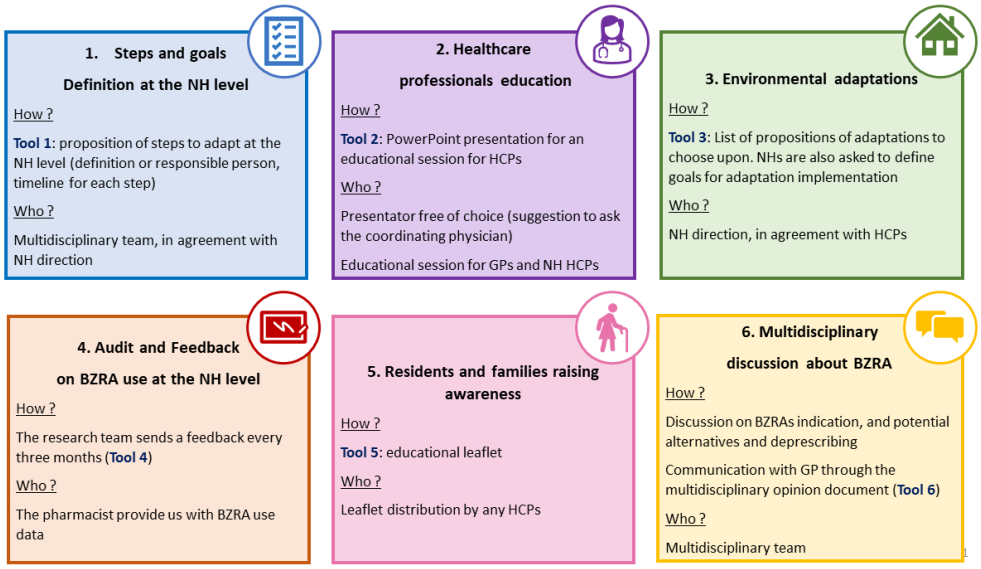


Figure1: Summary of the intervention components
Legend: BZRA= benzodiazepine receptor agonists, GP= general practitioner, HCP= healthcare professional, NH= nursing home

Control

NHs in the control group will keep working as usual. After the 6-month data collection, they will have access to the intervention material.

Measures

1. *Feasibility of intervention implementation*

Our plan to evaluate the feasibility of the intervention follows the approach for process evaluations recommended by the MRC guidance (36). We will collect information to better explore implementation fidelity, mechanisms of impact and contextual factors at patient-level, NH-level and HCP-level, using both quantitative and qualitative measures. First, we will assess implementation fidelity that refers to the degree to which an intervention or a programme is delivered as intended (37). According to the conceptual framework for implementation fidelity developed by Carroll et al., two essential aspects will be measured: **adherence** which is "how far

those responsible for delivering an intervention actually adhere to the intervention as it is outlined by the developers" and **participants' responsiveness** to the intervention which is "how far participants respond to, or are engaged by, an intervention" (37). Second, we will evaluate the mechanisms of impact, that is how the effects of the intervention occurred. And finally, we will assess how different elements of context can influence participant's responsiveness and adherence to the intervention as well as mechanisms of impact.

In addition to the quantitative data collection (see Table 1), two semi-structured interview guides, with open-ended questions and predefined major themes will be discussed with residents and HCPs. These themes have been identified to investigate the TDF domains targeted by the intervention. All interviews will be audio-taped, and the verbatim will be transcribed before analyses.

2. Feasibility of the study design

The feasibility of the study design will be evaluated through 4 aspects detailed below. First, while recruiting residents, NHs will be asked to record age and sex of approached residents, and whether the patient agrees, disagrees, or gives no answer regarding potential participation in the trial. These records will allow the estimation of the recruitment rate and of differences between participants and non-participants. NHs will also have to evaluate the necessary time for recruitment. Second, retention of participants will be assessed at each of the data collection points. We will record the number of study withdrawals along with the reasons for withdrawal, patients lost to follow-up, and deaths. Third, data will be collected in both study arms as they would be in a full implementation trial in order to assess the rate of missing data. Finally, we will also ask NHs study coordinators to complete a satisfaction survey, regarding the study process. This survey has been adapted from Smailes et al. 2016 (38).

3. Exploratory cost-effectiveness evaluation

A specified economic component will evaluate the feasibility of collecting data on resource use, health, and non-health-related benefits. More specifically, it will check the completeness and the ability to obtain data on quality of life using the EQ-5D-5L questionnaire and healthcare use from patients in the target population to allow estimation of healthcare costs (39). Information on resource

use will be obtained at three months and six months and combined with reference prices to measure the total healthcare costs for the treatment and control groups. The costs of medications will be estimated afterward based on the average national drug cost.

Data collection and management

Quantitative data

Three quantitative data collection points are planned: baseline, 3 months, and 6 months (end of the study). The types of data collected and the timeline are summarized in Table 1.

Table 1: Overview of quantitative data collected and time schedule					
			Data collection point		
Measure	Data collected/Instrument for data collection	Data source	Baseline	3m o	6 mo
Feasibility of intervention implementation					
Implementation fidelity					
Adherence at the NH level	Organisation of educational sessions for HCPs; Number of environmental adaptations implemented; Number of residents' brochures distributed; Number of included residents for whom BZRA was discussed in multidisciplinary meetings; Global number of implemented intervention components (0 to 6)	Intervention logs filled by NHS			X
HCPs' responsivenes s	Attendance to educational and multidisciplinary meetings; Number of multidisciplinary opinions sent to the GP and responded to by GP	Intervention logs filled by NHS			X
Patients' responsivenes s	Number of BZRA deprescribing attempts; Reasons for not attempting BZRA deprescribing; Number of BZRA deprescribing success (including dose reduction and complete cessation, and failure); Reasons for deprescribing failure; Switch to another sedative or anxiolytic medication	Intervention logs filled by NHS			X
Mechanisms of impact					
Patients' level mechanisms of impact*	NHRs' self-efficacy regarding BZRA deprescribing (Medication reduction self-efficacy scale, 1 item); knowledge regarding BZRA (5 items); intention regarding BZRA deprescribing (two global items of the rPATD-BZRA questionnaire)	NHR	X	X	X
NH's level mechanisms of impact	Quality of interdisciplinary collaboration (16 items, adapted from Orchad et al., 2018 (40))	HCPs	X	X	X

HCPs level mechanisms of impact	HCPs' perceived knowledge (4 items), skills (1 item), beliefs about capability (3 items), and prioritization (2 items) regarding BZRA deprescribing (Shapoval et al., in preparation)	HCPs	X	X	X
Contextual factors					
Patients-level contextual factors	Quality of life: EuroQol 5-Dimension Questionnaire (EQ- 5D- 5L)# (41) ; Length of BZRA intake; Main reason for BZRA intake; Number of previous deprescribing attempt	NHR or relative	X		
	Diagnostic of dementia	MR	X		
NH-level contextual factors	Type of NH ownership; Presence of a specific Alzheimer's unit; Use of automatized dispensing system; Existence of a collaboration between the NH and a geriatric team	NHS	X		
	Quality of interdisciplinary collaboration (16 items evaluated on a 5-points Likert scale)	HCPs	X		
Feasibility of study design					
Recruitment process	Time for NHR recruitment	NHS	X		
	Rate of NHRs' study participation acceptation	NHS	X		
Attrition rate	Rate of participants lost to follow-up	/			X
Data collection	Rate of missing data for patient-centred data	/			X
NH satisfaction with study process	Satisfaction survey, (10 items, adapted from Smailes et al. 2016 (38))	NHS			X
Additional patient-centred outcome					
Socio-demographic data	Age, gender, educational level, time since NH entry, MRS/MRPA status	NHR or relative, and MR	X		
Quality of life	EuroQol 5- Dimension Questionnaire (EQ- 5D- 5L)# (41)	NHR or relative	X	X	X
Quality of sleep*	Insomnia Severity Index# (ISI) (42)	NHR	X	X	X
Anxiety*	Geriatric Anxiety Inventory – short form# (43)	NHR	X	X	X

Patient's attitudes towards BZRA deprescribing*	rPATD-BZRA questionnaire[#] (44)	NHR	X		X
Comorbidities	History of dementia, delirium, fall	MR	X	X	X
Medication use	Number of regular medications, BZRA, other psychotropics (ATC codes N05, N06 and N02), and over-the-counter sleep or anxiety medication use (specialty used, dosage, frequency of use)	MR	X	X	X
Health-economic evaluation					
Sleep and Anxiety medication cost	BZRA and BZRA alternatives use and cost	MR	X	X	X
Healthcare use and available costs	Number of visits to the general practitioner, a specialist, a psychologist, or the emergency department; Any hospitalization (and length of stays); Falls	MR		X	X
Intervention cost	Budget allocated to the environmental adaptations in the NH	Intervention logs filled by NH staff			X

Legend: BZRA= Benzodiazepine Receptor Agonist, **GP=** General practitioner, **HCP=** Healthcare provider, **MR=** Medical record, **NH=** nursing home, **NHR=** nursing home resident, **NHS=** nursing home staff
MRS/MRPA status stands for "Maison de repos et de soin », or « Maison de repos pour personnes âgées », in French. This reflects the level of dependency and of care need of the resident.
*: Data not collected in residents with dementia
[#]: copyright license and rights were obtained to use these questionnaires

All data will be collected by one member of the research team, or by a study nurse/job student trained by the research team, at the site of the NH. Data on NHRs will be collected from the medical record and also directly from residents, using questionnaires. Proxy data will be collected from relatives of residents with dementia. Because all questionnaires do not have a version available for relatives, fewer data will be collected in residents with dementia (see Table 1 for details). Additionally, we will collect implementation data from intervention logs, and from questionnaires completed by HCPs and NHs study coordinators. For HCPs

questionnaire, in all participating NH, the NH study coordinator will recruit 4 to 7 HCPs. At minimum, we will ask for the coordinating physician, another GP, and two nurses to participate. These HCPs will give oral consent for participation.

All collected quantitative data will be collected and managed using REDCap electronic data capture tools hosted at UCLouvain (45, 46). REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies.

Qualitative data

Qualitative data will be collected by a trained psychologist, at the end of the study, through interviews with HCPs and NHRs from the intervention group. We will aim at interviewing 2 NHRs and 4 HCPs of each intervention NH. Purposive sampling will be used to ensure a good diversity representation of residents and HCPs included in the study. As an example, we plan on including residents with a long or short history of BZRA intake, and residents with and without successful deprescribing. Cognitively impaired NHRs unable to take part in a 45-minute interview will not be eligible, but their relative could be interviewed if relevant. Eligible HCPs will be approached by our research team and NHRs by HCPs to ask whether they would be willing to take part in a one-to-one 45-minutes interview. NHRs participating in the qualitative study will have to provide a specific written informed consent. HCPs will provide oral consent.

Statistical analysis

Quantitative data will be reported using descriptive statistics. Categorical variables will be expressed as numbers and percentages and continuous variables as mean ± standard deviation or median [P25 – P75] depending on normality assessment. Chi-square test (or Fisher exact test), Student's T test or Mann-Whitney test will be performed to assess differences between intervention and control group regarding patients' characteristics. Assessments will not be blinded. This feasibility study will not be powered to assess the effectiveness of the intervention. BZRA cessation at 6 months as well as BZRA dose reduction will be reported in each group, but no statistical evaluation will be performed on any primary or secondary outcome measure. Lost to follow-up patients or withdrawn patients will be classified with patients that would have failed BZRA deprescribing.

All qualitative interview transcripts will be entered into QSR Nvivo 11 for data analysis. Inductive and deductive thematic analysis will be used to analyse transcripts content. Interviews will mainly be coded into the TDF domains explored in the interview guides. However, new themes or subthemes may be identified inductively from the data. Two coders will individually analyse the first 2 interviews for NHRs and for HCPs. They will meet to compare their coding. If satisfying agreement is reached, the remaining interviews will be coded by a single coder. If not, another 2 interviews will be coded by both coders independently, and coding will again be compared. The above-mentioned method will be used until reaching satisfying agreement, ensuring results reliability and validity.

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 prior a potential full implementation trial.

Regarding the health-economic evaluation, provided that the feasibility of the needed data collection is validated, we will conduct an exploratory cost-effectiveness analysis on completed cases following the recommendations of the Belgian Healthcare Knowledge Centre (KCE) (47). 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 (48). It will estimate patients' quality-adjusted life years (QALYs) and associated costs. Given the findings from the analysis, we will conduct a value of information (VoI) analysis to determine whether future research is worthwhile to assess cost-effectiveness (49). We will also calculate the incremental cost per QALY gain to deprescribing BZRA at six months compared to usual care by dividing the average difference in cost by the average difference in QALYs to generate the incremental cost-effectiveness ratio (ICER). The ICER represents the additional cost per one unit of outcome gained and indicates the trade-off between total cost and effectiveness when choosing between deprescribing BZRA and usual care (39).

All quantitative analyses will be performed using R software (R Foundation for Statistical Computing, Vienna, Austria').

SECTION 3

Patient and Public involvement

NHRs and relatives representatives were involved in the development of the END-IT NH intervention, from the identification of barriers and enablers for BZRA deprescribing to the operationalisation of BCTs into intervention components. Results will be discussed with an advisory board that will include older adults' and carers' representatives in addition to HCPs and policymakers. This advisory board will help make decisions on the opportunity of refining the intervention components and proceeding to a full implementation trial. This advisory board will also be involved in results dissemination.

ETHICS AND DISSEMINATION

This study protocol has been submitted to the ethical committee of the CHU UCL Namur and received approval on the 20th of June 2023 (NUB: B0392023000052).

All data are confidential. Data will only be available to researchers involved in this study and they will be pseudo-anonymized prior to analysis. To do so, a coded number will be attributed to every participant. The correspondence between the coded number and participant's name will be kept in a separate numeric file, protected with a password, and destroyed after 7 years. Following the FAIR Data Principles (or Findable, Accessible, Interoperable, Reusable) recommend data sharing (50), de-identified data will be shared on a data depository (OSF (51)) with a period of embargo of 2 years. The DOI of the dataset will be communicated to the scientific journal to which we will submit the results of this study.

Results of the study will be disseminated through a scientific paper and will be communicated to local stakeholders and policy makers through a local symposium, along with resulting recommendations.

DISCUSSION

This study will evaluate the feasibility of implementing and evaluating our theory-based intervention towards BZRA deprescribing, through a cluster-randomized controlled trial study design. To our knowledge, this is the first study evaluating an intervention specifically developed towards BZRA deprescribing, in French-speaking Belgian NHs. Based on the results of this study, a decision will be

made to move forward or not with a larger-scale intervention effectiveness evaluation. The intervention itself and its methods of delivery might be adapted based on the implementation results, before moving on to the larger scale study. Study design and outcome measures may also evolve, depending on the results relative to study conduction and data collection.

We anticipate difficulties regarding recruitment and data collection process with nursing home residents. Indeed, older adults' recruitment in trials is a challenge that can be impacted by various factors (52, 53). A recent study reported that the three main reasons for older adults to decline participating in a deprescribing trial are (i) feeling overwhelmed by current health status, (ii) lack of interest or mistrust of research, and (iii) hesitancy to participate in a deprescribing study (54). Some of these barriers might be enhanced in the NH setting. The recruitment phase has been reported as the most difficult part of research in NH. NHRs often fail to see how they would benefit from research participation, and obtaining consent from cognitively impaired NHRs or their relatives also appears as a difficulty (55). We chose to have the recruitment process done by HCPs involved in the daily care of the NHRs (general practitioners or nurses), which might reduce NHRs' mistrust. Furthermore, our informed consent form does not mention the word 'deprescribing' but refers to 'reconsidering hypnotics and anxiolytics use'. This will also reduce the risk of recruiting only residents in favor of deprescribing. Regarding the data collection, several outcomes require long questionnaires to be filled with NHRs. Even if these questionnaires have generally been developed for older adults, and because NHRs are generally frailer than the average older adults, we expect that the length of the questionnaires might be an issue. Therefore, depending on the evaluated quality of collected data, questionnaires used might evolve before a larger-scale study. Additionally, to enhance study retention, in case of NHR tiredness, we will shorten data collected with NHRs and only collect data on quality of life.

Recently, Thorpe et al. developed a framework of factors/data that should be taken into consideration when designing an observational deprescribing trial in nursing homes, using routinely accessible data (56). In the Belgian NH context, such routine data are not available. Still, it is interesting to compare the factors they suggest exploring to what we have planned in our prospective design. According to their framework, the following factors should be explored as deprescribing

determinants: Intrapersonal factors (sociodemographic characteristics, condition and medication attributes, prognosis, and co-prescribed medications), Interpersonal factors (Family caregiver level of engagement, and HCPs predisposition to deprescribing), Organizational and Health System factors (facility resources, care coordination), Community factors (geographic patterns of healthcare use and deprescribing), and Policy factors (56). Most of the suggested factors will also be explored in our study. Geographic patterns of the NHs are not collected as such, but we will aim to involve NHs with variation in this regard. Finally, the impact of policies is being studied separately, as part of a broader project on deprescribing. Still, this was evaluated in our qualitative preparative work (23), and might be addressed in the qualitative process evaluation.

This study has several strengths. First, a feasibility study stage is likely to save resources by avoiding engaging in an unfeasible full trial and will enhance the probability of success of the intervention in a future full trial. Second, the design of the trial is as pragmatic as possible, and the intervention implementation is flexible, to enable variations regarding each NH specificities. Third, the intervention and its methods of delivery were developed with insights from theory and stakeholders' involvement, which should enhance its implementation and effectiveness. Finally, the intervention will be implemented at the level of the NH, and the randomization will be clustered, to avoid contamination bias.

This study also has limitations. First, because of the nature of the intervention, blinding of participants will not be feasible. Researchers responsible for data collection will also be aware of group allocation. To minimize the impact of this limitation, the baseline data collection will be performed in each site before randomization. Second, participating NHs are recruited on a voluntary basis and these may have higher awareness and motivation regarding BZRA (de)prescribing than other Belgian NHs. Third, some of the exclusion criteria are based on GPs' and nurses' clinical judgement and not on validated scales. Fourth, as the intervention is complex and includes 6 components, it will not be possible to know which intervention component is responsible for its effect. However, the mixed-method process evaluation will help us understand the impact of the intervention on potential mechanisms of impact. Fifth, potential harms and assessment of causality are not explicitly foreseen in this feasibility trial, but should be addressed in a full trial. Sixth, our intervention is implemented at the NH level, meaning that NHRs

not included in the trial might be exposed to it. However, for ethical reasons we are not able to assess the effects of the intervention on these NHRs. Finally, we did not predefine progression criteria to decide whether to go on with the evaluation in a full trial. Progression criteria, recommended by the MRC framework, "help researchers interpret their pilot trial findings to decide whether, and how, to proceed with a future definitive trial" (57). Defining these progression criteria would have been difficult, as the intervention is a novel combination of components, and its feasibility will partly be evaluated through a qualitative study. Therefore, the decision to move on with a full effectiveness trial will be made by the research team, without a priori defined progression criteria, but taking into consideration recommendations from the advisory board.

Supplemental materials:

Appendix 1: Intervention programme theory

Appendix 2: SPIRIT Checklist

Appendix 3: Study timeline – Recruitment and data collection

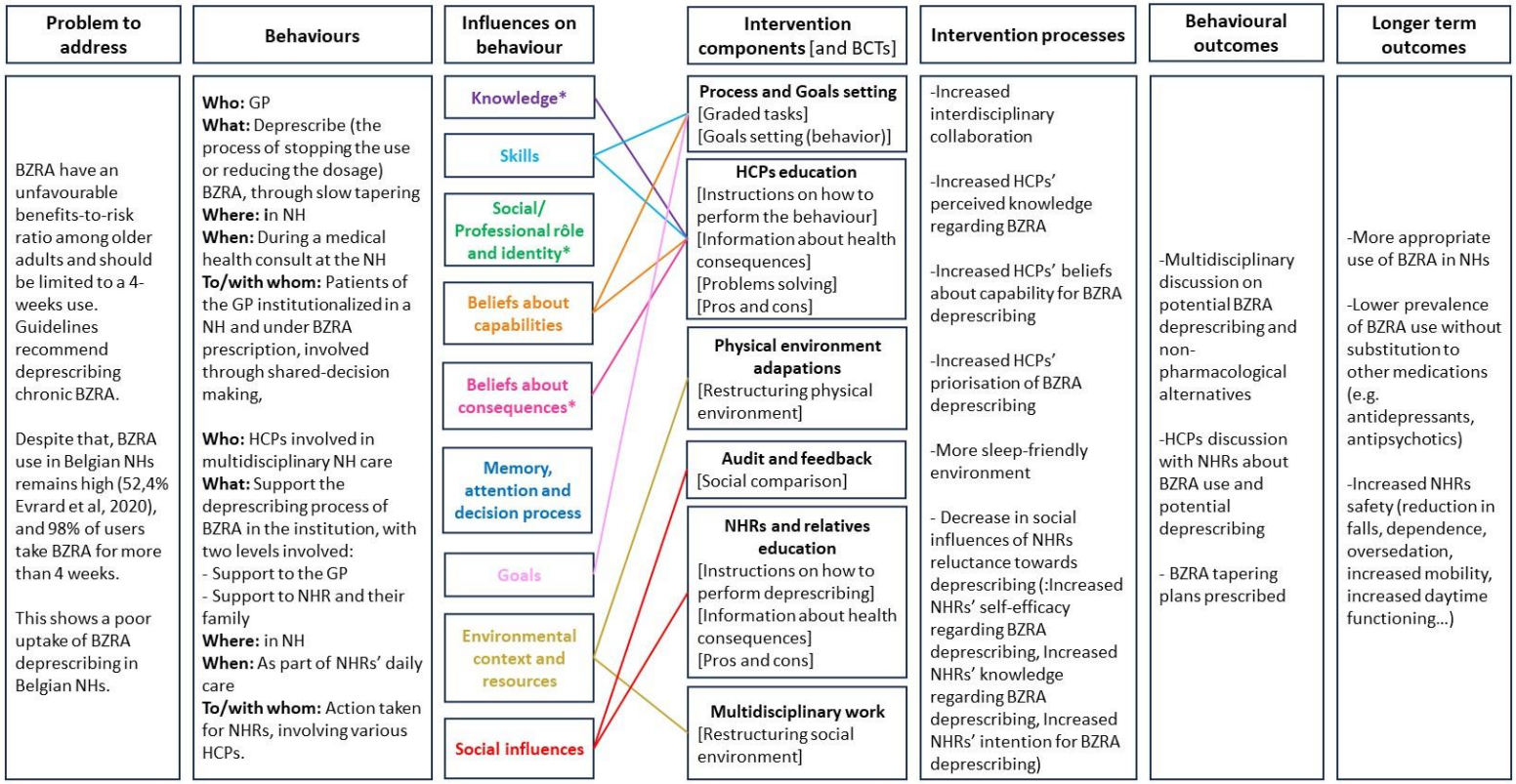
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Appendix 1: Programme theory of the END-IT NH intervention
Notes: BCT = Behaviour change technique, **BZRA** = Benzodiazepine Receptor Agonists, **GP** = General practitioner, **HCP** = Healthcare professional, **NH** = Nursing home, **NHR** = Nursing home resident
*: These domains were identified as most relevant only for HCPs other than general practitioners

Appendix 2: SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section /item	Item No	Description	Location in manuscript
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Chapter page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Abstract and Methods
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	Methods
Funding	4	Sources and types of financial, material, and other support	Fundings
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Chapter page
	5b	Name and contact information for the trial sponsor	Chapter page
	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	Fundings
	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)	NA
Introduction			

SECTION 3

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
	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	End of the introduction section
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, study design, setting and participants
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, study design, setting and participants
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)	Methods, recruitment process and eligibility criteria
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Methods, intervention
	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)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Methods, intervention
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA

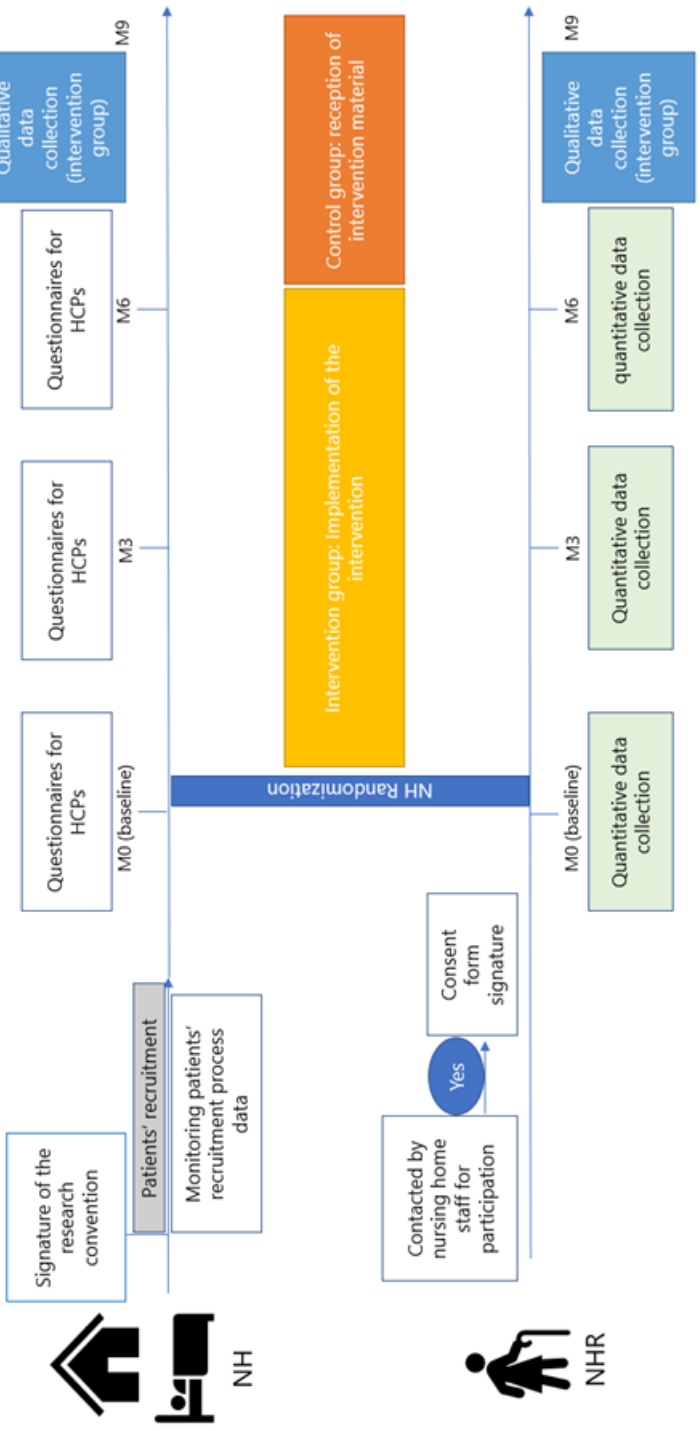
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Methods, Measures,
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)	Appendix 3
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, study design, setting and participants
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	NA
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, study design, setting and participants
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, study design, setting and participants
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Methods, study design, setting and participants

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Methods, study design, setting and participants
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
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	Table 1 Methods, measures
	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	Discussion
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 data management
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, Statistical analysis
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA
	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)	NA
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	NA
	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	NA
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	NA
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Ethics and dissemination
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)	NA
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 process and eligibility criteria
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA

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	Methods, Data collection and management. Ethics and dissemination
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	The authors have no conflict of interest
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
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	NA
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
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available upon 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	NA

*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.



Appendix 3: Study timeline: Recruitment and data collection

Legend: HCP= Healthcare professional, **M=** month, **NH=** nursing home, **NHR=** nursing home resident. Month 0 data collection was considered study baseline

Chapter 6. Partial Results of the END-IT NH study: feasibility of implementing and evaluating the END-IT NH intervention

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Manuscript in preparation (2024)

Authors' contributions:

Conceptualized and designed the study: All authors. Performed data collection, cleaning and initial data analysis: Evrard. Performed data analysis and interpretation: Evrard. Supervised the trial conduction: Spinewine. Wrote the initial draft of the manuscript: Evrard. Critically reviewed and edited the first and subsequent drafts of the manuscript: All authors. Critically revised the manuscript and read and approved the final manuscript: All authors.

Funding:

The present work is supported by EBPpracticenet (Projet d'implémentation EBPpracticenet 2023); by a research credit from the fond national de recherche scientifique (FNRS) (CDR40013898); 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.

Acknowledgements:

The authors thank Ms. Monineat Cheap and Ms. Anita Moghadam Far for their help in data collection. The authors would also like to thank the nursing homes, nursing home residents, and healthcare professionals who participated in this study.

ABSTRACT

BACKGROUND. Despite previous calls towards benzodiazepine receptor agonists (BZRA) deprescribing, prescribing rates in Belgian nursing homes (NHs) remain above 50%. We therefore developed a theory-based complex intervention towards BZRA deprescribing in the specific context of Belgian NHs. The END-IT NH intervention encompasses 6 components: process and goals setting, healthcare professionals' education, physical environment adaptations, audit and feedback, nursing home residents (NHRs) awareness raising, and multidisciplinary work.

OBJECTIVES. To evaluate the feasibility of implementing the END-IT NH intervention, and the feasibility of evaluating the effectiveness and cost-effectiveness.

METHODS. We conducted a cluster-randomized controlled trial in 6 voluntary NHs, with 10 to 15 NHRs included per NHs. 4 NHs were allocated to the intervention group, and 2 to the control group (usual care). Data collection occurred at baseline, 3 months, and 6 months (study end). The feasibility of the study conduction was assessed by measuring recruitment and attrition rates and completeness of data collection. Implementation fidelity, mechanisms of impact and contextual factors at patient-level, NH-level and healthcare professional-level, were assessed through both quantitative and qualitative measures. In this chapter, we present the results of the feasibility of study conduction and partial results of the feasibility of implementing the intervention, namely the quantitative evaluation of the implementation fidelity.

RESULTS. 66 NHRs agreed to participate. 5 NHRs dropped out before baseline data collection, leaving 45 NHRs in intervention group, and 16 in the control group. Study retention rate was 81%. Rates of missing data differ between the different measures, and ranged from 2% to 70%. The number of intervention components implemented per intervention NH ranged from 2 to 5. We observed a reduction of BZRA dosage or a complete BZRA cessation in 14 (31.1%) NHRs of the intervention group, and 2 (12.5%) NHRs of the control group.

CONCLUSION. These preliminary results show that the END-IT NH intervention is feasible, but implementation varies greatly between NHs. This calls for further investigations of the contextual factors impacting the implementation, and for

future refinement of the intervention. The overall study design appears to be feasible, but the relevance of some measures needs to be rediscussed, to shorten the length of data collection, and to reduce rates of missing data.

CHAPTER 6

INTRODUCTION

This chapter presents partial results of the END-IT NH study described in Chapter 5. This study was a cluster randomized controlled trial (RCT) of the END-IT NH intervention (summarized in Figure 1), aiming at enhancing the uptake of benzodiazepine receptor agonists (BZRA) deprescribing in Belgian nursing homes (NHs).

More precisely, this chapter elaborates on the two first aims of the END-IT NH study:

1. To assess the feasibility of conducting a larger cluster RCT to evaluate effectiveness and cost-effectiveness of the END-IT intervention.
2. To evaluate the feasibility of implementing the END-IT intervention in Belgian nursing homes

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. Therefore, neither of these analyses is presented in this manuscript.

METHODS

The complete methodology is presented in Chapter 5. The trial has been conducted between July 2023 and February 2024.

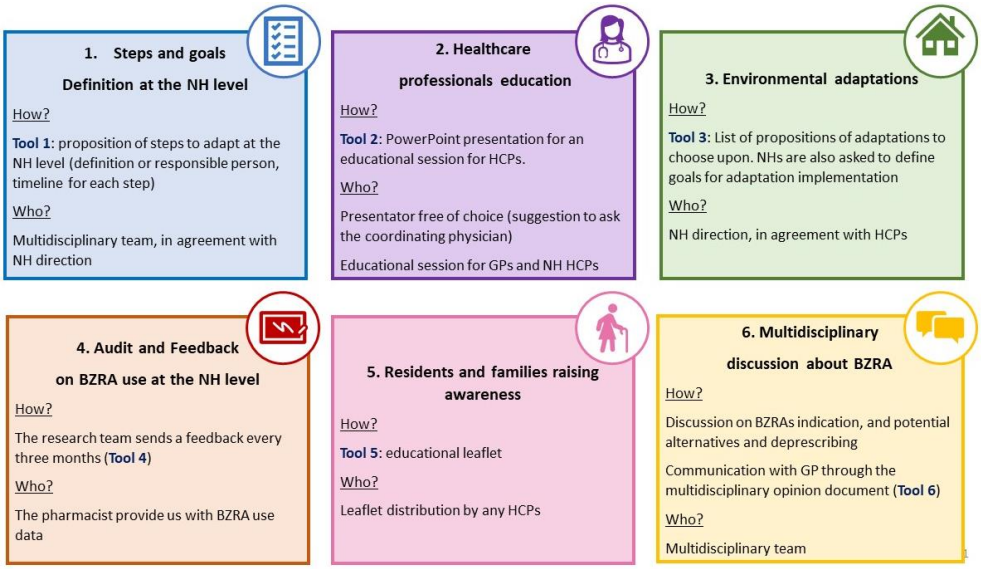


Figure1: The END-IT NH intervention; a 6-component complex intervention

Legend: BZRA: Benzodiazepine Receptor Agonists, GP: General Practitioner, HCP: Healthcare Professionals, NH: Nursing Home

RESULTS

Feasibility of conducting a larger cluster RCT

Study recruitment and retention rate

Eleven nursing homes (NHs) indicated interest in study participation. Among these, the research team selected 6 NHs with maximum variation with regards to ownerships status, size, localization (rural vs urban), and presence of a specific Alzheimer unit. After baseline data collection, 4 NHs (with 45 NHRs) were randomized in the intervention group, and 2 NHs (with 16 NHRs) were randomized into the control group. Characteristics of the NHs in each group are presented in Table 1.

Table 1: Characteristics of included nursing homes			
	Total population (N=6)	**Intervention group (N= 4)**	**Control group (N=2)**
Type of nursing home *n(%)*			
Public	3 (50.0)	2 (50.0)	1 (50.0)
Private, non-for-profit	1 (16.7)	0 (0)	1 (50.0)
Private, for profit	2 (33.3)	2 (50.0)	0 (0)
Localisation *n(%)*			
Rural	4 (66.7)	2 (50.0)	2 (100)
Urban	2 (33.3)	2 (50.0)	0 (0)
NH size (number of beds)			
Median	132	132	176,5
(range)	(50; 255)	(50; 154)	(98; 255)
Established collaboration with a geriatric team			
n(%)	4 (66.7)	3 (75.0)	1 (50.0)
Presence of a specific Alzheimer unit			
n(%)	4 (66.7)	2 (50.0)	2 (100)
Use of automated dispensing system for drugs			
n(%)	6 (100)	4 (100)	2 (100)

In the 6 NHs, overall, 108 nursing home residents (NHRs) were identified as potentially eligible. Among these, 66 (61.1%) agreed for study participation. In each NH, recruitment took 8 to 29 days (median: 9 days). We found no difference between study participants and NHRs refusing participation regarding age and gender. However, rate of acceptance significantly differed between NHs, and whether the agreement was asked to the resident himself or a relative (for residents with dementia) (Table 2).

Table 2: Comparison of residents who agreed vs residents who refused study participation			
	Agreed participation (N=66)	**Refused participation (N=42)**	**p-value***
Population Characteristics			
Age**			
Median [IQR]	87 [79.25; 90.0]	88 [81; 92.25]	0.174
Female gender			
n(%)	46 (69.7)	32 (76.2)	0.463
Person asked for agreement to participate in the study			
Resident	55 (83.3)	28 (66.7)	**0.045**
Relative	11 (16.7)	14 (33.3)	
NH identifier			
1	10 (15.1)	4 (9.5)	**<0.001**
2	15 (22.7)	4 (9.5)	
3	11 (16.7)	3 (7.1)	
4	14 (21.2)	0 (0)	
5	5 (7.6)	14 (33.3)	
6	11 (16.7)	17 (40.5)	
Legend: NH= nursing home *: Pearson chi-square test, Fisher test, or Mann-Whitney test **: 2 missing data			

Five NHRs dropped out before baseline data collection, resulting in a final population study of 61 NHRs. Fifty-five NHRs completed the study (83% retention rate, See Figure 2 for study Flowchart). We did not collect data on reasons for study participants' death, however, we were not made aware of any death related to either the intervention or BZRA deprescribing.

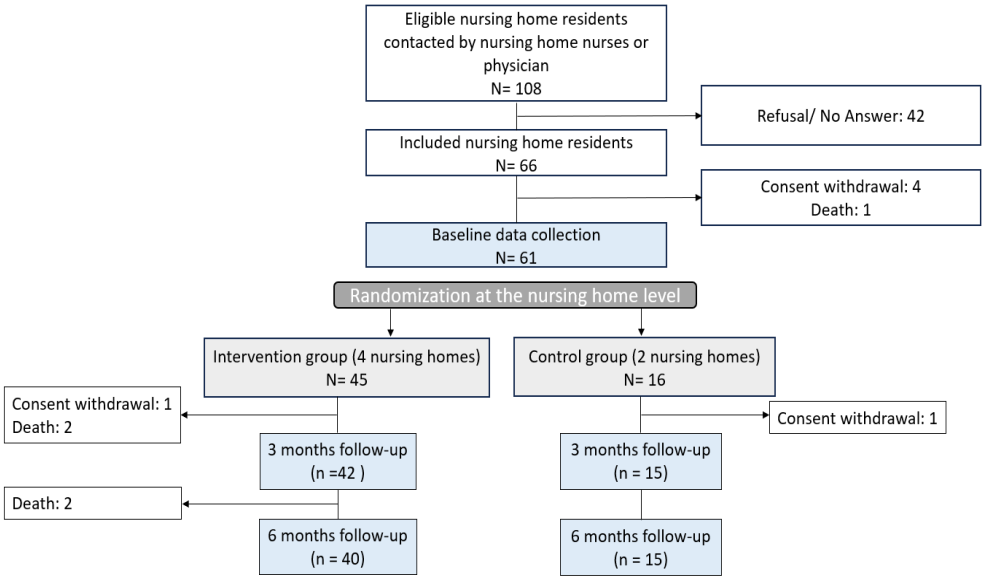


Figure 2: END-IT NH study flowchart

Among the 61 participating NHRs, 67.2% were female, median age was 87.5, and median number of medications taken per day was 11 (Table 3). Approximately two thirds of NHRs took only one BZRA and one third took at least two BZRA. The most NHR reported reasons for BZRA intake were insomnia (50.8%) and insomnia and anxiety equally (23.0%). Most prescribed BZRA was lorazepam, followed by lormetazepam, alprazolam, and zolpidem. When measured through the insomnia severity index (1), and the geriatric anxiety inventory- short form (2), respectively 12.2% and 34.8% of NHRs suffered from insomnia and anxiety. We did not find any difference between groups regarding NHRs socio-demographic characteristics and baseline benzodiazepine receptor agonists (BZRA) prescribing patterns. Baseline quality of life (measured through the EQ5D-5L questionnaire (3)), insomnia proportion, and anxiety proportion also were similar between groups. However, history of falls was significantly more prevalent in the intervention group (Table 3).

Table 3: Study Population characteristics and BZRA use historic in the intervention and the control group			
	Total population (N=61)	**Intervention group (N=45)**	**Control group (N=16)**
Population Characteristics			
Age*			
Median [IQR]	87.5 [78.75; 90]	88 [82.75; 90.25]	85 [75.5; 89.25]
Gender* *n(%)*			
Female	41 (67.2)	29 (64.4)	12 (75.0)
Bed status *n(%)*			
MRPA	41 (67.2)	29 (64.4)	12 (75.0)
MRS	20 (32.8)	16 (35.6)	4 (25.0)
Length of stay at the NH* *n(%)*			
< 1 month	0 (0)	0 (0)	0 (0)
1 month < x ≤ 6 months	6 (9.8)	4 (8.9)	2 (12.5)
6 months x ≤ 1 year	10 (16.4)	7 (15.6)	3 (18.8)
>1 year	44 (72.1)	33 (73.3)	11 (68.7)
Higher achieved educational level* *n(%)*			
Newer went to school	2 (3.0)	1 (2.2)	1 (6.2)
Primary school/ Middle school	30 (45.5)	22 (48.9)	8 (50.0)
Highschool	16 (24.2)	13 (28.9)	3 (18.8)
University or equivalent	12 (18.2)	8 (17.8)	4 (25.0)
Number of medicines taken			
Median [IQR]	11 [8; 13]	11 [8; 13]	10.5 [8.75 ; 13]
Dementia			
n(%)	16 (26.2)	10 (22.2)	6 (37.5)
History of falls			
n(%)	35 (57.4)	30 (66.7)	5 (31.3)
Baseline quality of life (EQ5D-5L)**			
Median [IQR]	0.59 [0.27; 0.78]	0.56 [0.26; 0.78]	0.60 [0.26; 0.78]
Baseline insomnia (ISI≥10)***			
n(%)	5 (12.2)	4 (13.8)	1 (8.3)
Baseline anxiety (GAI-SF ≥3)****			
n(%)	16 (34.8)	13 (39.4)	3 (23.1)

Table 3 (continued) **BZRA prescribing patterns**			
Number of prescribed BZRA n(%)			
1	40 (65.6)	28 (62.2)	12 (75.0)
2	19 (31.1)	15 (33.3)	4 (25.0)
3	2 (3.3)	2 (4.4)	0 (0)
Duration of use* n(%)			
< 6 months	1 (1.6)	1 (2.2)	0 (0)
≥ 6 months and < 1 year	6 (9.8)	5 (11.1)	1 (6.2)
≥ 1 year	48 (78.7)	33 (73.3)	15 (93.8)
Doesn't remember	5 (8.2)	5 (11.1)	0 (0)
Main reason for currently taking BZRA, reported by NHR* *n(%)*			
Insomnia/ sleep issues	31 (50.8)	22 (48.9)	9 (56.2)
Anxiety/ Stress	8 (13.1)	4 (8.9)	4 (25.0)
Anxiety and Insomnia equally	14 (23.0)	12 (26.7)	2 (12.5)
Other	3 (4.9)	2 (4.4)	1 (6.3)
Doesn't know	4 (6.6)	4 (8.9)	0 (0)
Previous attempts for BZRA deprescribing, reported by NHR* *n(%)*			
0	36 (59.0)	27 (60.0)	9 (56.2)
1	7 (11.5)	4 (8.9)	3 (18.9)
2 or more	4 (6.6)	3 (6.7)	1 (6.3)
Doesn't remember	12 (19.7)	9 (20.0)	3 (18.3)
Most prescribed BZRA *n(%)*			
lorazepam	19 (31.1)	15 (33.3)	4 (25.0)
lormetazepam	15 (24.6)	10 (22.2)	5 (31.3)
alprazolam	13 (21.3)	8 (17.8)	5 (31.3)
zolpidem	10 (16.4)	9 (20.0)	1 (6.3)

Legend: BZRA= Benzodiazepines Receptors Agonists (ATC N03AE01, N05BA, N05CD and N05CF), **MRPA**= Maison de repos pour personnes âgées, **MRS**= Maison de repos et de soin, **NH**= Nursing home, **NHR=** Nursing home resident
*: **1** missing data
**: EQ-5D-5L score calculated only for residents (or relatives) that answered all 5 items N=57 (intervention group:42, control group:15)
***: ISI score calculated only for residents without cognitive impairment, who answered all 7 ISI questions N=41 (intervention group:29, control group: 12)
****: GAI-SF score calculated only for residents without cognitive impairment, who answered all 5 GAI-SF questions N=46 (intervention group:33, control group: 13)

Quality of collected data

Quantitative data were collected from four different sources: patient medical records, questionnaires with NHRs or relatives (for NHRs with cognitive impairment), questionnaires with healthcare providers (HCPs), and intervention logs. Regarding questionnaires with residents, depending on the variables/instruments and on the data collection point, rate of missing data ranged from 2 to 50% (Table 4). According to the protocol, our retention strategy was to prioritize EQ5D5L with NHRs too tired or not willing to fill in all questionnaires. Rate of missing data in the EQ5D5L ranged from 4.0 to 6.3%. Although the questionnaire length was shorter with relatives, rate of missing data was higher. At both 3 months and 6 months, 4 questionnaires from relatives were missing. According to statistical guidances, a bias is likely when the rate of missing data exceeds 10%, and analysis conducted with more than 40% missing data should be interpreted cautiously, only to generate hypothesis (4). The rates of missing data are therefore presented in Table 4 with regards to these cutoffs. Over the 6 NHs, 33 HCPs agreed to complete questionnaires. All questionnaires were filled at baseline, but 5 were missing at 3 months, and 4 at 6 months. From medical records, researchers easily collected prescribed medications but had issues collecting data on healthcare use and related costs. Indeed, these were inconsistently reported between NHs and between NHRs. Costs often were unavailable. Finally, reporting on intervention logs was not consistent among NHs and was sometimes lacking.

Satisfaction with study participation

We received satisfaction surveys from identified partners in all 6 NHs. This showed an overall good satisfaction from NH partners. Detailed results are presented in Figure 3.

Table 4: Rate of missing data for measures collected through Residents and Relatives questionnaires						
	Patients with at least one missing value for the variable or instrument (n (%))					
	Baseline		3-month		6-month	
	Residents answering (N=50)	Relatives Answering (N=11)	Residents answering (N=47)	Relatives answering (N=10)	Residents answering (N=46)	Relatives answering (N=9)
Variables or instruments						
Socio-demographic data (6 items)	1 (2.0)	1 (9.1)	/	/	/	/
BZRA use history (3 items)	2 (6.0)	0 (0)	/	/	/	/
EQ5D-5L (5 items)	2 (4.0)	2 (18.2)	2 (4.3)	6 (60.0)	3 (6.5)	5 (55.6)
Visual Analogic Scale (1 item)	7 (14.0)	1 (9.1)	4 (8.5)	7 (70.0)	8 (17.4)	4 (44.4)
ISI (7 items)	9 (18.0)	/	11 (23.4)	/	12 (26.1)	/
GAI-SF (5 items)	4 (8.0)	/	9 (19.1)	/	7 (15.2)	/
rPATD-BZRA (13 items) *	15 (30.0)	/	6 (12.8)	/	20 (43.5)**	/
Knowledge (5 items)	25 (50.0)	/	15 (31.9)	/	23 (50.0)	/
Self-efficacy (1 item)	11 (22.0)	/	11 (23.4)	/	20 (43.5)**	/

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)
*: Only 2 items at 3-month
**: 5 missing values are due to the non-administration of these questionnaires to patients that stopped their BZRA
/: NA: questions not asked at that data collection point or to this population.
Green: Rate of missing data <10%
Orange: Rate of missing data ≥10% and <40%
Red: Rate of missing data ≥40%

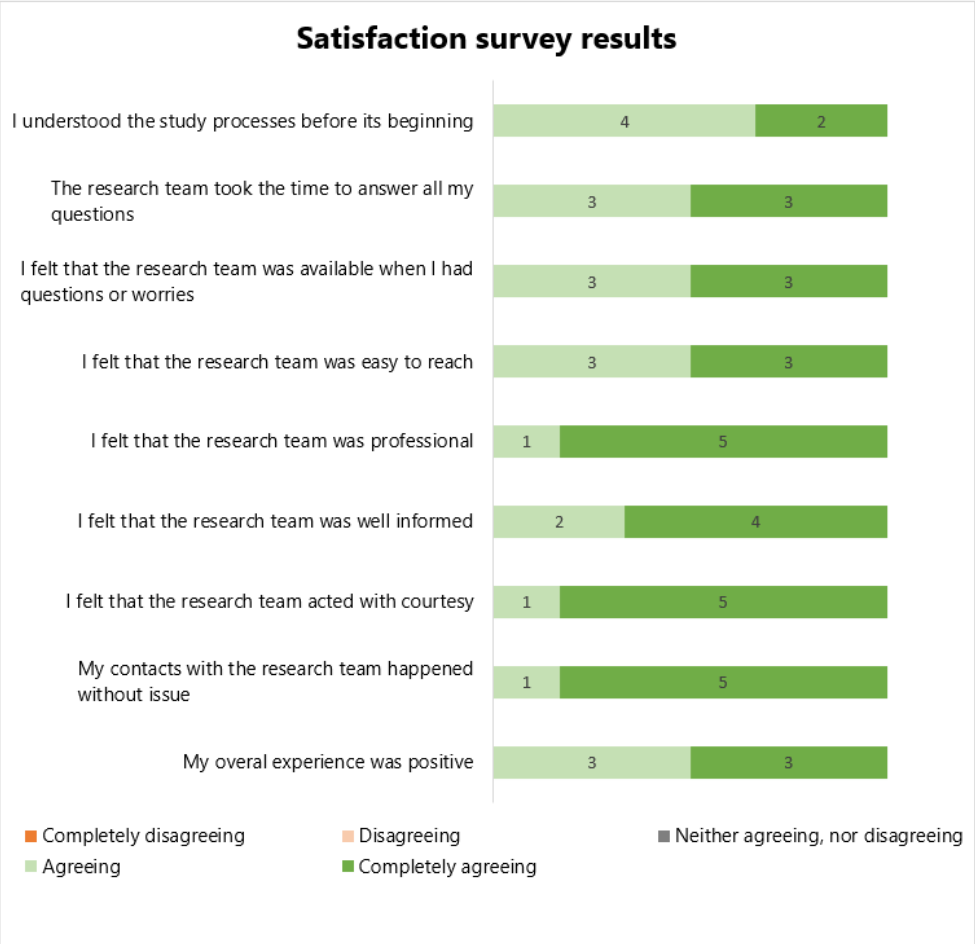


Figure 3: Results from the satisfaction survey with NH partners (N=6)

Feasibility of implementing the END-IT NH intervention

Intervention implementation fidelity

We evaluated the intervention implementation fidelity, which is the degree to which an intervention or a programme is delivered as intended (5). Two essential aspects were measured: **adherence,** which is "how far those responsible for delivering an intervention actually adhere to the intervention as it is outlined by the developers"; and **participants' responsiveness** to the intervention, which is "how far participants respond to, or are engaged by, an intervention" (5). Table 5A presents data on adherence at the NH level and HCPs responsiveness. Table 5B presents data on responsiveness at the NHRs level.

Overall, the number of intervention components implemented per NH ranged from 2 to 5 (on 6 components). Only two intervention components were implemented in all intervention NHs: the distribution of NHRs' and relatives' leaflets, and the audit and feedback. However, the research team also encountered issues in obtaining data from pharmacists to elaborate the audit and feedback document, partly because two NHs changed of pharmacist during the study. Therefore, one NH received one Audit and feedback less than planned. HCPs education session was organized in three NHs. Profiles of HCPs attending these sessions were the following: Coordinating physicians (in 3 NHs), general practitioner (2 NHs), nurses and/or head nurses (3 NHs), care aid (1 NH), Physical therapist (1 NH), animators (1 NH), psychologist (1NH), and NH director (1 NH). Only one NH reported the implementation of environmental adaptations (such as optimization of urinary protection absorption capacity). Still two other NHs reported some level of reflexions on future/ongoing adaptations. Multidisciplinary meetings were only reported in 2 NHs and for 7 (15.6%) of NHRs. However, discussions with NH collaborators suggest that multidisciplinary work happened for more NHRs, but in informal processes. This will have to be confirmed through the qualitative data collection of our study.

Table 5A: Intervention implementation – Adherence at the NH level and HCPs' responsiveness					
Measures	**Total: N NHs = 4 N NHRs = 45**	NH 1 (N NHRs=9)	NH 2 (N NHRs= 14)	NH 3 (N NHRs=10)	NH 4 (N NHRs = 12)
1st intervention component: Goals and steps setting					
NHs that set steps and goals *n(%)*	3 (75.0)	No	Yes	Yes	Yes
2nd intervention component: Educational meeting for HCPs					
NHs that organised the HCP educational meeting *n(%)*	3 (75.0)	No	Yes	Yes	Yes
Choice of session presenter		/	Head nurse	Coordinating physician	Coordinating physician
Number of HCPs attending *[Min; Max]*	[9;22]	/	22	14	9
Number of NH for which this type of HCP was present *n(%) (N=4)*					
Coordinating physician	3 (75.0)	/	Yes	Yes	Yes
General practitioner	2 (50.0)	/	/	Yes	Yes
Nurse / Head nurse	3 (75.0)	/	Yes	Yes	Yes
Care aid	1 (25.0))	/	Yes	/	/
Pharmacist	0 (0.0)	/	/	/	/
Physical therapist	1 (25.0)	/	Yes	/	/
Animators	1 (25.0)	/	Yes	/	/
Psychologist	1 (25.0)	/	/	/	Yes
NH director	1 (25.0)	/	Yes	/	/
3rd intervention component: Environmental adaptations					
Number of environmental adaptations implemented *[Min; Max]*	[0;4]	0	4	0	0
4th intervention component: Audit and feedback					
Number of Audit and Feedback document sent per NH *[Min; Max]*	[2;3]	3	2	3	3
5th intervention component: NHRs and relatives raising awareness					
Number of NHRs for which the education leaflet was distributed *n(%)*	37 (82.2)	9 (100)	13 (92.9)	6 (60)	9 (75)
6th intervention component: Multidisciplinary approach					
Number of NHRs for which a multidisciplinary meeting was organized *n(%)*	7 (15.6)	0 (0)	0 (0)	2 (20)	5 (41.7)

Number of NHR for whom this type of HCP was present *n(%)*					
General practitioner	7 (15.6)	/	/	2 (20)	5 (41.7)
Nurse	7 (15.6)	/	/	2 (20)	5 (41.7)
Care aid	3 (6.7)	/	/	0	3 (25)
Psychologist	5 (11.1)	/	/	0	5 (41.7)
Number of multidisciplinary opinion documents sent	0	0	0	0	0
Overall intervention implementation					
Total number of intervention components implemented (0 to 6) *[Min; Max]*	[2;5]	2	5	5	5
Legend: HCP= Healthcare Provider, **NH=** Nursing home, **NHR=** Nursing home resident					

Table 5B: Intervention implementation – Responsiveness at the NHRs level					
Measures	**Total: N NHRs = 45**	NH 1 (N NHRs=9)	NH 2 (N NHRs= 14)	NH 3 (N NHRs=10)	NH 4 (N NHRs = 12)
BZRA deprescribing					
Deprescribing: chronic BZRA cessation or dose reduction at 6 months *n(%)*	14 (31.1)	0 (0)	1 (7.1)	6 (60)	7 (58.3)
Deprescribing: minimum BZRA dose reduction of 25% at 6 months *n(%)*	12 (26.7)	0 (0)	1 (7.1)	5 (50)	6 (50)
Complete chronic BZRA cessation *n(%)*	7 (15.6)	0 (0)	1 (7.1)	3 (30)	3 (25)
Reasons for not attempting BZRA deprescribing (if reported)					
NHR's refusal	3	0	0	1	2
Unstable NHR health status	1	0	0	1	0
Ongoing change of general practitioner	1	0	0	0	1
BZRA deprescribing failure *n(%)*	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
BZRA alternatives, as reported on intervention logs					
Implementation of non-pharmacological approaches *n(%)*	1 (2.2)	0 (0)	0 (0)	1 (10)	0 (0)
Reported switch to another medication *n(%)*	1 (2.2)	0 (0)	0 (0)	1 (10)	0 (0)
Legend: BZRA= Benzodiazepine receptor agonists, **NH=** Nursing home, **NHR=** Nursing home resident					

We also asked HCPs from the intervention group to rank their level of agreement with the following sentence: "The intervention implementation brought me a considerable work overload". Responses varied greatly between respondents (Figure 4). It is possible that the answer depends on HCPs' role. However, our sample size is too low to allow further exploration.

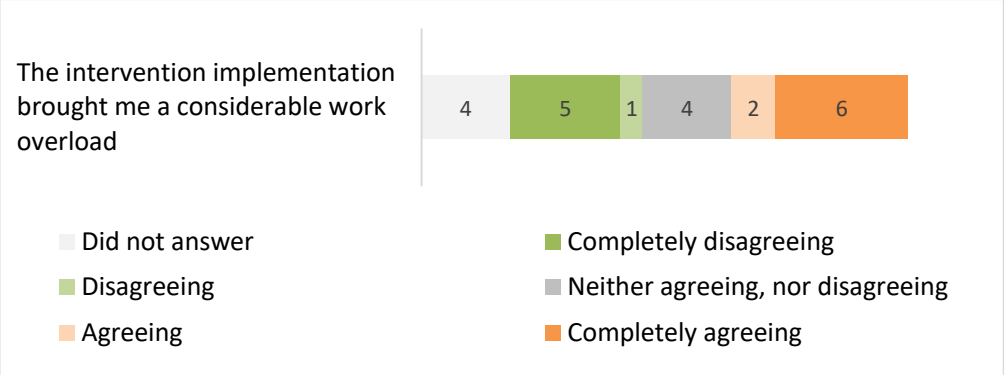


Figure 4: Healthcare professionals' perception of intervention implementation workload

Regarding NHRs responsiveness, BZRA deprescribing, defined as chronic BZRA cessation or dose reduction, occurred in 14 (31.1%) NHRs. The rate of deprescribing varied greatly between NHs, from 0% to 60%. Using a stricter definition for deprescribing (minimum dose reduction of 25%), we observed deprescribing in 12 (26.7%) of NHRs. Complete dose reduction occurred in 7 (15.6%) NHRs. Reasons for not attempting BZRA deprescribing were too poorly reported (Table 5B). Switch to another medication (trazodone) was reported for one NHR.

Exploratory analyses of the efficacy of the intervention on BZRA deprescribing

BZRA deprescribing rate at 6 months was compared between the two study groups, using two deprescribing definitions (Table 6). Because of the very low sample size of this study, these results are only presented for descriptive purposes, but no statistical analyses were performed**.** Deprescribing (chronic BZRA cessation or dose reduction) occurred in 14 (31.1%) NHRs in the intervention group, and in 2 (12.5%) NHRs in the control group.

Table 6: Comparison of BZRA deprescribing rate between intervention and control group (N=61)		
BZRA deprescribing measures n(%)	**Intervention group N = 45**	**Control group N = 16**
Deprescribing: Chronic BZRA cessation or dose reduction at 6 months *n(%)*	14 (31.1)	2 (12.5)
Deprescribing: minimum BZRA dose reduction of 25% at 6 months *n(%)*	12 (26.7)	2 (12.5)
Complete chronic BZRA cessation *n(%)*	7 (15.6)	1 (6.3)
BZRA chronic dose augmentation	1 (2.2)	0 (0)
Legend: BZRA= Benzodiazepines Receptors Agonists (ATC N03AE01, N05BA, N05CD and N05CF)		

BZRA withdrawal schedule among NHRs that deprescribe were underreported. Still, we know that 3 NHRs used magistral preparations, even though they are not reimbursed in NHs, but only in the ambulatory setting.

We also looked at the impact BZRA deprescribing might have had on other sedative medications (Table 7). Again, our two groups are too small to draw any conclusion, but our results do not suggest that the intervention leads to increased usage of other medications.

Table 7: Analysis of the effect of BZRA deprescribing (any dose reduction) on other medications (N=61)				
	BZRA deprescribing N= 16		**No BZRA deprescribing N = 45**	
Change in other medications *n(%)*	Chronic dose Increase or drug addition	Chronic dose decrease or drug suppression	Chronic dose Increase or drug addition	Chronic dose decrease or drug suppression
Melatonin	1 (6.3)	1 (6.3)	0 (0)	2 (4.4)
Phytotherapy for sleep issue or anxiety	1 (6.3)	1 (6.3)	1 (2.2)	1 (2.2)
Other complements for sleep issue or anxiety	1 (6.3)	0 (0)	2 (4.4)	0 (0)
Antidepressants (any)	2 (12.5)	4 (25.0)	3 (6.7)	2 (4.4)
Sedative antidepressants	2 (12.5)	1 (6.3)	1 (2.2)	0 (0)
Antipsychotics	1 (6.3)	2 (12.5)	5 (11.1)	1 (2.2)
Opioids	1 (6.3)	0 (0)	4 (8.9)	3 (6.7)
Legend: BZRA= Benzodiazepine receptor agonists. Only mirtazapine and trazodone were counted as sedative antidepressants.				

DISCUSSION

In this cluster-randomized controlled trial conducted among 6 NHs and 61 NHRs, we assessed the feasibility of evaluating the effectiveness of the END-IT NH intervention, and the feasibility of implementing the END-IT NH intervention. We showed that the overall recruitment and retention process of NHRs was good. Regarding the implementation of the intervention, if it appeared feasible, the results varied greatly between NHs.

Study design and outcome measures

The END-IT NH study had a participation rate of 61% and a retention rate of 83%. However, the rate of missing data was high for some measures, such as knowledge regarding BZRA or the rPATD-BZRA. Regarding the measure of knowledge on BZRA, it encompassed 5 affirmations for which NHRs had to state

whether they believed they were true or false. However, many NHRs admitted not knowing the answer, and we had not thought of including "I don't know" as a potential answer. Simply adding this possibility could have greatly reduced the number of missing data on these items. Regarding the rPATD-BZRA, several issues arose. First the questionnaire was too long and complicated for some NHRs. Second, they also failed to project themselves on items such as "If my doctor recommended deprescribing…", or other hypothetical situations because they believed these situations would never happen. Finally, questions of the rPATD-BZRA were not relevant anymore for participants who had already stopped taking BZRA at follow-up. Overall, before moving on to a larger scale evaluation, it is important to discuss the relevance of measures with a high rate of missing data, and probably to reduce the length of the data collection. Improvements also need to be made to enhance reporting on intervention logs, maybe by better integrating them into the intervention processes and HCPs' daily workflow. As an example, NHRs follow-up documents were kept altogether in a common file. Having each follow-up document in the NHRs medical record might ease its completion. Increasing the participation of NHRs' relatives could also help reducing the rate of missing data and recruiting NHRs with cognitive impairments. Allowing data collection through online forms or phone calls for relatives might prove beneficial.

It is interesting to notice that if most NHRs reported taking BZRA for insomnia (50.8%), or for both insomnia and anxiety (23.0%), when insomnia is measured through a standardized questionnaire such as the Insomnia Severity Index (ISI(1)), only 12.2% of NHRs were found to have insomnia. This calls for more objective measures of insomnia or sleep disturbances in clinical practice, before starting or continuing a medication such as BZRA. This also questions the available tools for measuring insomnia in NHRs. Ideally, the diagnostic of insomnia or sleep disturbances among NHRs should be based on clinical history from NHRs, family members and NH staff, physical examination, and observation of daytime and nighttime sleep (6). In the context of this pragmatic trial, this was not feasible. However, we could have chosen other questionnaires than the ISI, such as the Pittsburg Sleep Quality index (7) or the Functional outcomes of sleep questionnaire (8). We chose the ISI because it is significantly shorter than the other precited questionnaires. It is however noteworthy that none of these questionnaires have been specifically designed for older adults or for NHRs. We did not measure sleep disturbances in NHRs with cognitive impairment. Using a proxy questionnaire with

relatives would rely on how informed relatives are of the NHR nighttime sleep. A systematic review conducted in 2019 and evaluating sleep disturbances in older adults with dementia living in care homes reported a prevalence of significative sleep disturbances of 20% (9). Most studies based their evaluation on the neuropsychiatric inventory (NPI) sleep item (10), which has been specifically designed for carers of patients with dementia, but other questionnaires had also been used. Some studies also used wrist-worn actigraphy (9). In the prospect of a future larger-scale trial, insomnia measures will have to be rediscussed to better capture NHRs sleep disturbances. In the absence of a questionnaire specifically designed for NHRs, we could go on with the ISI (for which the rate of missing data was acceptable). The NPI sleep item might be considered for NHRs with cognitive impairment, but it should be filled by a person present at nighttime, therefore an HCP.

We evaluated BZRA deprescribing using two definitions: (i) any BZRA dose reduction or BZRA cessation, and (ii) a 25% minimum BZRA dose reduction or dose cessation. In case of a future larger-scale cluster-randomized controlled trial, the outcome definition will have to be chosen. The first definition of deprescribing might be chosen in order to best apprehend all BZRA deprescribing behaviour. Some tapering scheme also start with a 20% dose decrease. Choosing the first deprescribing definition therefore enables to capture NHRs at the very beginning of a tapering process. The second definition, with a threshold in dose reduction has also already been used in literature (11). Using it has the potential to reflect the intervention effect on potentially clinically significant BZRA deprescribing rather than reflecting all deprescribing behaviour. There is however no evidence on which dose reduction should be achieved to expect clinical positive outcomes, and current guidelines recommend a complete BZRA cessation (12).

Implementation of the END-IT NH intervention

None of the NH in the intervention group implemented all of the intervention components. However, 3 of them implemented 5 of the 6 components, and all components were implemented in at least one NH. Work has to be done to explore the contextual factors explaining the differences in implementation between NHs. Preliminary hypothesis and explanations are presented in Box1. It is also possible that intervention implementation occurred in

more informal ways than the one we measured. The qualitative process investigations will give further insights on this matter.

Box 1 – The history of intervention implementation in each NH

Note: the data presented below are to be considered with caution. They are only based on interactions between the research team and NH staff. The complete qualitative process evaluation will provide more robust data on this.

NH 1- The NH 1 joined the study through their pharmacist, who was interested in the project. Unfortunately, the NH resigned its contract with the pharmacy at the beginning of the study. In addition, the coordinating physician of the NH was absent for approximately 4 months of the implementation period. Altogether, this led to a high work burden on the head nurse, in charge of the intervention implementation. Only two intervention components were implemented: the distribution of the NHRs leaflets by the head nurse, and the audit and feedback on BZRA use, performed by the research team. These two components alone did not lead to any BZRA deprescribing in participating NHRs.

NH 2- The intervention implementation was mostly done by two head nurses. The coordinating physician attended the HCP training, and followed the project, but was not actively involved in other aspects of intervention implementation. The head nurses reported issues with engaging general practitioners (GPs), in the training or in multidisciplinary meetings. This therefore resulted in very few deprescribing. However, head nurses believed that the intervention helped raise awareness in all NH staff.

NH 3- Our contact person was the quality coordinator of the NH, who oversaw the intervention implementation, together with an appointed nurse. The coordinating physician was also actively involved in the intervention implementation and multidisciplinary meetings. The HCP training succeeded in gathering nurses and GPs. The appointed nurse questioned GPs regarding BZRA use, upon their regular NH visits. A 60% rate of deprescribing was observed in this NH. It is noteworthy that this NH also changed of pharmacy during the study period.

NH 4- The coordinating physician oversaw the intervention implementation, together with a head nurse. Due to staff turnover, this head nurse changed during the study period. General practitioners participated in the HCP training, but the

coordinating physician reported that multidisciplinary work was mostly informal. A psychologist inside the NH distributed most of the NHRs leaflets. The observed rate of BZRA deprescribing was 58.3%.

Based on these preliminary data, we hypothesized that an active involvement of the coordinating physician, together with a collaboration between nurses and general practitioners are key to intervention implementation and effectiveness.

Based on the data reported here and interactions between the research team and NH staff, here are preliminary elements of discussion on each of the 6 implementation components:

- **Goals and process setting:** This element was implemented in all NHs but one. It should likely be kept in future intervention refinements. However, potential changes could be made to the intervention tool itself to increase its completion by NH staff.
- **HCPs educational session:** The educational session occurred in 3 NHs, but gathered nurses and GPs in only two NHs. This interaction appears essential for intervention implementation and effectiveness. One NH reported shortening the PowerPoint presentation, to increase training acceptability. Efforts could therefore be made in that sense. Unfortunately, pharmacists were not involved in any HCP educational session.
- **Environmental adaptations:** Several intervention NHs had not implemented any environmental change at 6 months, but were on a reflection process or had already made environmental adaptations before the study. We failed to collect this baseline level of environmental adaptations and should consider them in a future trial. We strongly believe that this intervention component remains essential, even if its implementation takes time.
- **Audit and Feedback:** We were able to provide 3 audits and feedback (as planned) to 3 NHs, and only 2 audits and feedback to the last NH. As there is currently no routinely collected data on BZRA prescribing, we had to rely on pharmacists to know the rate of BZRA prescribing in each NH. However, we observed that pharmacists could not easily extract prescribing rates from their records, and sometimes lacked time to provide us with the data. In addition, 2 NHs changed of pharmacist during the study, which hardened the collection of prescribing rates. If this intervention component is kept in future refinements, we would need an easier way to extract prescribing rates, if possible through an automatized process at a macro level. In Belgium, such data on medication use are available for some medication classes, but not BZRA, and not in NHs.

Extending the possibility of audit and feedback to this medication and setting could be beneficial.

- **NHRs and relatives raising awareness:** The brochure was mostly distributed as intended. However, one coordinating physician felt that its content was too long and complicated for our targeted population. Further work is needed to improve it.
- **Multidisciplinary work:** NH partners revealed that they had some level of multidisciplinary work, as an example through nurses questioning GPs on BZRA use, outside of formal multidisciplinary meetings. None of the NHs used the multidisciplinary opinion document. The qualitative process evaluation should investigate whether this document was not used because HCPs believed it to be irrelevant, or because formal multidisciplinary meetings did not occur.

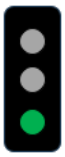
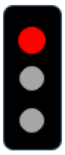
The intervention implementation might also have been altered by the high rate of turnover, and shortage in NH staff. Indeed, 3 of the 6 included NHs had a change in head nurses over the study period, and many NH partners reported lack of staff. The high turnover in NH staff previously has been reported as a barrier for HCPs collaboration in long-term care, and therefore multidisciplinary work (13). In 2022 in the United States of America, the average rate of yearly turnover in NH nursing staff was 52% (14). Higher rates of turnover were associated with lower quality of care for NHRs (14). The shortage of NH staff in Belgium has already been reported in the last national health system evaluation reports (15). In a context of an aging population and the increase in long-term care needs, this is of particular concern. Turnover in coordinating physicians appears to be less of an issue. We might therefore consider giving a more central role in coordinating physician for intervention implementation.

Finally, we observed that the implementation of our complex intervention took longer than what we have expected. Indeed, at 3 months, the implementation was only starting in the NHs. We therefore think that a longer follow-up is needed to assess the effect of the intervention on BZRA deprescribing and other patient-reported outcomes. Ideally, we suggest moving from a 6-month follow-up to a 1-year follow-up. However, it is possible that it would lead to higher drop-out and death rates.

The feasibility of the different aspects of our study design and intervention implementation is summarized in Table 8, using a traffic lights system. This traffic

lights system could be used to decide whether and how to move on with a full-effectiveness trial.

Table 8: Feasibility of the study conduction and of the intervention implementation summarized using a traffic light system.

	Feasibility of the study conduction	**Feasibility of intervention implementation**
	- Study agreement rate - Study retention rate - NH partners satisfaction survey	- Intervention responsiveness
	- Rate of missing data - Time needed for intervention implementation (potential need for an extension of the study follow-up period)	- Intervention implementation fidelity (Need to explore contextual differences between the nursing homes, and potential refinements to the intervention components)
	- Healthcare use data collection	

Legend: Results indicating that no or minor changes are required in study procedures and/or implementation process are classified as green traffic lights, Results indicating that substantial changes might be required in study procedures and/or implementation processes are classified as orange traffic lights. Results indicating that study procedures and/or implementation processes are not feasible are classified as red traffic lights.

Limitations of this work

Conducting this feasibility cluster-randomized controlled trial enabled us to spare time and resources and to potentially better refine our intervention. Nevertheless, this work has some limitations. First, we did not predefine progression criteria on whether or not to move further with a larger-scale intervention implementation, and a larger-scale randomized controlled trial to evaluate its effectiveness and cost-effectiveness. The decision will be made based on the results of the END-IT NH study, within the research team, and with insights from an advisory board encompassing various stakeholders representants (including older adults). Second, the recruitment of NHs was made on a voluntary basis. Therefore, we only included NHs with interest for BZRA appropriateness. Altogether, we observed that public NHs were more voluntary to participate than private NHs, and we had difficulties recruiting NHs in Brussels or other large cities. Third, we have a high imbalance between our groups' sizes. We initially chose to have more NHs in the intervention group because of our study aim of evaluating the feasibility of implementing the intervention. In addition, a NH with only 5 participating NHRs was randomized into the control group, which led to a higher imbalance than planned. Finally, these are only partial results of the feasibility study. Analysis regarding the cost-effectiveness evaluation and the evaluation of contextual factors and potential mechanisms of action are still to be performed. Final decision on the conduction of a larger-scale study will have to be based on all results.

CONCLUSION

To conclude, these partial results of the END-IT NH study show that implementing the intervention is feasible, but refinement is necessary to ease its implementation and better apprehend contextual differences between NHs. The evaluation of the intervention effect in a robust cluster-randomized controlled trial also should be feasible, but the relevance of some measures should be discussed to reduce data collection length and rate of missing data.

Although this study was not powered to assess the effectiveness of the intervention, and despite that the intervention was not implemented as intended, we believe these deprescribing rates to be encouraging. This suggests a potential benefit from moving further with a refined version of the END-IT NH intervention.

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GENERAL DISCUSSION

1. Summary of key findings

This thesis describes the thorough development of an intervention towards benzodiazepine receptor agonists (BZRA) deprescribing in Belgian nursing homes (NHs), with various stakeholders' involvement, and insights from behaviour theories.

In the first section, we focused on evaluating current practices in BZRA prescribing and deprescribing in Belgian NHs.

CHAPTER 1 is a posthoc analysis of the COME-ON study (1, 2). Among 797 nursing home residents (NHRs), we found a prevalence of use of BZRA of 52.4%. BZRA prescriptions were potentially inappropriate for 21.1% to 98.2% of users, depending on the analysed criteria. The main reason for BZRA potential inappropriateness was a length of use above 4 weeks. Over the 15 months of the study, BZRA deprescribing occurred in 28.1% of baseline users. The COME-ON intervention, alongside some NHRs characteristics (dementia, Parkinson, and past hospitalizations), and NH characteristics (number of beds and type of ownership), was associated with BZRA deprescribing. This was the bottom line for the development of a novel intervention, specifically targeting BZRA deprescribing and supposedly more effective.

In the second section, we developed a theory-based intervention towards BZRA deprescribing, in the specific context of Belgian NHs. The logic model of this intervention can be found in Figure 1. It describes the behaviours we targeted, along with the identified barriers and enablers for the needed change, the intervention components targeting them, and how they are supposed to have their effect.

CHAPTER 2 is a systematic review of barriers and enablers for BZRA deprescribing in older adults. It included a total of 23 studies reporting perspectives of older adults (19 studies), general practitioners (9 studies), and nurses (3 studies). Eight studies were conducted in the NH setting. Seven most relevant theoretical domains framework (TDF) domains were identified: Beliefs about capabilities, Beliefs about consequences, Environmental context and resources, Intention, Goals, Social influences, and Memory, attention and decision processes. The impact of the environment and the setting appeared to be of critical importance. This called for a specific evaluation of barriers and enablers for BZRA deprescribing in Belgian NHs.

CHAPTER 3 was a qualitative study on barriers and enablers for BZRA deprescribing, conducted in 6 NHs, with 13 general practitioners, 35 other healthcare professionals (HCPs), 22 NHRs, and 5 relatives. 9 TDF domains were identified as most relevant among HCPs interviewed (See Figure 1). Five additional themes emerged from residents' and relatives' interviews: knowledge about medications used, communication with NH staff and general practitioners, perceived efficacy and necessity of BZRA, influence of the environment, and reluctance towards BZRA deprescribing. These results were used as a basis for the development of our intervention.

CHAPTER 4 describes the muti-steps process followed for the development of our behaviour-change intervention. Nine behaviour change techniques (BCTs), all linked to the previously identified TDF domains, were selected. These BCTs were: Instructions on how to perform the behaviour, Information about health consequences, Pros and cons, Problem solving, Goals setting (behaviour), Graded tasks, Social comparison, Restructuring the physical environment, and Restructuring the social environment. Selected BCTs were operationalized into the END-IT NH intervention, encompassing Process and goals setting, Healthcare providers education, Physical environment adaptation, Audit and feedback, NHRs and relatives' awareness, and Multidisciplinary work (Figure 1).

In the third section, we describe a feasibility study of the END-IT NH study.

CHAPTER 5 encompasses the complete protocol of the END-IT NH study, a cluster-randomized controlled trial with three aims:

- Evaluating the feasibility of evaluating the END-IT NH intervention effectiveness and cost-effectiveness in a larger RCT
- Evaluating the feasibility and acceptability of implementing the END-IT NH intervention
- Conducting an exploratory cost-effectiveness analysis of the intervention.

CHAPTER 6 showed that the END-IT study was feasible, with good NHRs participation and retention rates. However, there is a need to simplify data collection. The intervention implementation differed between NHs. Further intervention refinements must be done to ease intervention implementation, and to enable measures of more informal implementation of intervention components such as multidisciplinary work. We observed a rate of BZRA deprescribing of 31.1% in the intervention group and 12.5% in the control group.

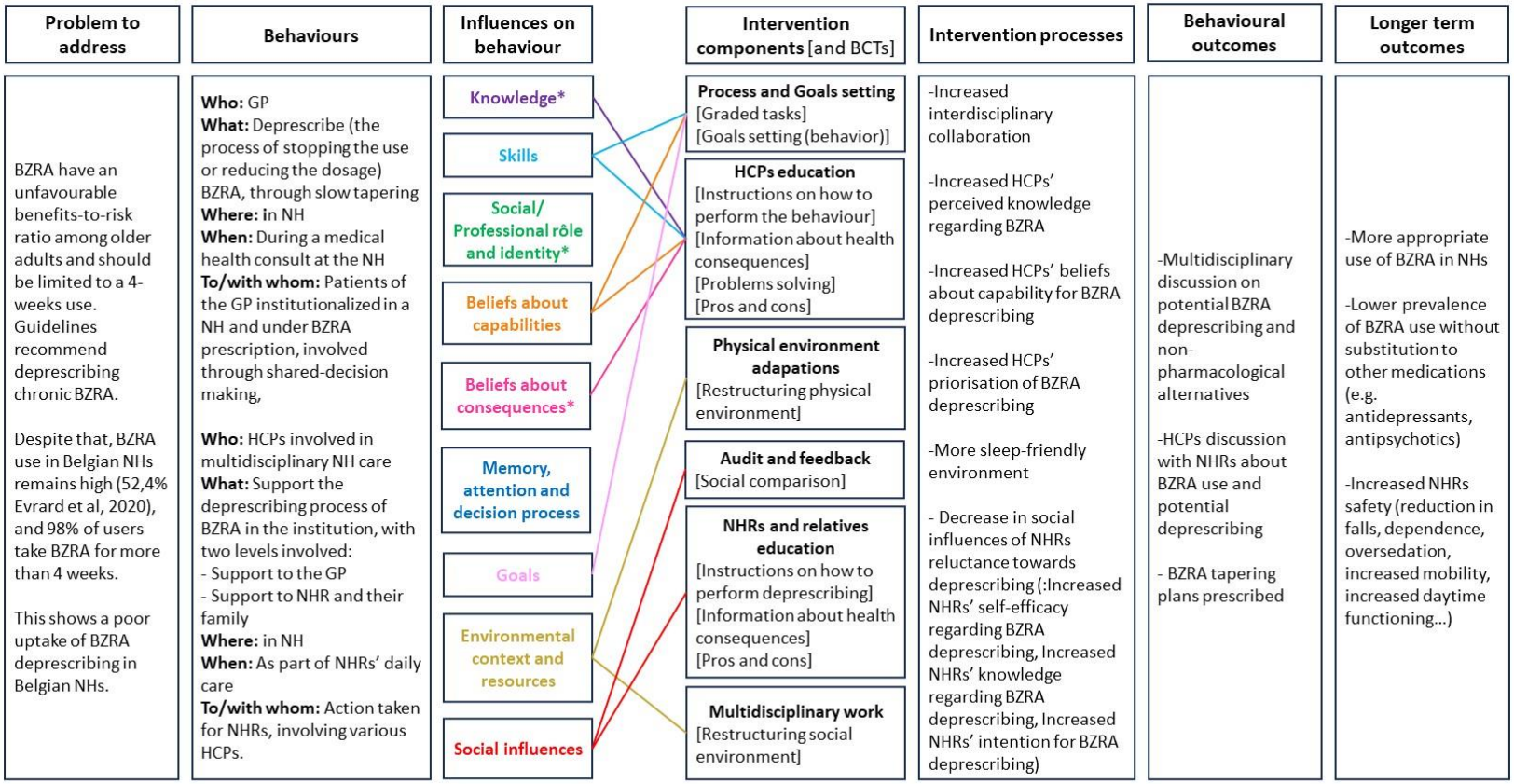


Figure 1: Programme theory of the END-IT NH intervention
Notes: BCT = Behaviour change technique, **BZRA** = Benzodiazepine Receptor Agonists, **GP** = General practitioner, **HCP** = Healthcare professional, **NH** = Nursing home, **NHR** = Nursing home resident
*: These domains were identified as most relevant only for HCPs other than general practitioners

2. *Discussion*

2.1. Reflections on Implementation Science use

This work was conducted following a meticulous implementation science approach. We followed the steps of the Choosing Wisely framework for de-implementing low-value care (3) but also used various tools derived from behaviour-change theories. First, we used the TDF (4, 5), in both our systematic review (Chapter 2) and our qualitative study (Chapter 3), to analyse and classify behaviour change determinants. We then used the BCT taxonomy v1 (6), in association with the theory and techniques tool (7), to identify potential BCTs linked to relevant TDF domains, and to develop our behaviour change intervention (Chapter 4). The TDF was once again used later, in the process evaluation of our intervention (Chapter 5).

2.1.1. Advantages and disadvantages of the tools we used

Overall, the use of implementation science strengthens our findings and the probability of implementation and success of our intervention. However, specifically using the TDF and the BCTs taxonomy proved to have both advantages and disadvantages/difficulties. These are summarized in Table 1.

Table 1: Advantages and Disadvantages of the behaviour-change theory tools used in this thesis

Tool	Advantages	Disadvantages and encountered difficulties
TDF	- Maps 33 theories. - Validated by experts. - Great subdivision of behaviour determinants. - Made specifically to be useful for researchers without psychological background. - Easy comparison of results between studies/settings/pop	- Some behaviour determinants we found, such as patients' characteristics of health status did not fit into the TDF. → Our interpretation is that these determinants did not fit into the TDF because they cannot be impacted to trigger the behaviour. - Not easy to use to analyse patients' and NHRs' perspective (as it has initially been developed for studying HCPs perspectives). → Using the TDF with this aim has been done in literature before (8, 9), but for our qualitative study

	ulation.	(Chapter 3) we chose to use inductive thematic analysis for analysing NHRs and relatives focus groups. - Potential overlap between domains sometimes make classification difficult. → Example: difficulties to distinguish Goals and Intention. - Framework with no link between the different domains. →The TDF is not a theory. There is no explanation of potential links between the different domains, and how they interact.
BCT taxon--omy v1	- Comprehensive list of BCTs with provided definition. - Evidence of links between BCTs and TDF domains. - Makes intervention description, adaptations, and replications easier.	- BCT language not easily accessible for stakeholders. → Difficulties to understand BCTs definitions. → Difficulties to think about the BCTs beyond the examples we provided. → Difficulties also reported in literature for BCT use with public representatives (10). - Potential overlapping in some BCTs. - No existing guideline on how best to move from BCTs to actual intervention components. →Stakeholders input at this step is crucial, but there is no guideline on how best to involve them.
Legend: BCT= Behaviour change technique, **HCP=** Healthcare professional, **NHR=** Nursing home resident, **TDF=** Theoretical domains framework		

2.1.2. Other existing tools from behaviour change theories.

As said above, we chose to use the TDF and the BCT taxonomy. However, other behaviour-change tools could have been used at various stages of this work. Table 2 gathers some of these tools, with their potential uses, and advantages and disadvantages in comparison to the tools we used.

We could have used the consolidated framework for implementation research (CFIR) (11) in place of the TDF to evaluate the determinants of implementing BZRA deprescribing. In particular, the CFIR encompasses more detailed coverage of barriers and enablers coming from the contextual level (12). As we were working in a complex setting that has multilevel organization and individual interactions, this might have been interesting. The CFIR has already been used in the NH setting, as an example for evaluating barriers and enablers for implementing quality improvement initiatives (13) or for their process evaluation (14, 15). However, as stated in Table 2, the CFIR has not been developed directly for intervention development (16), and there is no evidence on how to move from CFIR domains to intervention components.

Overall, we could have also chosen to use the COM-B model (17) to evaluate the barriers and enablers for BZRA deprescribing, and then the behaviour change wheel to develop an intervention based on that. However, we believe that using the TDF was more accessible than COM-B for us as it, again, has been developed for researchers without a psychological background. With our barriers and enablers mapped into TDF domains, going on with BCTs' identification based on the theory and techniques tool was the logical next step. Still, one may wonder how the END-IT NH intervention might have differed, had we chosen to start with the COM-B model in the first step.

Table 2: Examples of tools from behaviour change theories we could have used, with potential advantages and disadvantages in comparison to the TDF and the BCT taxonomy

Tool	Description	Potential uses	Potential advantages	Potential disadvantages
CFIR (11)	- Consolidated framework for implementation research - Implementation determinant framework including 39 constructs over 5 domains: innovation domain, outer setting domain, inner setting domain, individuals domain, and implementation process domain. - Apparent similarities with the TDF in terms of purpose, multi-level framework, operationalizability, and degree of theoretical heritage (16)	- Predict or Explain barriers and enablers for implementation effectiveness - Mostly used in post-implementation phase (11)	- Does encompass attributes of the intervention itself, that were excluded in the second TDF version - More detailed coverage of determinants outside the individual level (internal organizational context and external environment) (12)	- CFIR is intended "to promote theory development and facili-tate synthesis of research findings across studies and contexts" (16), not directly to develop intervention - TDF has a more detailed coverage of individual level determinants (12) - No evidence on how to link CFIR domains and intervention components or BCTs
COM-B (17)	- Behaviour system describing how "capacity", "opportunity", and "motivation" interact to create a behaviour. In turn, this behaviour also influences its initial components.  *The COM-B system – a framework for understanding behaviour, from Michie et al. (17), reproduced with kind authorisation*	- Evaluation of barriers and enablers for the behaviour change: what components of the behaviour system would need to be changed -Mapping of the TDF domains into the COM-B model is possible.	- Encompasses influences between the different elements of the system: how they interact and can reduce or amplify effects on behaviour	- Less accessible than the TDF to researchers without a psychological background - Only 3 categories. The TDF allows for more precisions in the description of behaviour determinants.

Behaviour change wheel (17)	Wheel encompassing policies, intervention function (potentially enabled by policies), and the source of behaviour impacted.  *The Behaviour change wheel, from Michie et al. (17), reproduced with kind authorisation*	- Categorization of existing intervention - Intervention development based on evaluated barriers and enablers	- Direct evidence of how policies can support the interventions	- No evidence of which BCT can be used to develop the various intervention function
Legend: BCT= Behaviour change technique, **CFIR**= Consolidated framework for implementation research, **COM-B**= Capacity, Opportunity, Motivation, Behaviour, **TDF**= Theoretical domains framework				

2.1.3. New ontologies available

In 2023, Marques et al published a transformation of the BCT taxonomy v1: The **BCT ontology** (18). The BCT ontology development was, among other things, based on feedback from users of the BCT taxonomy v1 (19), and expert stakeholders' review. This led to a final list of 281 BCTs arranged into 20 higher-level groups. Should we start our work now, we would likely use the BCT ontology in place of the BCT taxonomy v1. The main differences are the number of BCTs (281 vs 93) and the deeper hierarchical structures in the ontology classification. The majority of BCTs from the taxonomy v1 can be mapped to one or more of the BCTs from the ontology. Using the BCT ontology, our intervention content would likely have been described more precisely. However, it is possible that the higher level of complexity of this ontology would have made it harder for us to use than the BCT Taxonomy v1. In addition, we used the theory and techniques tool (7) to link our pre-identified TDF domains to potential BCTs, and such a tool does not exist yet for all BCTs included in the new ontology. Developing it should help using the BCT ontology in intervention development.

In the last year of this work (in 2023), Schenck et al. introduced an **ontology of mechanisms of action** (MoA) in behaviour-change interventions (20). A MoA is defined as "the type(s) of process by which interventions influence the target behaviour" (21). The aim of this new ontology was to develop a clear, extensive and usable classification of these MoAs, and therefore to provide a shared vocabulary for reporting behaviour change interventions MoAs, and their evaluations (20).

Had the ontology been available at the beginning of this work, we could have used it in our intervention development and strengthened the program theory of our intervention. Indeed, our current program theory describes the link between the BCTs we included and the TDF domains they impact. By using the MoA ontology and the BCT ontology together, we could have gone further and described the MoA through which our BCTs could theoretically impact the targeted TDF domains. This could also have been used in the elaboration of our intervention process evaluation (see Chapter 5). However, as the MoA ontology is very recent, only few guidelines and training on how to use it are currently available. This might have been problematic for us, as results from the ontology development showed

that further guidance and training would be necessary for researchers unfamiliar with intervention annotations and ontologies (20).

2.2. Stakeholders' and Patient and Public involvement in research

Stakeholders involvement (both HCPs and patients) is a recommended practice in health research, and for developing and evaluating complex interventions (22). In 2020, Ludwig et al. conducted a systematic review of studies partnering with seriously ill or frail patients at a higher level than only consultation (23). They included 30 studies, as examples among patients with cancers or frails, but none of them was conducted in the NH setting (23). In a systematic review conducted by Backhouse et al. and exploring the subject of older care-home residents as collaborators or advisors in research, it has also been reported that HCPs were often more involved than NHRs (24). Altogether, this shows that NHRs involvement in research is still too scarce and should be improved.

Throughout this thesis, we involved various stakeholders, NHRs and relatives but also HCPs and policymakers, for various aims (barriers and enablers evaluation, BCT selection, intervention tool design), and in various ways (face-to-face or focus group interviews, online survey, and panel discussions). It brought us insights from field perspectives, enabled us to make sure we were orienting research on subjects that matter for them and their day-to-day practice/life, and increased the acceptability and appropriateness of the intervention we developed. As an example, stakeholders helped us draw a list of acceptable non-pharmacological approaches or environmental adaptations.

We encountered several barriers, of which several were also reported in the SR of Backhouse et al.: power relations, length of reports, cognitive impairments of NHRs, and residents changing health (24).

One barrier we would like to elaborate on is the difficulty of stakeholders' recruitment, particularly for some groups, such as NHRs and relatives, or nurses. It was also difficult to recruit stakeholders with a variety of points of view, and not only in favour of the project. Stakeholders' recruitment was also hindered by the COVID-19 pandemic. To overcome this challenge, establishing relations with gatekeepers in the research setting is of major importance. Multiplying recruitment channels is also a potential strategy. Backhouse et al. reported other enablers that could be explored: the development of a trust relationship, the use of creative

contents to engage residents, funding, flexibility in involvement, and supportive organizational culture (24).

Making research processes understandable for stakeholders was also a challenge, in particular implementation science processes and vocabulary. For this matter, the development and use of pedagogic tools should be encouraged. As an example, cards explaining BCTs in lay terms are available and can be used in a meeting with stakeholders. It is however likely that these would not be understandable for all NHRs.

If we involved stakeholders, this involvement could have gone further. Patient and Public involvement (PPI) is defined as "research being carried out 'with' or 'by' patients and members of the public rather than 'to', 'about' or 'for' them" (25). PPI partners can involve members of the public, patients, service users, and carers at any step of the research process: choice of research topic, design, planning, conduct, or dissemination of research (26). PPI differs from qualitative and survey research in which stakeholders' perspectives are explored to inform the decisions of the research team, it encompasses a more active contribution of PPI partners, in more research steps (25). If NHRs were involved in various steps of our research, one may not consider that we did perform PPI. In research focusing on older adults, PPI activities are more and more frequent. In a recent survey conducted among 92 authors of pragmatic trials involving older adults only, 50% of them reported PPI (26). Research on current PPI practices in the NH setting could help future initiatives.

We always interviewed NHRs on their own or with relatives, but never in mixed stakeholder groups. First, we needed them to speak freely, and some NHRs thanked us for this separation. Second, we explored different behaviour from HCPs and NHRs in BZRA deprescribing and therefore asked different questions. Still involving NHRs in mixed stakeholder groups would also have been an interesting approach and would have enabled exploring their interactions with HCPs. This has already been done before, for example in focus groups or nominal groups (24).

2.3. Health policies: impacts and recommendations

2.3.1. Extension of current initiatives from the ambulatory setting to the nursing home setting

In a systematic review of policies aiming at deprescribing sedative-hypnotic medications in community-dwelling older adults, Shaw et al. included 9 different studies (27). The evaluated policies included loss of medication coverage, public awareness campaigns, driving license restriction policy, prescriber monitoring, and promotion of non-pharmacological approaches. These policies, although coming with unintended consequences, effectively led to decreased BZRA prescribing rates (27). If data on loss of BZRA coverage are interesting (28), this strategy is not relevant to Belgium, as the national health insurance does not reimburse BZRA, and the price for these medications is low. In contrast, some of the other cited policies are already in place in the Belgian ambulatory setting but are not implemented in NHs. We believe that extending these policies to the NH setting should be an explored strategy.

Regarding **public awareness campaigns**, the Belgian government has launched several awareness campaigns on psychotropics use, but none of them target specifically older adults, or NHRs. These campaigns currently include posters and leaflets to raise public awareness; and practical tools and information for general practitioners, pharmacists, and psychologists (communication tools to address deprescribing with patients, tools to implement non-pharmacological approaches…). Several actions could be taken to extend current public campaigns to NHRs:

- Development of communication tools specifically designed for NHRs, without and with cognitive impairments, and relatives. The brochure we developed (Chapter 4) and used (Chapter 5 and 6), after refinement, could be integrated into future campaigns.
- Better representation of older adults and NHRs in the graphic designs of the campaign tools.
- Development of tools specifically designed for NH staff. The current campaign should in priority be extended to nurses, but could also include other NH staff, HCPs, and others. Our results indeed strongly support a greater involvement of nurses and multidisciplinary collaboration.

Public campaigns could be associated with the **promotion of non-pharmacological approaches** in the NH setting. In the feasibility study of the END-IT NH intervention (Chapter 6), we observed that only very few switches to non-pharmacological approaches were reported. This could be due to the many barriers for their implementation (Chapter 2 and 3), that health policies could help overcome. First, access to psychotherapist and reimbursement of such care should be eased. Second, an increase in the number of nurses and NH staff could give them more time to dispense non-pharmacological approaches rather than having to rely on faster pharmacological alternatives. Third, specific guidelines could be developed for physical environment adaptation, in order to promote sleep and relaxation. A list of suggestions was developed in the END-IT NH intervention (Chapter 4) and could be further used and refined.

Implementing a **monitoring of BZRA prescribing**, in the primary care setting and more specifically in the NH setting, could be of great help. Indeed, there is currently no available data on prescribing rate, which makes it difficult to assess an evolution, evaluate the effect of the national campaigns, and conduct an **audit and feedback** on BZRA use and prescription. Indeed, for our intervention, we based our audit and feedback document on data given by the pharmacist, but reliable data were difficult to obtain (Chapter 6). In addition, we compared prescribing rates to what we obtained in our posthoc analysis of the COME-ON study (Chapter 1), but these data were collected in 2015. To our knowledge, no recent data are available in Belgium. Enabling easier audit and feedback on BZRA use could be an interesting strategy, as audit and feedback have been shown to effectively improve HCPs compliance with the desired practice (29). Additionally, during our intervention development (Chapter 4), HCPs highlighted the importance for them to be able to monitor their progress. The development of audit and feedback on medication use currently is a priority of the Belgian national health insurance, but these are only developed for some medication classes and for the ambulatory setting (30). This initiative should be extended to BZRAs, and to the NH setting.

In the same idea of making prescribing data accessible, public reporting is defined as "data, publicly available or available to a broad audience free of charge or at a nominal cost, about a health care structure, process, or outcome at any provider level (individual clinician, group, or organizations [e.g., hospitals, nursing facilities])or at the health plan level" (31), and has been shown to be an effective

public health strategy (32). Ontario, following massive media reports on antipsychotic use, launched an online public reporting initiative on antipsychotic prescribing at NH level. A trend towards a reduction in antipsychotic use was observed after the media coverage, but this trend was not accentuated by the public reporting initiative (33). A public reporting initiative regarding BZRA prescribing in Belgian NHs could probably help trigger deprescribing and could generate interrogations from NHRs and relatives on their medications, and deprescribing discussions. Work needs to be done to determine how to best implement this public reporting initiative.

Finally, the Belgian national health insurance recently authorised, under some conditions, the **reimbursement of magistral preparations** by the pharmacist to follow a gradual BZRA tapering scheme. Unfortunately, NHRs cannot access this reimbursement. The HCPs we worked with thought this could have been a great opportunity, and several NHRs included in the END-IT NH study had recourse to these magistral preparations, even though they had to pay for them (Chapter 6). We therefore strongly believe that the national health insurance coverage for this program should be extended to NHRs. Policymakers in charge of this project showed strong interest in this thesis, and in a potential extension to the NH setting.

2.3.2. Revise and refine process around multidisciplinary work

Multidisciplinary work and medication review has been identified as an enabler for BZRA deprescribing in both our systematic review (Chapter 2) and our qualitative study (Chapter 3). In the END-IT NH study, only few formal multidisciplinary meetings were reported (Chapter 6). Health policies should be developed to create new opportunities and facilitate multidisciplinary work. Funding these **multidisciplinary medication reviews** has been reported as a determinant of deprescribing (34), and should therefore be considered. Other factors, potentially impacting multidisciplinary work are discussed below.

In 2022, a systematic review by Doornebosch et al. assessed the barriers and enablers for multidisciplinary collaboration in long-term care and geriatric rehabilitation (35). It included 22 studies conducted in the long-term care setting, mainly in Northern America but also in Australia, and European countries. Three themes emerged from this systematic review: *Team performance* (Collaboration

among HCPs, patients, and family caregivers, Behaviour and attitude of team members, Shared goals, and Clarity of roles), *Organizational conditions* (Workplace process, Availability of resources, Leadership), and *Sharing Information* (Basic communication skills, Communication process, Developing and utilizing knowledge) (35). Health policies, by targeting these aspects could facilitate multidisciplinary work.

First, the role of different HCPs could be strengthened (*Team performance*). A recent scoping review assessed **nurses**' responsibilities and tasks in pharmaceutical care (36). Seven responsibilities were identified: management of therapeutic and adverse effects of medication, management of medication adherence, management of patient medication self-management, management of patient education and information about medication, prescription management, medication safety management, and care coordination (36). Supporting BZRA deprescribing, through raising patient awareness and managing medication side effects and safety, completely falls into nurses' responsibilities. Still, our qualitative study in Belgian NHs (Chapter 3) revealed that some nurses thought this was more the responsibility of the general practitioners, and that they were dependent on their decisions (*Team performance, Clarity of roles*). A survey conducted among 1807 European nurses students reported that 84% of them believed that their curriculum had insufficient pharmaceutical care content (37) *(Sharing information, Developing and utilizing knowledge)*. This is also in line with what we found in our qualitative study (Chapter 3), in which knowledge was found as a barrier for HCPs other than general practitioners. Enhancing nurses' (and nurse aids) knowledge and skills regarding pharmaceutical care, psychotropics, and their alternatives, is therefore a potential strategy. Health policies could help to achieve this aim, by providing adequate training during HCPs' formation and after. These formations could be made mandatory, or it could be mandatory, in each NH, to have a percentage of trained staff in this matter. According to existing literature, a key step to integrate nurses in multidisciplinary pharmaceutical care and for their education, is to clearly recognize their role in this matter (*Team performance, Clarity of role*), and to provide a framework for their integration (38, 39).

A royal decree from the 14th of April 2024 allows advanced practice nurses to prescribe medications and medical products. We do not know yet how this would translate into clinical practices. Nevertheless, this could mean that nurses could, as an example, reconduct BZRA prescriptions in NHs. This would put them in

an ideal position for treatment revaluation and deprescribing proposition and/or initiation. Still, this could only be done by advanced practice nurses (nurses who chose to follow an additional master degree) and there are currently very few advanced practice nurses working in NHs. The short-term impact of this new legislation in this setting should therefore be limited.

Currently, Belgian **pharmacists** mainly have a role in medication delivery in NHs. Expanding pharmacists' role to clinical pharmacy activities seems essential. Unfortunately, in the END-IT NH study, no pharmacist participated to the HCPs training or multidisciplinary meetings (Chapter 6). In a qualitative study conducted in Switzerland, the remuneration of the pharmacist based on medication dispensation instead of pharmaceutical care services was reported as a deprescribing determinant (34) (*Organizational conditions*). This should be targeted by future health policies. Since 2022, in Flanders, a university training for coordinating pharmacists in NHs is available, despite the fact that this role is not yet funded. This role should encompass an overview of medication use at the NH level and clinical pharmacy activities such as medication review. It will be evaluated in the future POOMAH trial (40). The training and implementation of coordinating pharmacists should be funded and expanded to the French-speaking parts of Belgium, to enhance collaboration of pharmacists with other HCPs, and to have them physically in the same location (*Team performance, Organizational conditions*). A recent cluster-randomized controlled trial evaluated the effectiveness and safety of pharmacist independent prescribers in England and Northern Ireland care homes (41). These prescribing pharmacists were responsible for performing medication reviews, optimizing therapy, and supporting the improvement of the medication pathway (including staff training). Introducing pharmacist independent prescribers did not reduce falls but led to a reduction in drug burden index (representing the anticholinergic and sedative load) by almost a fifth in comparison to usual care (41). No concern regarding safety was raised. If implementing prescribing pharmacists in Belgium is probably not feasible at this point, this study shows an interest for health policies to support pharmacists' activities in NHs (*Team performance, Organizational conditions*).

The involvement of the **coordinating physician** also appeared to be a crucial element in the implementation of our intervention (Chapter 6). Currently, coordinating physicians are a contact person for NH staff, oversee medication use,

and training. However, they do not have any control on individual NHRs medication. Extending the influence of coordinating physicians, while preserving the therapeutic freedom of each general practitioner could be an explored strategy.

Second, **NHRs and relatives** could also be involved as active members of the multidisciplinary team. Indeed, we have reported that they could influence HCPs' behaviour regarding BZRA deprescribing (Chapter 2 and 3). According to a qualitative study performed in Flemish NHs, NHRs and relatives reported various attitudes regarding being involved in the medicines pathway (42). HCPs reported that NHRs involvement was currently unstructured and depended on the NH's philosophy *(Organizational conditions)*. The potential consequences they perceived from NHRs involvement included increased NHRs autonomy, but also organizational difficulties and decreased safety of the medication pathway (43). Still in Belgian NHs, The RESPECT study developed tools to help involve NHRs in the medication optimization process and define person-centred goals (44, 45). Promoting the use of these tools could help involve NHRs and strengthen their role.

Third, another opportunity to improve multidisciplinary work could be **implementing multidisciplinary training in future HCPs cursus** *(Sharing information, Developing and Utilizing knowledge)*. In 2023, Farrell et al. proposed a curricular framework for an interprofessional approach to deprescribing (46). The rationale for an interprofessional curricular is to demonstrate how all HCPs can collaborate and how a multidisciplinary team can function (46). In Belgium, research is currently ongoing on how to improve future HCPs' training regarding deprescribing, and multidisciplinary courses are in development (*Laudine Ackermans, PhD thesis in progress*).

Finally, it has been reported that the high rate of **turnover** among HCPs hindered collaboration *(Team performance)* (35). The 1-year turnover rate of NH nurses is estimated to be up to 55% (47), suggesting that improvements could be made in this area. A survey conducted in the United States among 101 NH managers, and 899 NH employees showed that greater job satisfaction, quality of supervision, safety culture, more schedule control, and decision-making power were associated with lower intention to quit (48). As job satisfaction appears to be a major factor (47, 48), policies could aim at improving it, as an example through reducing workload, increasing job compensations and benefits, and providing

training opportunities. These factors, among others, were indeed found to impact job satisfaction (49).

Recommendations for future health policies towards BZRA deprescribing in Belgian NHs are summarized in Box 1. These recommendations are applicable beyond BZRA and could be applied to other psychotropic classes that are also overused.

Box 1: Recommendations for future policies – Summary

Extension of current initiatives to the nursing home setting

- Develop public awareness campaign adapted to the nursing home setting
- Promotion of non-pharmacological approaches
- Make BZRA prescribing data available for monitoring, feedback, and research purposes.
- Extend reimbursement of magistral preparations for BZRA withdrawal to NHRs.

Revise and reinforce process around multidisciplinary work

- Funding of multidisciplinary medication reviews in NHs.
- Increase knowledge of NH staff regarding psychotropic medications and their alternatives, through funded mandatory trainings.
- Funding of pharmaceutical activities in NHs such as medication review and implementation of pharmaceutical care coordinators.
- Strengthen the position of the coordinating physician.
- Promote involvement of NHRs and relatives.
- Implementation of multidisciplinary courses in future HCPs cursus.
- Increase the attractiveness of NH staff position and job satisfaction, through decrease in workload, salary revalorisation, and training offers, to reduce NH staff shortage and turnover.

3. Future perspectives

This thesis reports on the different steps of development of an intervention towards BZRA deprescribing in the Belgian NH setting. If this thesis ends with the END-IT NH study, a feasibility study of the intervention, further work is to be done, and this does not mark the end of the intervention development.

First, the results of the END-IT NH study will be discussed to decide whether and how to go further with a larger-scale implementation and effectiveness trial. The END-IT NH project was embedded into a broader research project: "DI-PRESCRIBE", standing for "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 DI-PRESCRIBE project is an *Action de recherche concertée*, funded at *UCLouvain*, and gathering researchers with various backgrounds (Pharmacists, Geriatricians, Health economists, Psychologists, and Healthcare systems researchers). The complete results of our feasibility study (including results of the qualitative process evaluation) will be discussed with the research team, and with the project stakeholders' advisory board. It would also be interesting to involve behavioural scientists in the decision process. Should the decision be taken to go on with the END-IT NH intervention, we will have to refine its design and tools. These refinements will be based on the results of the feasibility study (both quantitative and qualitative results) and will be done in collaboration with appropriate stakeholders. At this step, NHRs' involvement could go further from what we have previously done, and we could build an advisory board of NHRs and relatives. Hopefully, this will lead to a larger trial, evaluating the effectiveness and cost-effectiveness of a refined END-IT NH intervention, which could be conducted within the DI-PRESCRIBE research project.

Depending on the results of the process evaluation, we might also choose to develop an implementation package to go along with our intervention to ease its implementation. As an example, this could encompass detailed instructions on how to reach a consensus on objectives, or a specific briefing for the HCPs' educational session presenter. The content of this package should be developed with insights from stakeholders and an implementation framework such as the CFIR.

Second, a broader stakeholders' consultation could be planned. Indeed, all involved stakeholders and study participants were recruited on a voluntary basis, and among voluntary NHs. It is therefore possible that they do not represent the point of view of their entire groups, but only of the most motivated. In addition, the sample of stakeholders consulted was sometimes small. As an example, a larger-scale survey could be planned. This has already been done for other contexts or settings, such as barriers and enablers for BZRA deprescribing in hospitalized

older adults *(Shapoval et al., manuscript in preparation)*. However, work has to be done to investigate how to reach stakeholders who do not have a specific interest in deprescribing.

Third, work has to be done on the dissemination of our results and intervention. Indeed, we developed the END-IT NH intervention following the Choosing wisely de-implementation framework (3), but we did not address phase 4 of this framework yet: "spread of effective implementation framework". After the future refinement and evaluation of the intervention, one possibility could be to write a lay language report of the END-IT NH study together with a toolkit for future intervention implementation. These documents will have to be written in collaboration with HCPs, NH administrators, and NHRs representatives, to ensure their comprehensiveness and appropriateness for our targeted audience. This report could then be shared through HCPs' and patients' associations, and the research project website. The advisory board of the DI-PRESCRIBE project could also be involved in dissemination initiatives and could help identify appropriate ways to share our results. In addition to written reports, we would like to film testimonies from the END-IT NH participants, starting with HCPs. We believe these testimonies could be a great opportunity to increase other HCPs' intention towards BZRA deprescribing. This could be particularly interesting as intention was reported as a major TDF domain in our systematic review (Chapter 2). Finally, a future national symposium is planned within the DI-PRESCRIBE project. Targeted audience includes HCPs, researchers, policymakers, and older adults. This symposium could be the first step of dissemination of our results.

Finally, our work could be used as a basis for future broader quality improvement initiatives regarding medication use in NHs. Indeed, if our approach proves effective, it could be replicated to other medication classes, or to other steps of the medication pathway such as medication reconciliation at NHRs transfer.

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List of Publications and Communications

Scientific publications related to this thesis.

- **Evrard P**, Henrard S, Spinewine A. Development of a behavior-change intervention toward benzodiazepines deprescribing in older adults living in nursing homes. *J Am Med Dir Assoc*. 2024;25(8). doi: 10.1016/j.jamda.2024.105053
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Oral communications in national and international meetings

- "Barriers and enablers for benzodiazepine receptor agonists deprescribing in older adults: A systematic mixed-methods review using the Theoretical domains framework as an analysis guide" **Evrard P**, Pétein C, Spinewine A, European Geriatric Medicine Society 17th congress, online presentation (11th of October 2021)
- "Barriers and enablers for benzodiazepine receptor agonists deprescribing in Belgian nursing homes. A qualitative study" **Evrard P**, Damiaens A, Spinewine A, 24èmes journées d'automne, Société Belge Gériatrie et Gérontologie, online presentation (21st of October 2021)
- "Theory-based development of an intervention towards benzodiazepines deprescribing in nursing homes" **Evrard P**, Henrard S, Spinewine A, FIP Pharmacy practice research summer meeting, Granada, Spain (3rd of July 2023)

Poster in a national meeting.

- "Benzodiazepines prescribing patterns in Belgian Nursing homes, A Posthoc Analysis of the COME-ON Study" **Evrard P**, Henrard S, Foulon V, Anne Spinewine, 22èmes journées d'automne, Société Belge Gériatrie et Gérontologie, Liège, Belgium (17th and 18th of October, 2019)