CHRONIC BENZODIAZEPINE USE IN NURSING HOME RESIDENTS:
assessment of benefits and risks in insomnia

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CHRONISCH BENZODIAZEPINE GEBRUIK BIJ RUSTHUISBEWONERS:

evaluatie van baten en risico's voor slaapproblemen

Jolyce Bourgeois

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1. GENERAL INTRODUCTION

The aim of this doctoral thesis is to investigate the use, the benefits, the risks and possible discontinuation of the most prevalent (psychotropic) drug in older nursing home residents for its most frequent indication: benzodiazepines and Z-drugs used for insomnia.

1.1 BENZODIAZEPINES WITHIN POLYPHARMACY IN OLDER PEOPLE

Age-related pharmacokinetic- and dynamic alterations make older adults more sensitive to their medications and also more susceptible for adverse effects [1]. Moreover, with aging, multiple pathologies can emerge, which require a complex treatment approach as there is not just one specific organ failure. This often results in polypharmacy (5 or more medications per day) and a complex medication regimen [2]. Moreover, older people can develop functional and cognitive impairment which additionally impedes the (pharmacological) treatment.

The Belgian health survey in 2008 showed that polypharmacy is frequent (40%) in people aged 75 or more [3]. Also in other countries, medication use among older adults is high and even increased in the last years [4, 5]. This increase in concomitant medication use can be explained by the rise of preventive medicine and the occurrence of the "prescribing cascade", where one medication causes adverse effects which are countered with another medication [5].

Older adults living in residential care have even higher polypharmacy compared to older adults living at home [3, 6, 7]. However, these frail (and often cognitively impaired) residents have an increased susceptibility to adverse medication effects [8]. Psychotropic drugs, such as hypnotics, anxiolytics, antidepressants and antipsychotics dominate the medication chart of these older adults [6, 9, 10]. Moreover, use of multiple psychotropic drugs is common. In Belgian nursing homes, 47% of the residents took two or more psychotropic drugs in 2006 [11] and in Norwegian nursing homes, this was 33% in 2009 [9]. This high prevalence of psychotropic drug use increases the risk of side-effects in this frail older population.

Benzodiazepines, together with the related Z-drugs, are the most recurring group of drugs in terms of chronic prescribing and in terms of inappropriate psychotropic polypharmacy (included in explicit criteria for detecting inappropriate prescribing such as the Beers criteria [12, 13], STOPP criteria [14], Priscus list [15], Rancourt [16] and Laroche criteria [17]). Prescribing patterns vary widely between countries but long-term use is common [18].

In the UK and the US, the prevalence is somewhat lower [7, 19] due to special warnings (OBRA-87 in the US[20] and a warning to prescribing physicians on dependence in the UK in '88[21]), and to government initiatives in the late '80s and '90s such as the exclusion of BZD coverage in Medicare in the US[22] and the New York State triplicate prescription policy[23] which constituted a barrier to accessing BZDs. These policies reduced BZD prescribing, though a shift towards other (psychotropic) medications could not be totally avoided[24, 25]. Some saw an increased use in the nonbenzodiazepine sedatives and even barbiturates (early '90s)[23, 26]. In order to avoid prescribing BZDs, sedative antidepressants such as trazodone are increasingly prescribed to treat insomnia problems[27, 28]. However, the evidence for trazodone for insomnia without depressive symptoms in older people is rather scarce and controversial[29].

In Belgium, the consumption of benzodiazepine and Z-drugs is high[30] -485 million DDD in

2012 as reported by de Algemene Pharmaceutische Bond)- especially among older adults (in 2008, 13% used an anxiolytic BZD and 10% used a hypnotic BZD in the past 24h [3]). In comparison to other European countries, Belgium together with France, Portugal and Sweden are large consumers of these drugs (rapport ANSM 2013)[31]. In the neighbouring country, the Netherlands, the consumption is lower and decreased due to the cancellation of the reimbursement in 2009 [32]. There are several possible hypothesis that can explain why the Belgian consumption is high. Though BZD/Zs are not reimbursed by the health care system, the out-of-pocket cost is relatively low. Furthermore, there is the global medicalization of psycho-social problems [33].The patient's expectation together with the lack of communication and motivational techniques can pressure the physician to prescribe medications [34, 35]. Cultural aspects such as religious background have also been shown to impact the cross-national differences in medication use (difference in antibiotic use [36]). Although the physician is the only person allowed to prescribe medication, the final decision is the result of a complex interaction between patient and physician [37]. In comparison to the UK and US, there was a relative late start of federal campaigns to increase the awareness of BZD/Z consumption in Belgium (public campaigns and educational programs for physicians and pharmacists were launched after 2001). Moreover, in Belgium the patient is free to choose both his general practitioner (GP) and pharmacist and can easy switch or consult multiple caregivers. The remuneration of the GP is based on a fee-for-service principle which can influence the already complex patient-doctor relationship.

In general, the use of benzodiazepine and Z-drugs (BZD/Z) is linked to older age [38, 39], with the highest prevalence in older adults in residential care [40].

Benzodiazepines have several pharmacological actions, but are mainly used to treat sleep problems and anxiety [41]. Though BZD/Zs are effective and relatively safe medication when used acutely, many national and international guidelines [41-44] warn for chronic BZD/Z use because of the lack of effectiveness after 4 weeks, the increased risk of dependence, and side-effects [45-47]. BZD/Zs have reinforcing effects which can result in abuse liability (nonmedical use). However, the abuse for recreational purpose is rare in older adults [48, 49].

A remarkable contradiction between recommendations against long-term use of BDZ/Z drugs and their high prevalence, especially in older adults, raises several questions: are the guidelines too strict; is the evidence of associated risk not convincing; are prescribers reluctant; or is it too difficult to overcome habitual prescribing in this older population?

1.2 BENZODIAZEPINES, AN OVERVIEW

The benzodiazepines (BZDs) are a group of psychoactive drugs with sedative, hypnotic (sleep-inducing), anxiolytic, anticonvulsant (anti-epileptic), muscle relaxant and amnesic action. Since their development in the mid '50s by Leo Sternbach and his colleagues at Roche, they quickly replaced the less safe barbiturates and became a frequently prescribed drug for anxiety and/or insomnia [50, 51].

The more recently developed benzodiazepine receptor agonists (Z-drugs), zolpidem, zopiclone, eszopiclone and zaleplon entered the market in the late '80s. They work similar as the BZDs, though they are mainly indicated for hypnotic use. Since the '80s, several guidelines and campaigns warned for the detrimental effects of BZDs (tolerance and dependence) and the newer Z-drugs were promoted as more selective and with less side-effects, despite the lack of evidence[52]. Consequently, Z-drugs were increasingly prescribed, while the use of benzodiazepine hypnotics decreased [53, 54]. Later research showed that Z-drugs have an equally

harmful risk profile as BZDs [54, 55].

Due to the BZDs' differential kinetics and interaction with the receptor, they somewhat differ in usage. Short- and intermediate-acting benzodiazepines (duration of action around 24h or less) are preferred for the treatment of insomnia; longer-acting benzodiazepines (duration of action exceeding 24h) are recommended for the treatment of anxiety [41]. The Anatomical Therapeutic Chemical (ATC) system from the World Health Organisation [56] classifies the BZDs and Z-drugs into Hypnotics (N05CD), Anxiolytics (N05BA) and Z-drugs (N05CF). This classification is not really instrumental to distinguish between clinical indications, as most BZDs have diverse pharmacological properties: sedative, anxiolytic, hypnotic, antiepileptic, muscle relaxant and amnesic.

1.2.1 Pharmacodynamics

BZDs interact with the gamma (γ)-aminobutyric acid (GABA) receptor, which is a part of the major inhibitory neurotransmitter system in the brain [57, 58]. There are three families of the GABA receptor: $GABA_A$ and $GABA_B$ and $GABA_C$(GABAA-ρ subclass) , but the BZDs only bind with the $GABA_A$ receptor at a specific BZD site. BZDs facilitate the action of the neurotransmitter GABA by increasing the influx of negatively charged chloride ions and enhance the neuronal inhibition of GABA, resulting in the hypnotic, anxiolytic, sedative, muscle relaxant action. The $GABA_A$ receptor consists of 5 different transmembrane subunits. There are several possible subunits (α1-6, ß1-3, γ1-3, δ, ε, θ and π) that result in the heterogeneity of the $GABA_A$ receptor [59]. The most common receptor type is composed of two α, two ß and one γ subunit [60]. Depending on the subtype of the $GABA_A$ receptor, they are present in different locations throughout the brain, indicating that they have different functional properties. Each receptor complex has two GABA binding sites but only one BZD binding site (located between α and γ subunit [61]). Not all BZDs interact with the same type of $GABA_A$ receptor or with equal affinity, which results in the more selective work profile of the BZDs [58].

More into detail, α1 containing $GABA_A$ receptors are probably more sedative, amnesic and anticonvulsant. Muscle relaxation and anxiety reduction are primarily ascribed to α2 and possibly α3. Researchers are still not sure of the clinical relevance of pharmacodynamic differences among BZDs caused by the differential selectivity for the $GABA_A$ subtypes.[59]. Clinicians more often use the pharmacokinetic properties to categorise BZDs.

The Z-drugs also interact with the $GABA_A$ receptor similarly to the BZDs and at the same binding site (between the α and the γ subunit). Zolpidem has a preferential agonistic activity at the α1 subunit [62].

With aging, pharmacodynamics change: the atrophy of neurons, loss of receptors and altered receptor affinity leads to a changed sensitivity of the central nervous system (CNS) which increases the possibility of CNS side effects, such as confusion, increased postural sway and subsequent risk of falling [1, 63].

1.2.2 Pharmacokinetics

The pharmacokinetic properties of BZD/Zs describe their absorption, distribution, metabolism, and excretion (i.e. what the body does to the drug). This pharmacokinetic profile determines the onset and the duration of action. The most common way to classify BZD/Z drugs is based on their elimination half-life ($T_{1/2}$: the time needed to reduce the drug concentration in the plasma by half)[58]. In our studies, we categorize BZD/Zs according to half-life in short/intermediate ($T_{1/2}$<24h) and long-acting ($T_{1/2}$≥24h) [41, 64]. However, these arbitrary cut-offs are

not universal and vary per country[65]. Some BZD/Zs produce active metabolites and this extends their duration of action (see box 1).

BZD/Zs can be administered via oral, sublingual, intramuscular, intravenous, intranasal or rectal route, of which the oral route is the most common. BZD/Zs are usually well absorbed by the gastrointestinal tract after oral administration. The lipid solubility of the BZD/Z increases the absorption and distribution. The fast absorption through the blood-brain barrier results in a quick onset of clinical effect. The increased distribution extends the plasma half-life. Most BZD/Zs and their metabolites are highly protein bound. They are widely distributed in the body and preferentially accumulate in lipid-rich areas such as the central nervous system (CNS) and the adipose tissue. Most of the BZD/Zs are oxidatively metabolized by the cytochrome P450 enzymes in the liver (phase I metabolism), conjugated with glucuronide to make them more water soluble (phase II metabolism), and excreted almost entirely in the urine [58]. Long-term use and repeated daily doses result in accumulation in fatty tissue and possible hangover effects (residual drowsiness i.e., day-time somnolence and marked psychomotor and cognitive impairment)[66, 67].

Box 1. Characteristics of all available Benzodiazepines and Z-drugs in Belgium (in 2014)*

BZD	Protein binding (%)	Half-life (active metabolite)	Active Metabolites	10mg diazepam equivalent	Defined Daily Dose-oral administration
LONG-ACTING					
Clobazam (Frisium®)	83%	12u-60u	Yes	20mg	20mg
Clonazepam (Rivotril®)	85%	18u-50u	Inactive	0,5mg	8mg
Chlorazepate (Tranxene®)	98%	(36u-200u)	Yes	7.5-15mg	20mg
Cloxazolam (Akton®)	97%	(50u-80u)	Yes	1-2mg	no DDD
Diazepam (Valium®)	98%	20u-80u (36u-200u)	Yes	10mg	10mg
Ethyl loflazepate (Victan®)	99%	(50-100)	Yes	1-3mg	2mg
Flunitrazepam (Rohypnol®)	78%	18u-26u (36-200)	Yes	1mg	1mg
Flurazepam (Staurodorm®)	98%	40min (40u-100u)	Yes	15-30mg	30mg
Nitrazepam (Mogadon®)	87%	15u-38u	Inactive	5-10mg	5mg
Nordazepam (Calmday®)	95-98%	36u-200u	Yes	10mg	15mg
Prazepam (Lysanxia®)	97%	(36u-200u)	Yes	30-60mg	30mg
INTERMEDIATE-ACTING					
Alprazolam (Xanax®)	80%	6u-27u	Inactive	0,5mg	1mg
Bromazepam (Lexotan®)	70%	8u-22u	Inactive	5-6mg	10mg
Brotizolam (Lendormin®)	90%	3u-8u	Yes	0.25-0.5mg	0.25mg
Clotiazepam (Clozan®)	95%	4u	Yes	5-10mg	No DDD
Loprazolam (Dormonoct®)	80%	6-12u	Yes	1-2mg	1mg
Lorazepam (Temesta ®)	85%	10u-20u	none	1mg	2,5mg
Lormetazepam (Stilaze®)	85%	10u	Yes	1-2mg	1mg
Oxazepam	97%	5u-15u	none	20mg	50mg
SHORT-ACTING					
Triazolam (Halcion®)	89%	2u	Inactive	0.5mg	0,25mg
Midazolam (Dormicum®)	97%	1,5u-2,5u	Yes	7,5-15mg	15mg
Z- drug	**Protein binding (%)**	**Half-life (active metabolite)**	**Active Metabolites**	**10mg diazepam equivalent**	**Defined Daily Dose (oral administration)**
Zolpidem (Stilnoct®)	92%	1,5u-2,5u	none	20mg	10mg
Zopiclon (Imovane®)	45%	5u	Yes	15mg	7,5mg

*based on the information of the Ashton Manual, the World Health Organisation Defined Daily Dose, the Belgian Centrum for Pharmacotherapeutic Information and the company's summary of product characteristics; temazepam was not commercialised on the Belgian market;, tetrazepam and zaleplon were removed from the Belgian market in the last 3 years

Aging has also some pharmacokinetic implications. While BZD/Z absorption is not really altered, the reduced first-pass metabolism due to a reduction in liver mass and blood flow can lead to an altered clearance of drugs through the liver. The drug metabolizing enzymes and conjugation process is not really altered. However, multiple drug use can impede drug metabolisation. The body composition changes with a progressive reduction in total body mass resulting in a relative increase in body fat. Therefore, the lipid soluble BZD/Zs have an increased distribution and a prolonged half-life [1, 63].

1.2.3 Efficacy

Benzodiazepines are considered to be acutely effective for the treatment of insomnia, anxiety, epilepsy, muscle cramps, and as (pre) anaesthetic.
The efficacy of BZD/Zs for insomnia will be addressed in section 1.3.

Anxiety disorder is an umbrella term that covers several different forms such as generalised anxiety (GAD), panic disorder, posttraumatic stress, social phobia (social anxiety disorder SAD), specific phobias and obsessive compulsive disorder (OCD)[68]. Anxiety disorders can exist in isolation but often co-exist with psychiatric disorders, most commonly depression [69]. BZD are efficacious in the acute treatment of GAD, SAD and panic disorder, but have limited effect on other anxiety conditions (OCD, agoraphobia, phobias) [70]. Because most anxiety disorders tend to be chronic for which long-term treatment is often necessary and because it rarely exists as a single condition, guidelines (NICE guideline on GAD and panic disorder in adults[71], national guideline[72], Trimbos guideline[73]) recommend use of psychological therapy or an antidepressant. Non-pharmacological therapy such as cognitive behavioural therapy (CBT) has proven to be effective in the long-term (>1 year) [69]. Tolerance and dependency problems of BZDs and the concurrence of depression are the reasons why antidepressants are the pharmacological choice for (chronic) anxiety [68]. Selective serotonine reuptake inhibitors (SSRI's) are preferred above tricyclic antidepressants because of their less severe side-effect risk. However, a recent review questions the superiority of antidepressants over BZDs in terms of efficacy and tolerability [74].

Epilepsy, more specifically status epilepticus (prolonged or repeated generalised, convulsive seizures) can be successfully treated with an acute administration of BZDs (diazepam, lorazepam, midazolam) (NICE clinical guidelines 2012[75]). Also muscle spasms can be effectively treated with BZDs (mainly diazepam and tetrazepam) [76]. Although they are not recommended for low back pain (NICE 2009[77]), some studies showed that tetrazepam was beneficial in improving pain [78]. However, muscle spasm can be seen as a protective mechanism that should not be inhibited by muscle relaxants. BZDs are not effective for muscle spasm in rheumatoid arthritis [79].

1.2.4 Tolerance

BZDs and related Z-drugs are initially efficacious, but after 2 to 4 weeks, the effects fade and tolerance develops. Tolerance is defined as a decrease over time in the ability of the drug to produce the same degree of pharmacological effect [80].Tolerance is a major factor, impeding on the efficacy of long-term use. It appears at different rates and to a different degree for each of the BZD's effects, including the side-effects [80, 81]. BZDs with short half-life are more likely to produce tolerance [82, 83]. Clinical studies showed that tolerance to the sedative and hypnotic effect occurs more quickly than for the anticonvulsant effect [80, 82]. Full tolerance to the anxiolytic effect has not been demonstrated [80]. Most clinical data do not support the existence of tolerance to the BZDs' induced cognitive impairments (memory impairment)[57, 84]. The neuro-adaptive mechanism that underlies BZD tolerance is still unclear and several hy-

potheses are possible: down-regulation of the $GABA_A$ receptor is an obvious potential mechanism explaining both tolerance and withdrawal when stopped. However, there is increasing experimental evidence for different neuro-adaptive mechanisms: uncoupling of the linkage between GABA en BZD site on the receptor, intracellular changes (subunit gene turnover and changes in receptor gene expression), compensatory mechanism of glutamate receptors, interaction with other neurotransmitters and neurosteroids [57].
Tolerance implies that a dose escalation is necessary in order to maintain the desired clinical effects. However, in most studies investigating prescribing of BZDs and Z drugs, such a dose escalation was not seen among low-dose users [85, 86]. Though hypnotic and anxiolytic effects fade, patients do not ask for a dose increase. This is also a reason to belief that there is a strong placebo effect and/or psychological dependence present. The minority of patients that do ask for a higher dose have specific personality traits [87] or severer psychiatric problems, and combine psychotropic medication [85].

1.2.5 Dependence and withdrawal symptoms

BZD/Zs dependence is multidimensional and includes both physical and psychological elements (WHO definition). The term addiction should be considered a synonym for dependence, though in many contexts, the former term has a different connotation (behaviour that is out of control). In the '60s the WHO recommended to abandon 'addiction' in favour of 'dependence', which can exist in various degrees of severity. BZD/Z dependence/addiction is distinct from BZD/Z misuse, which implies nonmedical use, use for pleasurable purpose, and criminal use (out of scope in this thesis).

Physical dependence refers to the development of withdrawal symptoms in response to drug cessation or decrease in dose [88]. The main withdrawal effects are agitation, irritability, increased sensitivity to light and sound, muscle cramps, headache, dizziness, nausea, loss of appetite, and also rebound insomnia or anxiety, which can be more intense than the initial symptoms for which the BZD/Z was started[89]. These symptoms can be mistakenly seen as the persistent efficacy of the BZD/Z and are often the reason to continue use. The duration of (chronic) use, the BZD/Z half-life (the longer the half-life, the longer the timespan of the appearance of withdrawal symptoms) and the dose all affect the start and duration of withdrawal symptoms [81]. Rebound insomnia and anxiety are more intense in BZD/Zs with a short elimination half-life [83]. The rebound insomnia and tolerance are commonly perceived to be derived from the same compensatory mechanism by which the $GABA_A$ receptor becomes less responsive to the continuing acute effects of BZDs due to several adaptation (see tolerance) [57, 80].

The most recommended clinical option to overcome withdrawal symptoms is supervised gradual tapering [90], though abrupt discontinuation of long-term low-dose treatment seems feasible [91].

Psychological dependence is a more complex concept. Psychological dependence is a dependency of the mind (cravings, irritability) and includes some form of loss of control (lack of respect for dose restrictions and treatment periods, compulsive drug-seeking behaviour e.g. forging prescriptions, going to multiple doctors for prescriptions). Psychological dependence is believed to be strongly associated with particular areas of the brain's rewarding system (dopamine)[92]. Craving is regarded as an important aspect of dependence as this can be the reason why patients relapse after a discontinuation [93]. BZD/Zs craving is still a vague concept and appears in varying degrees. In some research [94] drug insistence (not wanting to discontinue) is labelled craving. As shown in another study, the majority of the long-term BZD/Z users show minor signs of craving (positive evaluation of initial effectiveness, fear of relapse

upon withdrawal)[95].

BZD/Z dependence (both physical and psychological) can lead to a 'substance related and addictive disorder' (as defined by the DSM-V criteria) and refers to problematic pattern of BZD/Z use leading to clinically significant impairment or distress[81].

1.2.6 Side-effects of benzodiazepine use

The acute side-effects of benzodiazepines and Z-drugs are inherent to their working mechanism. BZD/Z drugs induce sedation and muscle relaxation, which can cause impaired alertness, drowsiness, impaired driving skills, and increased risk of falling[47, 96] . A common side effect of BZDs, especially of long-acting drugs, is the residual drowsiness i.e. day-time somnolence, and marked psychomotor and cognitive impairment [66, 97]. Depending on someone's susceptibility, the BZD's potency and dose, BZD/Zs can cause paradoxical effects such as increased anxiety, seizures, and disinhibiting effects such as aggression [98, 99] (occurs in less than 1% of patients). Other rare paradoxical effects related to the hypnotic use of BZD/Zs, include complex sleep-related behaviours (sleep walking, eating, driving and aggressive behaviour) [100, 101]. Upon acute use, BZD/Z drugs impair several areas of cognition (attention, reaction time and psychomotor functions) and cause anterograde amnesia [102, 103]. Cognitive and psychomotor impairment can be detected even at ostensibly therapeutic doses (1 DDD).

Although most BZDs and Z-drugs are often used chronically, the evidence on side-effects is as inconclusive as the evidence on the effectiveness. Cognitive impairment and incident dementia has been linked to long-term BZD/Z use, but the literature is inconclusive [104]. While some studies suggest a negative effect of chronic BZD/Z use on cognitive decline [105-108] and even an increased risk for dementia[109-112], others did not find an association [113-115], and some even found a protective effect of BZD use on cognition [116, 117]. These studies are not equally comparable with each other due to different methodological design (prospective cohort, whether or not controlled, nested case control), due to the used outcome measurements to evaluate cognition (ceiling effects, varying sensitivity to change) [118, 119] and due to the heterogeneity of the study population (some were psychiatric patients, some healthy adults,…).
Most of the abovementioned side-effects are not life-threatening, some fade due to tolerance, and some might be reversible [47]. However, several studies have postulated an increased mortality risk (an association) in chronic BZD/Z users [120-124], while others failed to draw such conclusions [125, 126]. The inconsistent findings are mostly due to methodological limitations, the study design, the duration of follow-up (2.5y till 20years), the heterogeneity in age ranges and heterogeneity in sample size, the type of hypnotic, and finally, the lack of distinction between indications (use for psychiatric disorders or for sleep disorders [125]).

1.3 BENZODIAZEPINES FOR SLEEP PROBLEMS

Benzodiazepines and Z-drugs are the most commonly used symptomatic treatment for sleep problems [127, 128]. The BZD/Zs that are used for this indication have fast absorption and distribution rates, which result in rapid sleep induction and is particularly important since delayed sleep onset is a major complaint of sleep problems.

Sleep problems affect 10-15% of the general population and increase with growing age [128, 129]. In the normal aging process, changes in the sleep structure occur with less restorative deep sleep (i.e. stage III of the nonrapid eye movement NREM) and a more fragmented sleep pattern [130]. In addition, comorbidities, medication use and sleep-related disorders (restless legs, periodic limb movement, sleep apnoea), all affect sleep quality and increase with age

[131]. In Belgium, more than one in four adults aged 65 or more experienced sleep problems (27% in the 2008 Health Interview Survey Belgium)[3].

Sleep problems are categorised into dyssomnia (restless legs, periodic limb movement, sleep apnoea, narcolepsy), into parasomnia (REM sleep behaviour disorder, night terrors, sleep waking) and into insomnia, of which the latter is the most common disorder and therefore the most researched. The diagnostic systems (such as the American Psychiatric Association DSM-V[132], the American Academy of Sleep Medicine International Classification of Sleep Disorder ICSD-2[133], the World Health Organisation International Classification of Diseases ICD-10), use different definitions for insomnia, which makes mutual comparison of insomnia research difficult [134]. Although all systems include daytime impairment in their criteria for insomnia, this requirement is not always fulfilled when BZD/Zs are prescribed in clinical practice. In this thesis, as well as in clinical practice, poor sleep and problems with initiating and maintaining sleep (even without daytime impairment) is often labelled as insomnia.

Box 2. Diagnostic criteria for common insomnia types (adopted from the ICSD-2, 2005 of the American Academy of Sleep Medicine, the WHO ICD-10 classification, and from the American Psychiatric Association's DSM-V, 2013

INSOMNIA		
Primary insomnia	-	problems with initiating sleep, maintaining sleep, waking up too early, or nonrestorative sleep although there is adequate opportunity for sleep
	AND	
	-	daytime impairment
	EXCLUDE Sleep disturbance DUE TO underlying medical, psychiatric, or environmental problem	
Psychophysiological insomnia	-	idem primary insomnia
	AND	
	-	at least present for 1 month
	AND	
	-	the patient has evidence of conditioned sleep difficulty and/or heightened arousal in bed
Comorbid insomnia	-	sleep disturbance is comorbid with an underlying problem
Paradoxical (Pseudo) insomnia	-	complaints of insufficient and/or unsatisfying sleep
	BUT	
	-	no daytime impairment

In terms of BZD/Z efficacy research, the most studied indication is primary insomnia (insomnia without any underlying problem or comorbidity). However, a majority of insomnia patients have sleep problems originating from an underlying disorder, such as cardio-metabolic disorders, musculoskeletal conditions (arthritis, chronic back or neck pain), respiratory disorders, digestive disorders, chronic pain, all known as comorbid (or secondary) insomnia [135]. Psychiatric disorders (with anxiety disorder, depressive disorder, bipolar disorder and adjustment disorder) are the most common conditions comorbid with insomnia[135, 136]. In the older (nursing home) population, the aging process causes a fragmented sleep pattern, which is more vulnerable to the underlying comorbidities [131, 137]. Unfortunately, these patients are often either excluded in clinical research, either not recognised as such. Therefore, there is no effectiveness data available for this large patient group.

Insomnia is a clinical diagnosis based on the reporting of the patient. Therefore, clinical studies on the effectiveness of BZD/Zs should combine objective and subjective evaluation of sleep parameters. Next to the decrease in sleep latency and increase in total sleep duration, it is important to measure the feeling of being well rested and daytime fatigue. Therefore, in our studies we will use a subjective scale that measures different aspects of sleep quality (The Pittsburgh Sleep Quality Index- Buysse 1989[138]).

BZDs and Z-drugs are effective for short-term treatment of insomnia [139]. Systematic reviews showed that time to fall asleep is decreased and total sleep duration enhanced [127, 140-142]. Objective polysomnographic research showed also an altered sleep structure, with an increase in NREM, a decrease in deep sleep (SWS) and a prolonged REM latency. A meta-analysis in older people with insomnia [143] showed an improvement in sleep quality, an increased total sleep time (mean 25min), and a decreased number of night-time awakenings when using BZDs and/or Z-drugs compared to placebo. Though the effect sizes are significant, their magnitude is small. Moreover, a meta-analysis indicated that the objective polysomnographic measurements show small improvement in sleep latency and sleep duration, while the patient's reported subjective sleep latency (assessed with sleep diaries or questionnaires) was more optimistic[140]. This indicates that there may be an overestimation of the BZD's effects on sleep outcome parameters [140]. Moreover, the selective reporting and publishing of positive studies and results also indicates that there is an overestimation favouring the BZD/Z drugs' effects [141, 144]. In addition to the possible overestimation of the BZD/Z's effects, several meta-analysis showed that placebo treatment also improves the sleep significantly [145, 146]. Because BZD/Zs are not free of side-effects, the overall risk/benefit balance must be taken into account. Moreover, all these studies investigated the effect of a short-term treatment. The maximum study duration for BZDs is 8 weeks[147] and for Z-drugs it is 1 year [148, 149]. Although the majority of BZD/Z users are chronic users, research on long-term BZD or Z-drug use is lacking.

Till now, there is a lack of a credible evidence base for the long-term efficacy of BZD/Z use. Because of practical obstacles but also because long-term BZD/Z therapy is not concordant with the guidelines, it is difficult to initiate randomised controlled trials with incident users and follow the sleep longitudinal. The studies that did try to evaluate long-term effectiveness found a worse sleep quality in long-term users [46, 111, 150]. After taking into account both the short-term and long-term risks of BZD/Z use, and in the light of questionable effect of these drugs on sleep problems in the long-term, guidelines discourage chronic BZD/Z use.

1.4 BENZODIAZEPINES IN THE NURSING HOMES

The prevalence of BZD/Z use in older adults in residential care ranges from 28% to 55% in European [40, 151-153] and Australian nursing homes (32%)[154]. In the UK and US the prevalence is somewhat lower, 13% and 14% respectively [7, 19], due to special warnings (OBRA-87 and government initiatives) and a shift towards sedative antidepressants [27].
In Belgium, more than 50% of the older nursing home residents (PHEBE in 2006) received BZD/Z drugs. In nine out of ten residents, this use was longer than 3 months indicating chronic use[11].

1.4.1 Belgian nursing home setting

Belgium has a mixed, public (community health services)/private (predominantly non-profit) health care system, with little difference in quality. The payment system is fee for service. An essential principle of the Belgian health care system is the patient's

freedom of choice of his primary and specialist care provider. When entering the nursing home, most of the residents retain their own GP, which leads to an average of 32 visiting GPs per nursing home. Although each nursing home has a medical coordinator who is a general practitioner to a certain extent trained in care for older people, the GP retains the responsibility for the treatment and the medication policy[155].

1.4.2 The high use and associated problems of benzodiazepines in the nursing homes

Coming into a nursing home can be stressful and can provoke anxiety. Moreover, sleep problems are common in institutionalised settings. Not only because aging negatively affects sleep architecture, but also because environmental factors such as high level of noise, light and care routines can disrupt sleep [128]. Although one may expect that this is a place where a lot of BZD/Z drugs are initiated, most older adults enter the nursing home with already established BZD/Z use; the BZD or Z-drug is fixed on their medication list for years, even decades [114, 156, 157]. Often, the BZD/Z is initiated in primary care by their general physician [35] or during a hospital admission [158, 159]. The acute effectiveness, the establishment of dependency problems and the lack of reassessment leads to chronic continuation of these drugs. Although tolerance to the hypnotic and anxiolytic effects occur, aging increases the susceptibility towards the side-effects of medication. The atrophy of neurons and the intensified sensitivity of the central nervous system, together with pharmacokinetic alterations, which lead to BZD/Z accumulation, increases the possibility of confusion and CNS side-effects, hangover effects and subsequent risk of falling [1, 160, 161]. Often falls have no major consequences, but in older fragile adults this can cause injury and fractures, leading to hospitalisation and serious disability[162]. When BZD/Zs are used as sleep promoting agents, nocturia with frequent midnight visits to the bathroom increase fall risk [96]. It has been questioned whether there is an independent association between BZD/Z use and increased fall risk. Not only have falls a multifactorial aetiology (environmental, intrinsic muscle strength and extrinsic factors), but other psychotropic drugs are also associated with a 30-70% increased risk of falls [163-165].

This age group, with a higher risk of abovementioned side-effects, needs tailored prescribing which includes de-prescribing[166]. Discontinuation of BZD/Z is widely advised, but has not reached global acceptance among prescribers, care givers and patients.

When confronting both the benefit and risk of BZD/Zs, their use seems to have drawbacks, especially for long-term use, and in this older population. Research on effectiveness and side-effects of chronic BZD/Z use remains inconclusive with few studies in the setting with the most abundant use, the nursing home setting.

2 RESEARCH QUESTIONS

Although guidelines and national campaigns discouraged chronic benzodiazepine and Z-drug (BZD/Z) use, the Prescribing for Homes in the Elderly in BElgium (PHEBE) study in 2006 revealed that the psychotropic drug use in the Belgian nursing homes was high (79%) and the BZD/Zs were the most abundant drugs on the medication chart (53%). This was the trigger for our research.

The research questions are:

1. What are the indications of the benzodiazepines and Z-drugs used in the nursing home and at which dosages (chapter 2.1)?
2. What is the proportion of antidepressants used for insomnia and anxiety in the nursing home and what are the dosages (chapter 2.2)?
3. What is the sleep quality of chronic BZD/Z use in nursing home residents and does it differ from nonusers (chapters 2.3 and 2.4)?
4. What is the relationship between chronic BZD/Z use and cognitive deterioration in nursing home residents? (chapter 2.5).
5. Is it feasible to implement discontinuation in the nursing home (chapter 2.6 and 2.7)?

3 THESIS OUTLINE

In Chapter 2.1, we describe the indications and dosages of BZDs and Z-drugs in Belgian nursing homes in order to understand the highly prevalent use in this setting.

Antidepressants and benzodiazepines have overlapping indications and are both used for insomnia and anxiety (trazodone is becoming a popular sleeping aid). In Chapter 2.2, we investigate the indications and dosages of antidepressants for those overlapping indications. Both these studies (chapter 2.1 and 2.2) are based on a secondary analysis of a cross-sectional representative study on medication consumption in the Belgian nursing homes (PHEBE-study).

In Chapters 2.3 and 2.4, we focus on the BZD/Z use for insomnia. For this indication, we want to contribute to the questionable benefit and provide information on chronic effect of BZD/Z use in terms of sleep quality (Chapter 2.3 and 2.4). We set up a prospective cohort study, comparing chronic BZD/Z users and nonusers and provide a cross-sectional analysis of the sleep quality using a validated sleep questionnaire (Pittsburgh Sleep Quality Index) in Chapter 2.3. In Chapter 2.4, we analyse the temporal evolution of the sleep quality and the possible difference between chronic BZD/Z users and nonusers in a one-year follow-up.

In Chapter 2.5, we explore the worrisome link of BZD/Z use with cognitive decline. In the same cohort, we analyse whether chronic BZD/Z users have a different one-year evolution in cognition (as measured with the Mini Mental State Examination Score) compared to nonusers.

In the last two chapters, we want to analyse the feasibility of BZD/Z discontinuation in the nursing home setting.

In Chapter 2.6, we explore barriers towards discontinuation pertaining to an individual resident in a cross-sectional survey among GPs and nurses.

In Chapter 2.7, we investigate the feasibility of discontinuation in a pilot study. In a small sample of cognitively competent residents we investigate overall feasibility and several outcome parameters such as change in sleep quality, quality of life and withdrawal effects.

Finally, we present our discussion and several implications for research and practice.

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CHAPTER 2.1

Benzodiazepine use in Belgian nursing homes: a closer look into indications and dosages.

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ABSTRACT

Objectives:
(i) To describe the prevalence of benzodiazepine (BZD) and Z-drug use in Belgian nursing homes, with specific attention to indications and dosages.
(ii) To compare actual and recommended dosages of BZDs and Z-drugs for anxiety and insomnia.
(iii)To explore the risk profile for chronic BZD/Z use in institutionalised older adults.

Methods: Medication charts of 1730 residents from 76 nursing homes in Belgium were collected and analysed, using the ATC classification. Drug name, indication and daily dosage were recorded. From authoritative international sources, we extracted for each drug and each indication a daily dosage recommended not to be exceeded in older adults for comparison with observed actual dosages.

Results: Among the chronic BZD/Z users (50% of the residents), the leading indication was 'insomnia' (59% of the users) followed by 'anxiety' (17%) and 'unrest' (10%). In the chronic prescriptions of BZD/Zs indicated for insomnia, the actual daily dose exceeded the geriatric upper limit: with lormetazepam in 95% ,zolpidem in 82%, zopiclone in 78% and lorazepam in 35% of the prescriptions. In anxiety, daily doses also exceeded the limit but not to the same extent.

Multivariate analysis showed BZD/Z use was positively associated with pain (OR 1.58 CI95% 1.27-1.97), constipation (OR 1.43 CI95% 1.16-1.76) and depression (OR 1.68 CI95% 1.35-2.08). Residents with dementia were less likely to receive a BZD/Z (OR 0.60 CI95% 0.48-0.74).

Conclusion: Efforts to reduce the use of BZD/Zs in nursing homes should concentrate on insomnia, with interventions aimed at reducing too high prevalence of chronic use and too high daily dosages in this indication.

INTRODUCTION

Benzodiazepine utilisation in older adults is high, with intake rates varying from 28% to 55% in European nursing homes [1-4].

Benzodiazepines are mainly indicated for the short-term treatment of insomnia and anxiety [5, 6]. Long-term use of benzodiazepines is discouraged in guidelines [5, 7, 8] because of the lack of effectiveness after 4 weeks [9, 10], the increased risk of dependence and abuse, and withdrawal syndromes [11, 12]. Moreover, it has been hypothesised that long-term use might have a detrimental effect on cognition and a potential acceleration of cognitive impairment [13-15].

High benzodiazepine utilisation in older adults is especially worrying, since age-related pharmacokinetic-and dynamic alterations may lead to an increased risk of amnesia, confusion, sedation [16, 17], hangover effects [18, 19] and subsequent risk of falling [20].

International drug formularies [21-23] recommend dose reduction when using benzodiazepines in older adults. Moreover, in several attempts to develop prescribing quality indicators, upper limits for dosages in older adults have been established for some benzodiazepines as part of lists with explicit criteria for inappropriate prescribing [24-26]. In addition, benzodiazepines are the most recurring group of drugs in terms of chronic prescribing and in terms of inappropriate psychotropic polypharmacy. Numerous studies have explored benzodiazepine utilisation in older adults, but they are often limited to the description of crude utilisation data, without looking deeper into active substances, dosages and indications. Previous articles indicate the need for documentation of indications to properly evaluate the appropriateness of psychotropic drug use [27, 28]. Therefore, the aim of this study was to describe the prevalence of benzodiazepine use in Belgian nursing homes, with attention to indications and dosages for each of the commonly used drugs. Furthermore, we compared actual dosages with recommended dosages in older adults and explored the risk profile for chronic benzodiazepine use.

METHODS

Data for this secondary analysis study were obtained from a multicentre study, investigating the overall drug utilisation in Belgian nursing homes. A detailed description of the methods and findings of this study was published elsewhere [1, 29].

Setting:

Belgium has a mixed, public/private health care system. The system is fee for service. An essential principle of the Belgian health care system is the patient's freedom of choice between a wide range of independent care providers without listing system. In particular, the Belgian long-term residential care structure consists of residential and/or nursing homes for older people, which offer a home replacement with or without nursing care. Governance of nursing homes for older people is either public (community health services) or private (predominantly non-profit). Each nursing home has a medical coordinator who is a general practitioner, additionally educated in care for older people. Most of the residents are still treated by their own GP, with an average of 32 visiting GPs per nursing home. Thereby, the GP has the responsibility for the treatment and medication policy. Periodic reassessment of the medication charts (i.e. a protocol for monitoring and discontinuation of therapy) is not mandatory.

Data collection:

The PHEBE study (Prescribing in Homes for the Elderly in BElgium) was a cross-sectional, descriptive study of a representative, stratified random sample of 76 Belgian nursing homes. Data collection at resident level included administrative, clinical and medication data. To score the activities of daily living (ADL), we used the Katz scale[30] which is a mandatory instrument in Belgian nursing homes. The progression of disorientation as proxy for dementia severity was also scored by this instrument, ranging from a score 1 (no dementia) to 5 (severe dementia).
For collecting clinical data, a checklist with 28 items, focusing on clinical problems (i. e. diseases with a clear cut diagnosis such as COPD, cardiovascular diseases,…) and on care problems (i.e problems with a predominant nursing care burden such as incontinence, pain, risk of falling,…) was sent to the general practitioner (GP) of each included resident. The 28-item checklist of clinical conditions was ad hoc designed for this study, with the items selected based on existing prescribing quality indicators for the elderly (BEERS, BEDNURS, ACOVE). It was pilot tested in two nursing homes.
The GP received a printout of the medication chart for verification of the medication use, and was asked to tick a predefined list of main indications for each medication. Residents considered by their GP as having a palliative status were excluded from the analysis.

Classification of benzodiazepines:

Benzodiazepines (BZD), a group of psychoactive drugs with sedative, hypnotic, anxiolytic, anticonvulsant, muscle relaxant and amnesic action [5] were coded according to the Anatomical Therapeutic and Chemical classification [31]. We investigated the benzodiazepines, available on the Belgian pharmaceutical market of the ATC classes hypnotics (N05CD), anxiolytics (N05BA) and also the related Z-drugs (N05CF). This classification is not strictly linked to the clinical indication, as most of the BZDs have a mix of different pharmacological actions, and Z-drugs act mainly hypnotic. Clonazepam (N03AE01) mostly used for the indications 'restless legs' and 'epilepsy', and tetrazepam (M03BX07), used as a muscle relaxant, were not included in this study. Duplicate use therapy was defined as the concomitant use of 2 or more differ-

ent benzodiazepines or Z-drugs (BZD/Z). The focus of this study was chronic use, which was defined as daily use for at least 3 months. We analysed 2 levels of describing BZD/Z use: the prescription (medication) and the resident level. Indications were analysed at resident and prescription level and dosages at prescription level only.

Indications and dosages:

The indication of each BZD/Z drug was obtained from the GP who ticked an item on a predefined list of indications: anxiety, insomnia, unrest, epilepsy, muscle tension and acute agitation. Only the indications anxiety, insomnia and unrest were analysed in depth, as the other indications were not prevalent enough. Unrest is the symptom targeted by mild sedatives, intended to calm a restless patient. It is to be distinguished from the narcotic sedation used in palliative setting. When a physician ticked 2 or more indications for the same BZD/Z, we classified this as 'multiple indications'. Only BZD/Zs with a minimum frequency of 15 prescriptions were reported in this study.
The daily dosage of each BZD/Z in each patient was recorded by summing the doses taken at the different moments of intake during one day. Comparison between prescribed daily dosages of a BZD/Z for different indications was made when at least 5 prescriptions for each indication were present. We also analysed the different moments of intake to see fractionation.

Determination of the daily dose recommended not to be exceeded in older adults:

Reviewing several international pharmaceutical sources with dose recommendations for older adults, we selected 3 international formularia [21-23] and 3 explicit criteria for inappropriate prescribing for older adults [24-26] that mentioned detailed information per active substance. These sources were the basis of selecting 'the geriatric upper limit' i.e. the daily dose recommended not to be exceeded in the geriatric population. We focused on specific doses associated with the indications 'insomnia' and 'anxiety' and selected the dose which was advised by the majority of the sources. Specific dose recommendations for sedative action in the indication 'unrest' were not found in these sources.
For lorazepam only, we found separate doses for insomnia and for anxiety. For alprazolam, bromazepam and prazepam, our sources only mentioned a dose for the indication of anxiety. For the indication of insomnia, we found specific dose recommendations for lormetazepam, zolpidem and zopiclone. The recommendations retrieved from the various sources, the selected geriatric upper limit, and the relation with the Defined Daily Dose(DDD) and diazepam equivalent are presented in Box 1.
To calculate the percentage of prescriptions exceeding the 'geriatric upper limit', we compared the actual daily dosages for each prescription identified in the study with the geriatric upper limit.

BOX 1: Recommended daily doses not to be exceeded in older adults

GERIATRIC UPPER LIMIT

We based our selected dose adaptations on 3 formularia and 3 explicit criteria about inappropriate prescribing in the elderly:

formularia	explicit criteria
Britisch National Formularium (BNF) (United Kingdom)	*BEERS 2003 (USA)*
the Martindale 36ste edition (2009)	*Rancourt 2004 (Canada)*
Informatorium medicamentorum 2009 (the Netherlands)	*Laroche 2007 (France)*

Recommended daily doses were investigated for the most relevant BZD/Z and for the indications insomnia and anxiety.

RECOMMENDED DAILY DOSES NOT TO EXCEED IN OLDER ADULTS

	LORAZEPAM		ALPRAZOLAM	BROMAZEPAM	PRAZEPAM	LORMETAZEPAM	ZOLPIDEM	ZOPICLONE
Sources	*insomnia*	*anxiety*	*anxiety*	*anxiety*	*anxiety*	*insomnia*	*insomnia*	*insomnia*
BNF	1mg	2mg	0.75mg	*	*	0.5mg	5mg	3.75mg
Martindale	2mg	3mg	0.75mg	9mg	30mg	0.5mg	5mg	3.75mg
Inform. Medica	2mg	4mg	0.75mg	10mg	30mg	1mg	*	3.75mg
BEERS	*	3mg	2mg	*	*	*	*	*
Rancourt	*	3mg	0.75mg	*	*	*	*	*
Laroche	*	3mg	2mg	*	*	0.5mg	5mg	3.75mg
Geriatric upper limit (in mg/day)	**2mg**	**3mg**	**0.75mg**	**10mg**	**30mg**	**0.5mg**	**5mg**	**3.75mg**
Geriatric upper limit expressed in								
- DDD	0,8	1,2	0,75	1	1	0,5	0,5	0,5
- Diazepam equivalent	20mg	30mg	15mg	20mg	20mg	3,3mg	2,5mg	2,5mg

* the BZD has no recommended doses for this indication or the BZD/ Z is not listed in the formularium/explicit criteria

Statistics:

The data were analysed using the statistical package SPSS version 18. The alpha level of significance was set at $p< 0.05$.
In a preliminary analysis investigating BZD and Z-drug use separately, we found no differences in residents characteristics. Consequently, all users were concatenated in one "BZD/Z" group for further analysis.
We used descriptive statistics to explore indications and dosages. To detect differences in prescribed daily doses for different indications, we used non-parametric statistics (medians and the Mann-Whitney U test). To explore a risk profile for BZD/Z use, we compared users and non-users. In univariate analysis, we used Chi^2 for dichotomous variables and independent T-tests for continuous variables. For multivariate analysis, we used a stepwise regression model with the statistically significant variables from the univariate analysis. To compare the characteristics of chronic users of BZD/Zs in different indications (anxiety, insomnia, unrest), we used Chi^2 for dichotomous variables and one way ANOVA for continuous variables.

RESULTS

Description of the study population:

Medication data and clinical information of 1730 residents were included in the analysis. The mean age was 85 (range 60-104) years and 78% was female. In 48% of the population, the treating physician diagnosed dementia and in 36% depression (Table 1). A combination of these two care problems was seen in 15% of the residents.

The residents used a mean of 7 chronic medications per resident, ranging from no medication (in less than 1% of the residents) to 22 medications. The most frequently used drugs were central nervous system drugs with benzodiazepines and Z-drugs (BZD/Z), antidepressant, antipsychotic and anti-dementia drug prevalence in respectively 53%, 40%, 33% and 8% of all residents (Table 1).

Table 1. Description of the study population

RESIDENT CHARACTERISTICS	Total population n= 1730
Demografical charateristics	
Age (mean+range)	84.8 (60-104)
Gender (% female)	78.1
Main clinical problems(%)	
cardiovascular	75.7
Peptic ulcer	24.6
COPD	17.2
Diabetes	16.8
Renal failure	12.6
Hepatic problems	1.4
Main care problems(%)	
Dementia	47.7
Insomnia	44.0
Constipation	41.9
Incontinence	35.9
Depression	35.7
Chronic pain	35.1
Risk of falling	45.5
Medication information	
Number of (mean+range)	
Medications	8.0 (0-22)
Chronic medications	7.1 (0-22)
Prevalence of overall psychotropic use(%)	77.5
Antipsychotics	32.9
Antidepressants	39.5
BZD/Z	53.1
Anti dementia drugs	7.5

Descriptive analysis on resident level: prevalence of BZD/Z users and indications:

The prevalence of BZD/Z drug utilisation among Belgian nursing home residents (n=1730) was 53 % (n=918). Chronic use was present in 50% (n=859) of the residents, and 3% used a BZD/Z only occasionally. The use of a single chronic BZD/Z was seen in 42% of the residents, while 8% had 2 to 3 chronic BZD/Zs on their medication chart (Table 2).
Among the chronic users using a single BZD/Z (n=729), the indication was missing in 126 residents. An analysis of the characteristics of residents for whom the indication was missing revealed no significant differences. Hence, the distribution of indications was extrapolated to the group of chronic users of a single BZD/Z.

The leading indication was insomnia (59%), followed by anxiety (17%), unrest (10%), and "other indications"(4%); the use of one BZD/Z for multiple indications was 10% (Table 2). When a resident received two or three chronic BZD/Zs, there was mostly a different indication for each of the prescribed BZD/Z, most often a mix of anxiety, insomnia or unrest.

Table 2. Prevalence of benzodiazepines and Z-drug use (BZD/Z) among 1730 nursing home residents and distribution of chronic users of a single BD/Z per indication.

Prevalence of BZD/ Z use (n=1730)		
BZD/Z users	53.1%	
Chronic BDZ/Z users	49.7%	
Chronic users of a single BZD/Z	42.1%	
Distribution of indications among single chronic BZD/Z users (n=603*)		
	Insomnia	58.7%
	Anxiety	17.4%
	Unrest	10.4%
	Others**	3.6%
	Multiple indications	9.8%

*729 residents receiving a single chronic BZD/Z corrected for 126 missing indications

** Epilepsy, muscle spasm, panic attack

Descriptive analysis at prescription level: prevalence and dose analysis per indication:

The 859 residents on chronic BZD/Zs received a total of 1001 chronic BZD/Z prescriptions for different indications (Table 3).

On a total of 448 chronic prescriptions for insomnia, physicians prescribed 16 different BZD/Z drugs: 46% hypnotics (N05CD) and 27% Z-drugs (N05CF), but also 27% anxiolytics (N05BA). The dominant sleeping pill was the hypnotic lormetazepam (38%), followed by zolpidem (23%). Of a total of 186 prescriptions to treat anxiety, physicians prescribed 13 different BDZ/Zs, predominantly anxiolytics (alprazolam 36% and lorazepam 27%). On a total of 94 prescriptions to treat unrest, 16 different BZD/Zs were prescribed with a wide spread of anxiolytics (but predominantly lorazepam 39%) and also some typical hypnotics and Z-drugs (27%) (Table 3).

When comparing the dosages on the prescriptions of an individual BZD/Z used for different indications, the prescribed daily dosages of prescriptions for insomnia were similar to the dosages of prescriptions for unrest, while for anxiety the daily dosages were higher (Table 3). For the treatment of anxiety, the daily dosage was divided into 2 to 4 administrations per day in 37% of these prescriptions. For the treatment of unrest, we saw fractionation in only 8% and no fractionation for insomnia as all prescriptions mentioned one dose at bedtime.

Table 3. Distribution of prescriptions for chronic BZD/Z drug use and median prescribed daily doses per indication and per active substance.

ATC-DRUG CLASS	Chronic prescriptions of BZD/Z				Prescribed dialy doses (MEDIAN-RANGE)						P value
	TOTAL	INSOMNIA	ANXIETY	UNREST	INSOMNIA		ANXIETY		UNREST		
	% (n=1001)	% (n=448)	% (n=186)	% (n=94)	mg	min-max	mg	min-max	mg	min-max	***
ANXIOLYTICS = N05BA	**48.8**	**26.8**	**96.8**	**73.4**							
-lorazepam	22.1	19.6	26.9	39.4	1.0	0.25-2.50	2.0	0.50-7.50	1.25	0.50-2.50	0.035
-alprazolam	10.3	0.4	36.0	8.5			0.5	0.07-2.00	0.375	0.13-1.00	0.087
-bromazepam	4.1	4.0	4.8	5.3	4.5	3.00-6.00	6.0	3.00-12.00			0.196
-prazepam	3.3	0.0	11.8	0.0			30.0	5.00-40.00			
other	9.0*	2.8	17.3	20.2							
HYPNOTICS = N05CD	**33.0**	**46.4**	**3.2**	**18.1**							
-lormetazepam	26.1	37.7	2.7	12.8	2.0	0.50-3.00			1.75	0.50-2.00	0.832
other	6.9**	8.7	0.5	5.3							
Z-DRUGS = N05CF	**18.3**	**26.8**	**0.0**	**8.5**							
-zolpidem	16.3	22.5	0.0	7.4	10.0	2.50-20.00			10.0	5.00-10.00	0.853
-zopiclone	1.9	4.0	0.0	1.1	7.5	3.75-7.50					
-zaleplon	0.1	0.2	0.0	0.0							

*other anxiolytics: oxazepam (2.1%); diazepam (2.0%); chlorazepate (1.9%); clotiazepam (1.5%) cloxazolam (1.1%); ethylloflazepam (0.2%), clobazan (0.1%), nordazepam (0.1%)

**other hypnotics: botizolam (2.6%); flunitrazepam (1.3%); triazolam (1.3%); flurazepam (0.9%); loprazolam (0.6%); nitrazepam (0.2%)

*** differences between Prescribed daily doses (Mann-Withney U); lorazepam differences only between insomia and anxiety

Compliance with 'the Geriatric Upper Limit':

In Table 4 we give the percentage of prescriptions with a dose higher than 'the geriatric upper limit'. In the prescriptions for insomnia, this limit was exceeded for lormetazepam in 95%, zolpidem in 82%, zopiclone in 78% and for lorazepam in 35% of all chronic prescriptions. In the prescriptions for anxiety the 'geriatric upper limit' was also exceeded but not in such high percentages: for alprazolam in 30%, lorazepam in 12%, bromazepam in 11% and for prazepam in 5% of all chronic prescriptions.

Table 4. Percentage of prescriptions exceeding the Geriatric Upper Limit per indication.

INDICATION	BZD/Z	DOSAGES		
		Geriatric Upper Limit	n**	%Exceeding***
INSOMNIA	Lormetazepam	0.5mg	169	94.7
	Zolpidem	5mg	101	82.2
	Lorazepam	2mg	88	35.2
	Zopiclone	3.75mg	18	77.8
ANXIETY	Alprazolam	0.75mg	67	29.9
	Lorazepam	3mg	50	12.0
	Prazepam	30mg	22	4.5
	Bromazepam	10mg	9	11.1

* Recommendations (see box)

** the number of chronic prescriptions for this specific drug for this indication

*** % of prescriptions for older adults exceeding the Geriatric Upper Limit

Comparison between BZD/Z users and non-users:

Univariate analysis showed that BZD/Z users had a significantly higher usage of chronic medications and antidepressants; a higher frequency of care problems such as constipation, depression and chronic pain; and a lower frequency of dementia and incontinence. We found no association between BZD/Z use and the physicians' perception of the risk of falling, nor with the frequency of clinical problems such as cardiovascular diseases, diabetes and COPD (Table 5).
In multivariate analysis, BZD/Z use was more frequent in female residents (OR 1.32 95%CI 1.03-1.68) and residents with chronic pain (OR 1.58 95%CI 1.27-1.97), constipation (OR 1.43 95%CI 1.16-1.76) and depression (OR 1.68 95%CI 1.35-2.08), and less frequent in residents with incontinence (OR=0.71 95%CI 0.57-0.88) and dementia (OR=0.60 95%CI 0.48-0.74 (Table 5).

Table 5. Comparison of characteristics between chronic benzodiazepine or z-drug users and non-users (n=1730).

RESIDENT CHARACTERISTICS	BZD/Z user n=859	non user n=871	P value*	UNIVARIATE ** OR	UNIVARIATE ** 95%CI	MULTIVARIATE*** OR	MULTIVARIATE*** 95%CI
Demographical							
Age (mean+range)	84.5[60-104]	85.1[60-104]	0.165	0.99	0.98-1.00		
Gender(% female)	80.3	75.7	**0.021**	1.31	**1.04-1.65**	1.32	**1.03-1.68**
Main clinical problems(%)							
Cardiovascular	77.3	74.1	0.112	1.20	0.96-1.49		
Peptic ulcer	24.9	24.3	0.766	1.03	0.83-1.29		
COPD	18.5	15.9	0.156	1.20	0.99-1.54		
Diabetes	15.9	17.8	0.303	0.88	0.68-1.13		
Renal failure	11.8	13.4	0.326	0.87	0.65-1.15		
Hepatic problems	1.6	1.2	0.441	1.38	0.61-3.12		
Main care problems(%)							
Constipation	46.8	36.9	**p<0.001**	1.50	**1.24-1.82**	1.43	1.16-1.76
Risk of falling	46.4	44.5	0.421	1.08	0.89-1.31		
Depression	42.2	29.0	**p<0.001**	1.79	**1.46-2.20**	1.68	**1.35-2.08**
Chronic pain	42.1	27.9	**p<0.001**	1.89	**1.54-2.31**	1.58	**1.27-1.97**
Dementia	40.1	55.5	**p<0.001**	0.54	**0.44-0.65**	0.60	**0.48-0.74**
Incontinence	32.1	39.7	**0.001**	0.72	**0.59-0.88**	0.71	**0.57-0.88**
Medication information							
Number of (mean+range)							
Medications	9.0[0-22]	7.0[1-22]	**P<0.001**	1.15	**1.12-1.19**		
Chronic medications	7.7[0-22]	6.2[0-22]	**P<0.001**	1.18	**1.15-1.22**		
Use of psychotropics(%)	100.0	54.6	**P<0.001**				
Antipsychotics	35.0	30.8	0.065	1.21	0.99-1.48		
Antidepressants	48.3	32.4	**P<0.001**	1.95	**1.61-2.37**		

* P value of the difference between user and non-user using χ^2 for categorical variables and independent t-test for continuous variables

**Odds Ratio: Risk of taking a BZD/Z

*** stepwise regression model (covariates: gender,constipation,depression,pain,dementia,incontinence)

Comparison between BZD/Z users for the different indications:

Depression, chronic medication, antidepressant and antipsychotic use were significantly more likely to be present when a resident took a BZD/Z for anxiety rather than for insomnia

and unrest. We found no significant differences in the risk profiles of residents with BZD/Z use for insomnia versus use for unrest (Table 6).
Especially among users with the indication of insomnia, we observed a gradual decrease in BZD/Z use as dementia progressed (Fig. 1).

Relationship with institutional characteristics:

BZD/Z drug use was not associated with institutional characteristics such as private or public facility, size, or staffing.

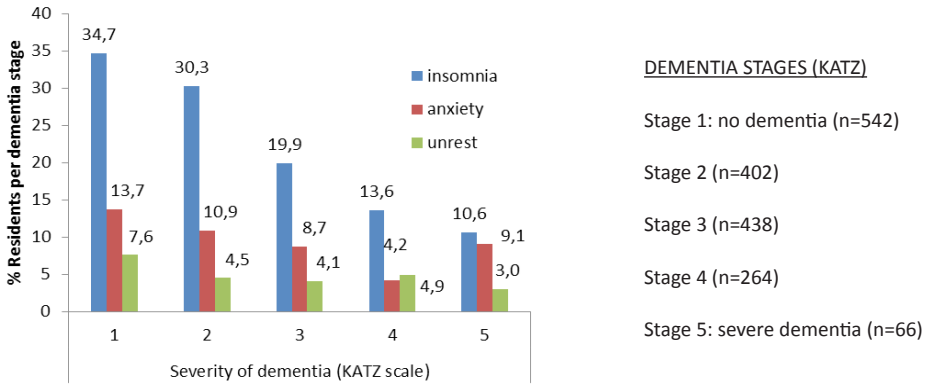
Table 6. Comparison of characteristics of chronic benzodiazepine and z-drug users for the indications 'insomnia', 'anxiety' and 'unrest'.

RESIDENT CHARACTERISTICS	Chronic BZD/Z user INSOMNIA (n= 354)*	Chronic BZD/Z user ANXIETY (n=105)*	Chronic BZD/Z user UNREST (n= 63)*	P value **
Demographical				
Age (mean+range)	85.5 (60-102)	84.9 (60-99)	83.6 (60-103)	0.224
Gender(% female)	80.5	78.8	74.6	0.562
Main care problems(%)				
Constipation	47.0	54.3	49.2	0.423
Risk of falling	48.0	51.9	50.8	0.752
Depression	36.3	61.2	28.3	**P<0.001**
Chronic pain	41.6	47.6	44.4	0.542
Dementia	36.0	43.1	41.9	0.343
Incontinence	31.5	28.8	33.3	0.811
Medication information				
Number of (mean+range)				
Medications	8.4 (1-20)	10.0 (2-21)	9.1 (3-17)	**P<0.001**
Chronic medications	7.5 (1-16)	8.9 (2-21)	8.1 (3-15)	**P<0.001**
Use of psychotropics(%)				
Antipsychotics	25.4	38.1	34.9	**0.024**
Antidepressants	39.5	61.9	36.5	**P<0.001**

* residents receiving a single BZD/Z for this specific indication

** P-value of differences using χ^2 for dichotomous variates and One-Way-Anova for continuous variates

Fig 1: Relation between indication for benzodiazepine and Z-drug use and increasing dementia



DEMENTIA STAGES (KATZ)

Stage 1: no dementia (n=542)

Stage 2 (n=402)

Stage 3 (n=438)

Stage 4 (n=264)

Stage 5: severe dementia (n=66)

DISCUSSION

Originality of the study:

In this observational cross-sectional study of chronic use of benzodiazepines and Z-drugs (BZD/Z) in Belgian nursing homes , the prevalence of usage of these drugs has been examined in depth per indication, and differences in dosing practices per indication have been analysed. We confirmed the high prevalence of chronic BZD/Z use (half of the residents) in this setting, as found in numerous other studies [2, 4, 32]. We found that insomnia was the main indication for chronic use, and was treated at higher dosages than recommended in older adults [21, 23, 25, 26]. This finding is not striking, but our study is the first to scientifically confirm the assumption that insomnia is most prevalent for BZD/Z use. We were able to determine interesting elements for a risk profile of BZD/Z use in multivariate analysis, such as positive associations with female gender, obstipation, depression, chronic pain and polypharmacy (including polypharmacy with other psychotropics), and negative associations with dementia and incontinence. There was a puzzling absence of association with age, risk of falling, clinical problems, and institutional characteristics.
This study in a large representative sample of Belgian nursing home residents provides long-awaited information on indications and dosages of benzodiazepines [33]. Actual daily dosages were compared to the geriatric upper limit, a pragmatic threshold determined from authoritative international pharmaceutical sources.

Strenghts and limitations:

One strength of our study was the substantial and representative sample of Belgian nursing home residents [29]. In neighbouring European countries [2-4] similar prevalence numbers of benzodiazepine use have been found. In the United States [27], there is a lower use of benzodiazepines due to the safety warnings issued in the late '80s and due to specific actions tackling the high use of these drugs (Medicare part D). Another strength of this study is that our data collection was based on reliable recording from primary sources, namely medication charts and direct clinical information from the treating GP. Another strong aspect of this study was our attempt to list most of the existing recommendations for older adults regarding dosages of BZD/Zs. However, we did not use an explicit method to extract the geriatric upper limit and we limited ourselves to the most abundantly prescribed BZD/Zs in Belgium. This geriatric upper limit is a threshold based on a pragmatic analysis of different sources, and therefore not a gold standard nor a rigid criteria for inappropriate prescribing.
One limitation was that we did not use internationally validated criteria to evaluate (severity of) dementia. In this cross-sectional study, we were not able to investigate the distribution of the duration of chronic use, nor it was possible to investigate temporal changes and the relationship between process and outcome. Indications for BZD/Z drugs were collected by interviewing the GP, which may have influenced data reliability. To reduce the complexity of the analysis, we narrowed our in-depth analysis of indications to chronic users with only one BZD/Z and therefore only one indication and disregarded residents on multiple BZD/Zs (8% of all residents) or residents on a BZD/Z with more than one indication (10% of the residents on a single chronic BZD/Z). In addition, there was a large number of missing indication data (17%) which might reflect an uncertainty of the treating GPs when discriminating among the indications of anxiety, insomnia, and unrest. This pragmatic approach might have introduced some bias in the estimation of the prevalence.

Critical discussion of the main findings:

Insomnia

Our study showed that the number one indication for BZD/Z drugs in this setting was insomnia and to a far lesser extent anxiety and unrest.
A striking finding was that almost all use of BDZ/Z drugs for insomnia was chronic, which is generally considered to be inappropriate [25, 34]. In order to avoid chronic prescribing, guidelines such as the British National Formulary and the Belgian drug code [21, 35] point out that before prescribing a hypnotic, the cause of the insomnia should be established and, where possible, underlying factors (such as depression or 'restless legs') should be treated [36, 37]. Establishing a good sleep hygiene is the first choice, but is not easy to implement in nursing homes. When a pharmacological treatment seems necessary, hypnotics should be reserved for short courses (<3weeks) in the acutely distressed and routine/chronic prescribing is undesirable [21].
With regard to the drug choice within the benzodiazepine drug class (with hypnotic, anxiolytic, -sedative, muscle-relaxant and amnesic action) for the indication of insomnia, mainly hypnotic benzodiazepines and Z-drugs were used, but also the anxiolytics lorazepam and bromazepam.
With regard to dosages for the different indications, we found that, especially in patients treated for insomnia, the daily dosages of the hypnotic benzodiazepines, of the Z-drugs, and of the anxiolytic lorazepam exceeded the geriatric upper limit. However, in terms of diazepam equivalence, the dosages were still considerably lower than the dosages used when treating patients with anxiety.
It is generally known that older adults need a dose reduction, but specific information about this reduction is hard to find. Most sources stay vague and point at a dose reduction of 50% and a slow titration. Hence, it is no surprise that there are no clear guidelines, and that GPs are not aware of geriatric optimal dosing. A comparison of the geriatric upper limit with the Defined Daily Dose (DDD) revealed that the two values coincided for anxiety, but for insomnia, the geriatric upper limit was half the DDD (BOX 1). This may be one methodological explanation for the high prevalence of dosages exceeding the limit in prescriptions indicated for insomnia. Another explanation is that physicians titrate the dosage upwards when tolerance sets in, as expected for benzodiazepines use. Also, one culprit may be the unavailability of geriatric package dosages. Lormetazepam for example, is on the Belgian market in package doses of 1 or 2 mg, and consequently exceeds the required 0,5mg a day for older adults. This is also the case for the package dosages of zolpidem (only packages of 10mg on the market).
In our study, the hypnotic users, but especially the residents receiving a BZD to treat anxiety were more associated with having a depression and a prescription for an antidepressant. This chronic concomitant use of psychotropic drugs to treat depression is not appropriate in the geriatric population who has already an increased risk of interactions and adverse drug reactions. On the one hand, it is not surprising we found an association between depression and BZD/Z use, because depression can be the reason of initiating a BZD/Z drug, definitely when depression is related to a disturbed sleep pattern and anxiety [38]. On the other hand, a study in 2007 revealed that the use of hypnotics was associated with an increased incidence of depression, suggesting hypnotics may be contra indicated when there is a risk for depression [39].
Unexpectedly, we saw a gradual decrease in the use of sleeping pills when dementia progressed, although it is well known that patients with dementia often have nocturnally disturbed sleep [40]. As a sleeping problem is frequently an explicit complaint, uttered by the patient [41], it is possible that prescribing sleeping pills is demand-driven. So, when residents with severe dementia lose the ability to express the need for sleeping pills, their prescription might not get renewed.

Anxiety

In patients using only a single BZD/Z chronically, the single indication of anxiety was limited to less than 1 in 5 patients. However, this indication was also present in patients using multiple BDZ/Z drugs, or a single BZD/Z drug for multiple indications. Using BZDs chronically to treat mild anxiety is considered to be inappropriate [8]. At the onset of treatment of depression, a benzodiazepine could be used as an adjuvant, as the anti-anxiety effect of some antidepressants can take 2 to 4 weeks [42]. However, to avoid chronic use, this dual therapy should be tapered in time [43].
In this indication, the drugs of choice were exclusively the anxiolytic ATC-class drugs, used in daily dosages higher than the dosages used when indicated for insomnia, but closer to the geriatric upper limit (and to the DDD). It is logical daily dosages are higher for anxiety as they are more frequently dispensed during the day, unlike for sleeping pills, which are administered once daily in the evening.
The indication of anxiety was associated with a more intense polypharmacy, more antidepressants (and more depression), and more antipsychotics. Hence, efforts to withdraw from BDZ/Z drug usage should be seen in the broader context of mental health, and treatment of behavioural and psychological symptoms of dementia.

Unrest

A variety of benzodiazepines in different ATC classes were used to treat this indication. The prescribed daily doses of these BZD/Z drugs for the indication 'unrest' were similar to the prescribed daily doses of these BZD/Z drugs used for the treatment of insomnia. Furthermore, we observed no differences in characteristics between a resident using a BZD/Z drug for insomnia and unrest. Sedative action in this setting is considered to provide calming effects (different from the narcotic aim in palliative care context and different from control of acute agitation). This suggests some semantic overlap between the terms "sedative" and "hypnotic" action, not only in literature but also in daily practice.

Risk profile of BDZ/Z drug users

Our multivariate comparison of users versus non-users revealed a positive association with care problems such as obstipation and chronic pain, possible causes of irritation and sleeplessness leading to BZD/Z use. The negative association between incontinence and BZD/Z use might be explained by covariance with dementia and the use of nocturnal incontinence material.
The association with polypharmacy (more specifically psychotropic polypharmacy) calls for comprehensive approach to assure the quality of psychotropic pharmacotherapy of mental health in nursing homes [44].
In other studies an association was found between BZD/Z use and risk of falling [20, 45-47]. In this cross-sectional study we could not observe this, possibly because treating physicians failed to perceive the risk of falling as a consequence of BZD/Z use, or because of the multifactorial nature of this association.
We did not find significant associations between BDZ/Z drug use and institutional characteristics (including staffing), contradicting the popular belief that high hypnotic usage is associated with low staffing [48].

Implications for practice and research:

The contradiction between recommendations against long-term use of BZD/Zs, and the high prevalence in older adults has already been discussed often but seldom explained. Prescrib-

ers seem to be convinced of the detrimental long-term effects of benzodiazepines in older adults [49], but it seems very hard to change habitual prescribing and to overcome the fear of possible relapse and withdrawal effects for both prescribers and caregivers and for patients [50].

It is difficult to persuade patients and their physicians to stop chronic use of BDZ/Z drugs. However, a small intervention study in primary care showed that sending a letter from the physician to the BZD/Z user could have a positive impact on successful withdrawal [51, 52]. Motivation together with gradual tapering seems to be the best strategy for discontinuation [11, 53]. Previous articles on BZDs supported non-pharmacological ways to address insomnia and to avoid the initiation of benzodiazepines use [54-56]. More efforts to motivate the residents as well as the care giving staff to do physical exercises and other activities to ameliorate the sleep quality of older adults must be made in order to reduce the persistent sleep problems and sleeping pill use [57, 58].

More emphasis should be given to at least avoiding high dosages during chronic use for older patients. This study found that prescribers do not pay attention to reducing the dosage according to existing recommendations, especially in patients treated for insomnia. We do not know whether this reluctance indirectly leads to a higher mortality [59], but several studies state the existence of adverse effects, such as cognitive impairment [14, 15] addictive properties and possible withdrawal effects. The pharmaceutical companies should produce packages with appropriate dosages for older adults. But nurses and pharmacists could also play an important role in the correct administration of these drugs in older adults [60, 61].

Future research on benzodiazepines should differentiate between insomnia and anxiety or other indications. Our findings suggest that insomnia, given its high prevalence as primary indication, deserves priority. Efforts to reduce chronic use should concentrate on reducing initiation, chronic use and excessively high dosages for this indication.

Furthermore, there is a need to strengthen the evidence base regarding the absence of long-term efficacy and the significance of adverse effects in order to persuade physicians, nurses, caregivers and patients of the positive risk benefit balance of discontinuation attempts.

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CHAPTER 2.2

The use of antidepressants in Belgian nursing homes: a focus on indications and dosages in the PHEBE study

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ABSTRACT

Background & objectives: Since antidepressants are prescribed for multiple indications, the use of an antidepressant cannot be equated with a diagnosis of depression. The objective of this study was to examine the quality of antidepressant prescribing in Belgian nursing homes, with a critical evaluation of indications and dosages: to see whether depression was appropriately treated in terms of drug choice, indication and whether there was underdosing.

Methods: Clinical and medication data was obtained from a cross-sectional study of a representative stratified random sample of 1730 residents from 76 Belgian nursing homes (PHEBE study 2006). A 28-item checklist of clinical conditions was designed ad hoc for the PHEBE study and sent to the residents' general practitioner (GP) to collect clinical information. We copied the medication chart, classified the drugs into codes with the Anatomical Therapeutic and Chemical classification system, and transferred the drug names and dosages into a database. Information on indications was retrospectively obtained from the GPs, so that we could link the indication to each medication. Minimal effective doses (MED) of antidepressants to treat major depression were obtained from the literature to assess under-dosing.

Results: The overall use of antidepressants in nursing homes was 39.5% (95%CI, 37.2-41.8). The physicians classified 34.2% (95% CI 32.0-36.4) of the residents as having depression and 80.9% of these patients were treated with an antidepressant. Indications among the single antidepressant users (n= 551) were depression (66.2%), insomnia (13.4%), anxiety (6.2%) and neuropathic pain (1.6%). In the indication of 'depression', 74.8% used a Selective Serotonine Reuptake Inhibitor (SSRI), predominantly citalopram, sertraline and escitalopram. Venlafaxine was used by 10.7% of the residents. Dosages for these antidepressants were equal to or higher than the MED. But when trazodone, amitriptyline or mirtazapine was used to treat depression, respectively 92.3%, 55.5% and 44.5% was dosed under the MED. In the indication of insomnia, most of the time, trazodone (90.5%) or mirtazapine (5.4%) were used and in lower dosages than those required for depression treatment (<MED). Tricyclic antidepressants were predominantly used for the treatment of neuropathic pain and also at lower dosages. Of all the residents receiving a medication for anxiety, only 13.9% received an antidepressant (mostly a SSRI), and the remaining received a benzodiazepine.

Conclusion: The number one indication for the use of an antidepressant was depression. Within this indication, mostly the recommended SSRIs were used, in dosages equal to or higher than the MED. Furthermore, we noticed that there was substantial use of sedative antidepressants for insomnia and that the physicians preferred to prescribe benzodiazepines over the recommended SSRIs to treat anxiety chronically.

INTRODUCTION

The prevalence of late-life depression in nursing homes varies from 11% to 50% [1-5] and is generally higher than in community dwelling older adults [6]. Depression is often reported to be under-recognised and undertreated in older adults [3, 7]. However, the use of antidepressants (ADs) has increased over the last decade [8] and this trend was also visible in the nursing home population [9, 10].

Depression often has an atypical presentation in older adults [11]. The poor recognition of clinical features of depression in old age and the overlap with symptoms of dementia or other co-morbidities makes a correct diagnosis difficult.

Depression negatively affects daily activities [12] and the quality of life [13], causes high treatment and societal costs[14, 15] and increases mortality [16]. Chronic diseases, pain and social deprivation are known risk factors for developing depression [17]. These elements are common in long-term care facilities. Moreover, transition from the community to a nursing home can trigger depression, which results in a high number of newly admitted residents developing depression [2, 18].

Depression is a treatable illness [19]; approximately 50-60% patients with a major depressive disorder are thought to improve clinically as a consequence of antidepressant treatment[20, 21]. In addition, there are other indications to prescribe an antidepressant. Anxiety, panic disorders, behavioural and psychological symptoms of dementia and neuropathic pain [22] are potential indications for antidepressants in the older population. In daily practice, antidepressants are also prescribed for insomnia without concomitant depressive symptoms, although this indication is not mentioned in the official labelling [23].

In order to make a complete evaluation of the antidepressant prescribing attitudes and to evaluate the pharmacotherapy of depression, both indication and dosage information are necessary. Drug utilisation studies that evaluate the indication and dosages of these medications are scarce [24-26]. In these studies, indication analysis is mostly done by linking clinical diagnoses (ICD-9 or DSM IV) and medication databases. This does not automatically provide information on the reason or the indication for which each antidepressant was prescribed. Similar to the BEACH project in Australia [27], the PHEBE study (Prescribing in Homes for the Elderly in Belgium) was designed to include the indication per medication as reported by the prescribing general practitioner (GP). The PHEBE study was a cross-sectional, descriptive study of a representative stratified random sample of 76 Belgian nursing homes, investigating the overall drug utilisation in Belgian nursing homes in 2006. A detailed description of the methods and findings of this study was published elsewhere[28-30].

The main objective of this subanalysis of the data obtained in the PHEBE study was to examine the quality of antidepressant prescribing in Belgian nursing homes with a critical evaluation of indications and dosages: to see whether depression was appropriately treated in terms of drug choice, the indications and whether there was underdosing. An additional objective was to investigate the resident characteristics associated with antidepressant use.

METHODS

Setting:

Belgium has a mixed, public/private health care system. The system works on a fee for service base. The Belgian long-term residential care structure consists of residential and/or nursing homes for older people, which offer a home replacement with or without nursing care. Governance of nursing homes for older people is either public (community health services) or private (predominantly non-profit) with little difference in quality. In Belgian nursing homes, residents are still supervised by their own GP, and this leads to an average of 32 GPs per nursing home.

Data collection:

In the PHEBE study, data collection at resident level included administrative, clinical and medication data. We obtained the medication data by copying the medication chart, transferring and coding it to a database. For collecting clinical data, we sent the GP a checklist with 28 items, focusing on clinical problems (i.e. cardiovascular disease, COPD, peptic ulcer) as well as focusing on care problems (i.e. problems with a predominant nursing care burden, such as dementia, insomnia, depression,…). The 28-item checklist of clinical conditions was ad hoc designed for this study, with the items selected based on existing prescribing quality indicators (BEERS[31], ACOVE[32], BEDNURS[33]) for older adults. The diagnosis of depression is in this study based on the clinical evaluation by the GP. In Belgium, the KATZ scale is a mandatory instrument in the nursing homes and it consist of two parts. The first part scores activities of daily living (ADL) and the second part scores disorientation in time and place. This second part is scored from 1 (no disorientation) to 5 (severe) and used as a proxy to estimate the severity of dementia in this study. Residents receiving palliative care were excluded from analysis.

Classification of Antidepressants:

Antidepressants were classified according to the Anatomical Therapeutic Chemical system (ATC) [34]. According to the availability on the Belgian pharmaceutical market, we investigated the classes N06AA Tricyclic Antidepressants (TCA), N06AB Selective Serotonin Reuptake Inhibitors (SSRI), N06AG Mono Amino Oxidase Inhibitors (MAO-I) and the class N06AX which includes serotonin-norepinephrine reuptake inhibitors and other antidepressants.
The SNRI, duloxetine, and bupropion are not included in the analysis because they were not yet commercialised in Belgium in 2006. Lithium, in ATC considered as an antipsychotic and mostly used to treat bipolar disorders, was excluded from analysis. Combination drugs of an antidepressant and an antipsychotic were also excluded. Duplicate use therapy was defined as the concomitant use of 2 or more ADs. Medication prescribed in short term and as-needed medications were excluded from analysis. We focused on chronic use (defined as daily use for at least 3 months).We analysed 2 levels of describing AD use: the prescription (medication) and the resident level. Indications were analysed at prescription and resident level and dosages at prescription level only.

Indication and dosages:

Data on indications were collected retrospectively: the GP received a printout of the resident's medication chart for verification of the medication use, and he/she was asked to tick relevant indications from a predefined list for ADs: depression, posttraumatic stress, anxiety, insomnia, neuropathic pain or other.

The prescribed daily dose (PDD) of each AD was recorded by summing the doses taken at the different moments of intake during one day. To interpret these doses, we chose the universal Defined Daily Dose (DDD), which is the assumed average maintenance dose per day for a drug used for its main indication in adults[34]. We described the distribution of the PDD using its median and range. To examine possible under-dosing in the treatment of depression, we used the Minimal Effective Dose (MED). The MED of an antidepressant serves as a threshold, below which all doses are not effective in treating major depressive episode [35]. The MED of the most common antidepressants were determined using the Prescribing guidelines [36] and Pharmacotherapy: A pathophysiologic Approach [37]. We considered under-dosing when the PDD of the antidepressant was under the MED.

Statistical analysis:

The data was analysed using the statistical package SPSS version 18. The alpha level of significance was set at $p< 0.05$. We used descriptive statistics to explore indications and dosages.
We examined the characteristics (demographical, clinical, medication and institutional information) of the AD users and the nonusers, and also compared characteristics of the AD users for the different indications (respectively for depression and all other indications). To investigate differences, we used χ^2 for discontinue variables, t-tests for continuous variables or non-parametric statistics (Mann-Whitney U test) for skewed distributions.
In a second analysis, we explored a risk profile for AD use. We calculated the Odds ratios and the 95% confidence intervals in univariate and multivariate analysis. For multivariate analysis, we used a stepwise regression model including the statistical significant variables from the univariate analysis.

RESULTS

Study population characteristics:

Medication data and clinical information of 1730 nursing home residents was included in the analysis. The mean age was 85 (range 60-104) yearsand 78.1% was female. The prevalence of depression was 34.2%[95% CI 32.0-36.4]. In 14.9% of the residents, a combination of depression and dementia was noted.
The mean number of chronic medication per resident was 7,and the number ranged from no medication (in less than 1% of the residents) to 22. The most frequently used drugs among the residents were the central nervous system drugs, with benzodiazepine, antidepressant, antipsychotic and anti-dementia drug use in respectively 53.1%, 39.5%, 32.9% and 8.3% of all residents. The demographical and clinical characteristics of the study population are shown in Table 1.

Table 1. Characteristics of the study population

RESIDENT CHARACTERISTICS	**total population n= 1730**
Demographical characteristics	
Age (mean + range)	84.8 (60-104)
Gender (% female)	78.1
Main Clinical problems(%)	
Cardiovascular	75.7
Peptic ulcer	24.6
COPD	17.2
Diabetes	16.8
Renal failure	12.6
Hepatic problems	1.4
Parkinson	8.3
Main Care problems(%)	
Dementia	47.7
Depression	34.2
Insomnia	44.0
Risk of falling	45.5
Constipation	41.9
Chronic pain	35.1
Incontinence	35.9
Medication Information	
Number of (mean + range)	
Medications	8.0 (0-22)
Chronic Medications	7.1 (0-22)
Use of Psychotropics (%)	77.7
Benzodiazepines/z-drugs	53.1
Antidepressants	39.5
Antipsychotics	32.9
Use of Antidementia drugs(%)	8.3
Use of AntiParkinson drugs(%)	10.9

Antidepressant use at Resident level: prevalence and indications:

The prevalence of chronic AD utilisation among 1730 residents was 39.5%[95% CI 37.2-41.8]. The use of a single AD was seen in 32.6% , while the concomitant use of 2 to 4 ADs was found in 6.9%. Among the antidepressant users using a single AD (n=551), the leading indication for this use was depression (66.2%), followed by insomnia (13.4%), anxiety (6.2%) and pain (1.6%). We found the use of a single AD for 'multiple indications' in 11.6% of residents. This category was used largely for depression associated with another indication (Table 2).
The physicians categorised 34.2% [95% CI 32.0-36.4] of the residents as depressed and 80.9% of these patients were treated with an AD; more specific indication analysis showed that 73.1% of the residents with noted depression received an AD for that very indication (Table 2).

Table 2. Prevalence of Antidepressant (AD) use and Depression and the distribution of users per indication.

Prevalence		**n**	**%**
total AD use (N=1730)		684	39.5
single AD use		565	32.6
multiple AD use		119	6.9
total prevalence of depression (N=1730)		591	34.2
AD use among residents with depression (N=591)		478	80.9
AD use specific for the indication depression among residents with depression (N=591)		432	73.1
Indications among single AD users (N=551*)		**n**	**%**
	Depression	365	66.2
	Insomnia	74	13.4
	Anxiety	34	6.2
	Pain	9	1.6
	Multiple indications	64	11.6
	depression+ insomnia	22	4.0
	depression+anxiety	23	4.2
	depression + pain	8	1.5
	Other indications	5	0.9

*total residents receiving a single AD(n=565) corrected for 14 missing indications

Table 3 shows which AD was most used for which indication. When the indication of the AD was depression, 74.8% of the residents took a SSRI, 10.7% venlafaxine and 8.2% mirtazapine. For the single indication 'insomnia' and for the combination of 'insomnia and depression', in respectively 90.5% and 53.3% trazodone was used. When the indication was 'anxiety', different AD classes were used, but mostly SSRIs (64.7%), trazodone (14.7%) and venlafaxine (8.8%). Of all residents receiving a medication for anxiety only 13.9% received an AD (mostly an SSRI) and the remaining patients received a benzodiazepine. The indication of neuropathic pain was mostly treated with TCA (66.7%) (Table 3).

Table 3. Distribution of Indications of (single) antidepressant (AD) use in Belgian nursing home residents (at resident level).

ANTIDEPRESSANT	INDICATIONS for Antidepressant use among nursing home residents*				
	Depression n= 365	Insomnia n= 74	Anxiety n= 34	Pain n=9	Multiple n=64
TCA (=N06AA)	**8 (2.2%)**	**1 (1.4%)**	**2 (5.9%)**	**6 (66.7%)**	**4 (6.2%)**
Amitriptyline	3 (0.8%)		2 (5.9%)	5 (55.6%)	
SSRI (=N06AB)	**273 (74.8%)**	**1 (1.4%)**	**22 (64.7%)**	**1 (11.1%)**	**30 (46.9%)**
Citalopram	91 (24.9%)	1 (1.4%)	5 (14.7%)	1 (11.1%)	7 (10.9%)
Sertraline	67 (18.4%)		7 (20.6%)		9 (14.1%)
Escitalopram	60 (16.4%)		3 (8.8%)		3 (4.7%)
Paroxetine	39 (10.7%)		7 (20.6%)		10 (15.6%)
Fluoxetine	16 (4.4%)				1 (1.6%)
MAO-I (=N06AG)	**1 (0.3%)**				
OTHERS (=N06AX)	**83 (22.7%)**	**72 (97.3%)**	**10 (29.4%)**	**2 (22.2%)**	**30 (46.9%)**
Trazodone	10 (2.7%)	67 (90.5%)	5 (14.7%)	1 (11.1%)	18 (28.1%)
Venlafaxine (=SNRI)	39 (10.7%)		3 (8.8%)		6 (9.4%)
Mirtazapine	30 (8.2%)	4 (5.4%)	1 (2.9%)	1 (11.1%)	4 (6.3%)

*n=551 (single AD users corrected for 14 missing indications); The indication 'others' is not shown (n=5)

AD used by less than 10 residents are not shown:

TCA: dosulepine, imipramine,clomipramine,doxepine, nortriptyline, maprotiline

OTHERS:mianserine, reboxetine, hypericum perforatum and moclobemide (MAO-I)

TCA= Tricyclic Antidepressant; SSRI= selective serotonin reuptake inhibitor; MAO-I=monoamino oxidase inhibitor

Antidepressant use at Prescription level: prevalence and dose analysis:

The most frequently prescribed class of all 814 AD prescriptions was SSRI (52.8%) with citalopram, sertraline and escitalopram accounting for, respectively, 17.1%, 14.5% and 10.2%. Trazodone, which is a serotonin modulator, was the most prescribed drug (22.9%). Venlafaxine was found in 8.2% and mirtazapine was found in 7.7% of all AD prescriptions. The TCA group accounted for 5.8% with amitriptyline (3.6%) as the most representative TCA drug. MAO-I prescriptions were negligible (0.1%) (Table 4).

Of the 814 prescriptions, 72.5% were indicated for depression. Table 4 shows the frequency of use for all ADs and dosing information for the most common ADs for this indication. The amount of prescriptions with PDD below the MED for the treatment of depression was high for trazodone (92.3%), amitriptyline (55.5%) and mirtazapine (44.5%). We did not observe this underdosing when an SSRI or venlafaxine was prescribed.

When we used the DDD as a reference, we saw that for the indication of insomnia, the physicians prescribed daily dosages below the DDD (98.2%); this was also the case for the treatment of (neuropathic) pain (87.5%). For anxiety, mostly, 1 DDD (53.8%) or less than 1 DDD was prescribed (46.2%).

Table 4. Distribution of Antidepressants (AD) prescribed in Belgian nursing homes and dose information for the indication 'depression' (at prescription level)

ANTIDEPRESSANTS	TOTAL number of Prescriptions (n=814)	Prescriptions for depression (n= 590)	PDD median (range)	MED	number of prescriptions indicated for depression below MED
TCA (=N06AA)	**47 (5.8%)**	**22 (3.7%)**			
Amitriptyline	29 (3.6%)	9 (1.5%)	25mg (10-50)	50mg	5 (55.5%)
SSRI (=N06AB)	**430 (52.8%)**	**386 (65.4%)**			
Citalopram	139 (17.1%)	128 (21.7%)	20mg (10-40)	20mg	16 (12.5%)
Sertraline	118 (14.5%)	103 (17.5%)	50mg (10-100)	50mg	9 (8.9%)
Escitalopram	83 (10.2%)	77 (13.1%)	10mg (5-20)	10mg	15 (19.5%)
Paroxetine	69 (8.5%)	58 (9.8%)	20mg (10-40)	10mg	0
Fluoxetine	22 (2.1%)	20 (3.4)	20mg (10-20)	10mg	0
OTHERS (=N06AX)	**336 (41.3%)**	**181 (30.7%)**			
Trazodone	186 (22.9%)	52 (8.8%)	100mg (50-150)	150mg	48 (92.3%)
Venlafaxine	67 (8.2%)	61 (10.3%)	75mg (37.5-300)	75mg	3 (4.9%)
Mirtazapine	63 (7.7%)	54(9.2%)	30mg (7.5-30)	30mg	24 (44.5%)

ADs with less than 10 prescriptions are not shown:

MAO-I: Moclobemide n=1

TCAs: Dosulepine n=8, Imipramine n=4, Clomipramine n=2, Doxepine n=2, Nortriptyline n=1, Maprotiline n=1

OTHERS: Mianserine n=10 ; Reboxetine n=5; Hypericum=5;

PDD= prescribed daily dose (for depression); MED= Minimum Effective Dose (for depression)

TCA= Tricyclic Antidepressant; SSRI= selective serotonin reuptake inhibitor; MAO-I=monoamino oxidase inhibitor

Characteristics associated with AD use:

Univariate analysis showed that AD use was significantly associated with polypharmacy, peptic ulcer and some care problems such as depression, insomnia, pain and constipation. We registered a gradual decrease in AD use from the age of 80 years. In a public nursing home and where the medication was dispensed through a hospital pharmacy, there was less AD use (Table 5).
In multivariate analysis, AD use was more frequent in younger residents (OR 0.97, 95% CI 0.96-0.99), in residents with insomnia (OR 1.59, 95%CI 1.26-2.01) and in private nursing homes (OR 1.54, 95%CI 1.25-1.90). AD use was also more likely in residents with more chronic use of medications (OR 1.15 95%CI 1.11-1.19), concomitant use of benzodiazepines (OR 1.28, 95%CI 1.00-1.62), antipsychotics (OR 1.26, 95%CI 1.01-1.57), anti-dementia medication (OR 1.54, 95%CI 1.07-2.23) and antiparkinson medication (OR 1.58, 95%CI 1.14-2.18) (Table 5).

Table 5. Factors associated with Antidepressant use (AD).

CHARACTERISTICS	NON user	ANTIDEPRESSANT user				RISK CALCULATION**	
		Total	for depression	for other indications		UNIVARIATE	MULTIVARIATE
	N=1046	N= 684	N= 522	N= 162	p *	OR(95% CI)	OR(95% CI)
Demographical characteristics							
Age (mean + range)	85.7 (60-104)	83.5 (60-102)	83.5 (60-102)	83.6 (60-102)	0.897	**0.97(0.96-0.98)**	**0.97(0.96-0.99)**
Gender (% female)	77.6	78.4	80.1	74.7	0.143	1.03(0.82-1.31)	
Main Clinical problems(%)							
Cardiovascular	75.0	75.8	77.4	74.7	0.477	1.09(0.81-1.26)	
Peptic ulcer	22.1	27.8	29.6	24.7	0.230	**1.33(1.07-1.67)**	
COPD	16.0	18.9	20.9	13.0	**0.024**	1.22(0.95-1.57)	
Diabetes	16.3	17.4	18.7	14.8	0.264	1.06(0.82-1.37)	
Renal failure	12.3	12.8	13.1	13.0	0.977	1.05(0.77-1.37)	
Hepatic problems	1.2	1.6	1.5	1.9	0.780	1.25(0.56-2.80)	
Parkinson	7.3	9.8	10.8	7.4	0.212	1.36(0.97-1.91)	
Main Care problems(%)							
Dementia	47.3	48.0	47.0	52.8	0.202	1.02(0.84-1.24)	
Depression	11.5	70.3	84.2	29.2	**p<0.001**	**18.07(13.99-23.34)**	***
Insomnia	36.1	54.8	52.7	66.7	**0.002**	**2.09(1.72-2.55)**	**1.59(1.26-2.01)**
Risk of falling	43.9	47.8	48.6	45.6	0.516	1.17(0.97-1.42)	
Constipation	39.1	45.3	45.1	49.7	0.306	1.27(1.04-1.54)	
Chronic pain	32.6	38.3	40.8	32.7	0.066	1.27(1.04-1.55)	
Incontinence	34.6	37.3	36.0	43.5	0.089	1.12(0.91-1.35)	
Medication Information							
Number of (mean + range)							
Medications	7.1 (0-22)	9.2 (1-22)	9.5 (2-22)	8.9 (2-22)	**0.012**	**1.15(1.12-1.18)**	***
Chronic Medications	6.3 (0-22)	8.1 (0-22)	8.5 (2-21)	7.8 (2-19)	**0.008**	**1.18(1.14-1.21)**	**1.15(1.11-1.19)**
Use of Psychotropics (%)							
Benzodiazepines/zdrugs	47.9	63.9	64.6	58.6	0.173	**1.99(1.63-2.42)**	**1.28(1.00-1.62)**
Antipsychotics	30.5	38.1	36.4	37.7	0.772	**1.47(1.20-1.80)**	**1.26(1.01-1.57)**
Use of Antidementia drugs	8.2	10.4	9.4	5.6	0.126	**1.58(1.12-2.22)**	**1.54(1.07-2.23)**
Use of AntiParkinson drugs	9.6	14.9	14.2	9.3	0.104	**1.95(1.44-2.64)**	**1.58(1.14-2.18)**
Institutional(%)							
>90 beds	50.8	49.6	49.8	46.3	0.435	0.97(0.90-1.18)	
ownership: private	51.1	60.6	62.1	56.2	0.180	**1.47(1.21-1.78)**	**1.54(1.25-1.90)**
linked with hospitalpharmacy	17.7	13.0	11.9	16.0	0.166	**0.70(0.53-0.92)**	

*p value of difference between users for 'depression' and users for 'other' indications , using χ^2, t-test and Mann Whitney U

**RISK calculation: Risk of receiving an Antidepressant expressed as Odds Ratio (OR)

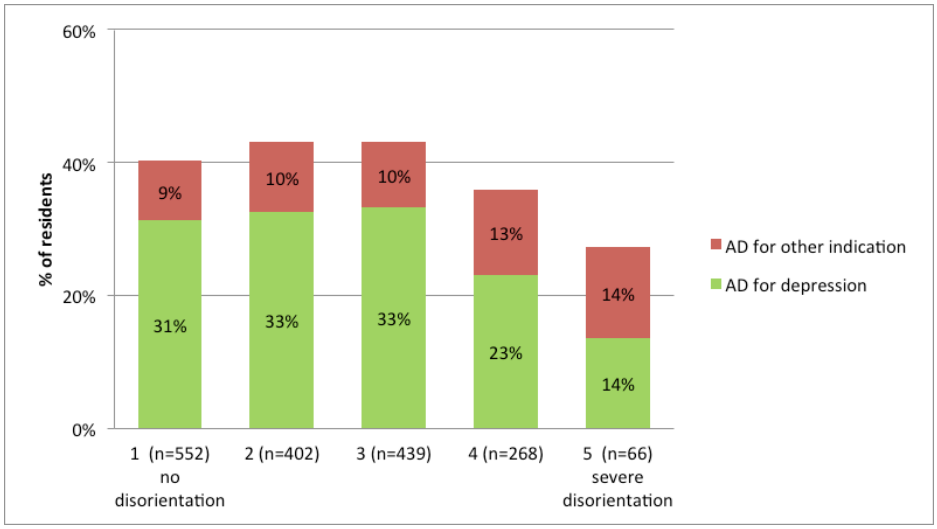
*** not included in multivariate analysis due to interacting effects

Characteristics associated with Antidepressant use for the indication 'depression' and 'other' indications: Residents who received an AD for the indication of depression had more chronic obstructive pulmonary disease and had a significant greater usage of (chronic) medication in comparison with the residents that received an AD for other indications. The residents that received an AD for other indications were more likely to be classified by their physician as insomniacs (Table 5).

Depression and dementia:

In more than one third (34.4%) of the nursing home residents with some form of dementia, the GP recorded depression. The prevalence of noted depression as well as the use of an AD for the indication 'depression' decreased as dementia progressed. On the other hand, the proportion of AD use for other indications slightly increased in patients with more advanced dementia (Fig. 1).

Fig 1: Antidepressant use in relation to increasing dementia (scored by the severity of disorientation axes in the KATZ scale)



DISCUSSION

To our knowledge, our study is the first European study to collect indication and dosage information for each antidepressant directly from the treating physician. Based on our results, depression is not undertreated in Belgian nursing homes. More than one third of Belgian nursing home residents were classified as having depression and 81% of them were treated with an AD. The prescribing physicians used suitable drug classes according to the guidelines for depression in older people [38]. Underdosing was not seen in the treatment of depression with the most prevalent AD classes, but when ADs were used for other indications, we saw the use of lower doses.
There was a substantial use of ADs (mainly trazodone) for insomnia. Furthermore, we noticed physicians were more likely to prescribe a benzodiazepine rather than the preferred SSRIs to treat (chronic) anxiety.

Strengths and limitations:

Our sample proved to be representative both on the institutional and residential level[39]. Moreover, the large size of our sample makes it possible to extrapolate our findings to the entire Belgian nursing home setting. Similar prevalence numbers for depression and AD use were found in European [1, 40] and American [9] studies, but for specific indication and dosage evaluation, no identical studies were available. The indications for AD prescribing were retrospectively collected by interviewing the GP. As the GP is the prescriber of the AD, this approach gives us a clearer view of the use of ADs than linking clinical diagnoses and medication databases would have. This strength can be a limitation as well because of the retrospective aspect of the method. Our interpretation of underdosing and the MED as a threshold was established by using a strict methodology.
A limitation of our study is that we did not collect information about alternative treatment strategies for depression such as psychotherapy, so we focused our discussion on the residents receiving an AD. Another limitation is that we did not use validated diagnostic criteria to evaluate the severity of depression and dementia, but we relied on the a posteriori clinical judgement of the treating physician. The physicians should have been aware that depression is not equal to depressive mood, but we do not know whether they had fully considered this. Moreover, we had no breakdown of various degrees of depression in our checklist of clinical diagnoses. The disorientation axes of the KATZ scale may not be an ideal dementia grading instrument as it can be influenced by other disorders (depression, delirium). However, we decided to use this tool for pragmatic reasons; use of this tool is mandatory in the Belgian context, and thus the data are readily available. In addition, in this cross-sectional study, we were not able to investigate the distribution of the duration of AD use; nor was it possible to investigate temporal changes and the relationship between process and outcome. Furthermore, we reduced the complexity of the analysis by narrowing our in-depth analysis of indications to single AD users, and we disregarded residents on more than one AD (6.9% of all residents).

Discussion of the main findings:

According to our study, in more than one third of the Belgian nursing home residents the treating physician noted depression. This percentage is situated in the middle segment of the prevalence range 11%-50% reported in other studies in different Western countries [1, 3-5]. Of all the residents classified as having depression, 81% was treated with an AD and 73% received an AD especially for the indication depression. Knowing that only major depression should be treated pharmacologically, our results do not support the hypothesis of under-

treatment in the group of residents with noted depression. Other recent articles also indicate an AD treatment percentage of more than 80% [9, 40] for depressed residents, but these percentages are irrespective of indication. In addition to reporting that there is no undertreatment, it could also be useful to examine the reason why about a third of all residents need pharmacological treatment of their depression.
In our study, more than one quarter of the AD prescriptions (28%) were not to treat depression. Other approved indications such as anxiety and neuropathic pain accounted for 7.8% of all AD use. Insomnia without depressive symptoms accounted for 13.4%.
Most of the ADs were prescribed at a dosage of 1 DDD or less and rarely exceeded 1 DDD. Possible depression underdosing in the nursing home population was checked by analysing the PDD in accordance with the MED. The SSRI group and venlafaxine were dosed above their MED. Trazodone, TCAs and mirtazapine were often dosed under their MED. It is important to keep in mind that when treating older adults, polypharmacy, polypathology, pharmacokinetic and –dynamic alterations can influence dosage response. The MED does not really consider these particular changes in determining the threshold. In the literature, there is not much guidance on antidepressant dosing in frail older adults; slow upwards titration and close monitoring of side-effects is recommended [41].

Antidepressants for the indication 'depression':

For the indication of depression in old age, SSRIs deserve a preference within the pharmacological approach [38, 42] and, as found in our study, were the most commonly prescribed ADs in Belgian nursing homes (citalopram, sertraline, escitalopram). Although SSRIs have a more appropriate side-effect profile and are safer in overdose for older adults than other antidepressants, still, physicians should prescribe these drugs with caution, because of the risk of drug-drug interactions and adverse effects such as hyponatraemia[43], upper gastrointestinal bleeding[44], insomnia, restless leg syndrome, agitation and the potential risk of serotonin syndrome[45, 46]. The Beers list [31] of inappropriate medications for use in older adults included fluoxetine, because of its long half-life and inhibition of cytochrome P 450 enzymes (mainly CYP2D6). In our study, this SSRI was prescribed only in 2% of the cases.
In our study, venlafaxine was also frequently prescribed for depression. Together with the SSRIs, it is known for its stimulating properties that can cause sleeplessness [47]. Venlafaxine should be reserved as a second-line treatment for depression and is not indicated in patients with heart failure, coronary disease and uncontrolled hypertension [38].
Mirtazapine is also a relatively often prescribed AD for older adults because it has less anticholinergic side effects (i.e. dry mouth, urinary retention, constipation) than TCAs [48].
TCAs, equally effective as SSRIs [49], are known for their toxicity in overdose [50] and their anticholinergic side-effect profile. Therefore, they are not recommended as a first choice to treat depression in older adults. However, a recent cohort study concluded that SSRIs and the newer ADs were associated with a higher risk of adverse events, such as stroke, fracture and all-cause mortality, compared with TCAs [40].
In our study, SSRIs and venlafaxine are prescribed above the MED. However, 45% of the mirtazapine, 96% of the trazodone and 56% of the TCA prescriptions are dosed under their MED, a possible precaution taken by prescribers aware of the sedative and/or anticholinergic properties of these drugs.

Antidepressants for 'other' indications:

The most frequently prescribed AD in this setting was trazodone. It was predominately prescribed at lower dosages for primary insomnia. The use of trazodone for sleep disturbance in adult and older patients is extensive in clinical practice [51]. In depressed adult patients, there is evidence for the efficacy of trazodone for sleep disturbance [52]. In non-depressed adult

patients, trazodone might be effective in primary insomnia[53]. However, the evidence for its use for primary insomnia in older people is rather scarce [23] and controversial [54]. Trazodone has so far not received an indication as sleep-promoting agent in the official labelling. The side effects of trazodone are not very different from other (non)benzodiazepine hypnotics in terms of residual daytime impairments, but priapism and orthostatic hypotension are important side effects of trazodone [55].
The amount of trazodone prescriptions intended for insomnia and not to treat depression is increasing [51, 56]. The (inter)national warnings and campaigns against the chronic use of benzodiazepines[57] [15] are a possible reason for the preferential prescribing of trazodone. Another consideration can be the relatively lower cost of trazodone in Belgium in comparison with (non)benzodiazepine hypnotics. Moreover, trazodone, unlike (non)benzodiazepines hypnotics, is reimbursed (75% of the cost) by the Belgium Health Care system. In order to maintain a healthy economic situation, it is important to ensure that no shift towards reimbursed sedative ADs takes place, particularly in the absence of convincing evidence.
Another indication for which an AD can be prescribed is neuropathic pain. Our study confirmed the assumption that TCAs are mostly prescribed for the treatment of pain [22], and at doses lower than the DDD [24]. Although not licensed for this indication, amitriptyline, which was in our study the most prevalent agent, is considered first-line treatment for neuropathic pain in guidelines[58]. Duloxetine is also indicated for neuropathic pain and is registered for this indication [58].
Although the first pharmacological choice to treat anxiety disorders chronically is an SSRI [59, 60], in our study, physicians were more likely to prescribe a benzodiazepine on a chronic base than an AD. Benzodiazepines can be used for acute anxiety or can be co-administered for a short period of time (max 4 weeks) to overcome the delayed pharmacological effect of the AD [59, 61, 62]. However, to avoid tolerance and dependence, this dual therapy should be tapered over time.

Characteristics associated with antidepressant use:

We found that older residents had lower AD use. This is also mentioned in other AD studies [9, 17] and with other medication groups. This can be partly explained by the increasing incidence of dementia in older residents and the growing inability of residents to utter specific complaints (e.g. feeling depressed) with deepening dementia. We also found that use of psychotropics and polypharmacy are inextricably linked, indicating the need for clinical practice guidelines and education focusing on initiation and reassessment of ADs and the use of psychotropic drugs in general. Antiparkinson drugs were significantly associated with AD use, which can be explained by the symptoms of parkinsonism: depression is a common neuropsychiatric manifestation in Parkinson's disease. As ADs may have sedative properties and are often used for the treatment of insomnia, it was no surprise that insomnia was correlated with AD use, and more specifically with AD use for indications other than depression. Because in Belgium the differences in institutional characteristics between a private and public nursing home are small, we cannot explain the association between the private nursing homes and the elevated likelihood of receiving an antidepressant.

Depression and dementia:

In our study, in one third of the residents with noted dementia, depression was also reported. This is higher than the prevalence rate in other European countries [5, 63] and the United States [64]. When analyzing the different stages of disorientation (expression of dementia), we found that both the prevalence of depression and the antidepressant use decreased with worsening disorientation. This could indicate the difficulty of diagnosing depression in cognitively impaired residents and a possible under-treatment in this specific patient group. However,

a recent publication in the Lancet [65] suggested the absence of benefit of antidepressants in dementia compared with placebo and the increased risk of adverse events. The trial underscores the need to think about creative but evidence-based alternatives (such as psychosocial interventions) for the management of depression in people with dementia. But because of organizational- and staffing problems, psychotherapy is not routinely available in Belgian nursing homes.

CONCLUSION

ADs were found to be used by 39.5% of the residents. Overall, the quality of AD prescribing in the Belgian nursing homes is relatively satisfactory. Most of the residents with reported depression were treated according to evidence-based recommendations with SSRIs (mainly citalopram, sertraline and escitalopram) in dosages equal to or higher than the MED. Venlafaxine, not the first-choice drug in the older population, was used by 1/10 and in dosages equal to or higher than the MED. All other antidepressants (TCAs, mirtazapine, trazodone) used for depression were dosed under the MED.
In the indication of anxiety, most of the time, the physicians did not prescribe the recommended SSRIs; they preferred the chronic use of benzodiazepines.
A controversial issue is the prescribing of sedative ADs (mostly trazodone) for insomnia (13.4%). A plausible explanation for this prescribing without clear evidence of efficacy and safety in frail older adults can be found in the reimbursed status of ADs in comparison with other sleeping pills.

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CHAPTER 2.3

Sleep Quality of benzodiazepine users in nursing homes: a comparative study with nonusers

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ABSTRACT

Objectives: We aim to describe subjective sleep quality among chronic users of benzodiazepines and Z-drugs (BZD/Zs) in Belgian nursing homes, to compare it to nonusers, and to investigate determinants of bad sleep quality.

Methods: All mentally competent residents from 10 nursing homes were screened and compiled in a group of chronic BZD/Zs users or in a group of nonusers based on the medication chart. We collected demographic, functional, and medication characteristics and global and specific sleep parameters using the Pittsburgh Sleep Quality Index (PSQI). Linear regression was used to investigate which parameters were associated with sleep quality.

Results: Of the 300 residents, 178 (59%) were chronic BZD/Z users and 122 nonusers. The two groups did not differ in demographic and functional characteristics (mean age= 85.5 years; range 57-100, 75% women). The users reported significantly more difficulties with falling asleep, had more midnight awakenings, felt less rested in the morning, and had a poorer self-perceived sleep quality compared to nonusers. Sleep duration and time to fall asleep did not differ.
The self-perceived sleep quality was mainly determined by difficulties during initiation of sleep.
After controlling for demographic, medication and functional characteristics, BZD/Z use remained strongly associated with bad sleep ($r=0.173$, $p=0.003$), and a study centre effect (differences among nursing homes) was observed ($r=0.229$, $p<0.001$).

Conclusion: Our findings do not support long-term effectiveness of BZD/Zs; chronic users slept more poorly than nonusers (even more outspoken in users of long-acting BZDs). In future longitudinal comparative studies of sleep quality, unexplained variability needs further assessment with medical, psychological and institutional parameters.

INTRODUCTION

Sleep problems are more frequent with growing age. In the normal aging process changes in the sleep structure occur, with less restorative deep sleep (i.e. stage III and IV of the non-REM sleep). A fragmented sleep pattern with more midnight awakenings is associated with aging[1, 2]. In addition, comorbidities, medication use, psychological distress and sleep-related disorders (e.g. sleep apnoea, restless legs syndrome), all affect sleep quality and increase with age[3].

Benzodiazepines (BZDs) and related Z-drugs (BZD/Zs) are the most frequent used symptomatic treatment for sleep problems in the older population[4] and particularly in the nursing home setting[5]. In a previously published study, we reported that 50% of the Belgian nursing home population used BZD/Zs chronically[6].

Although BZD/Zs alter the sleep architecture by supressing deep sleep stages, they are initiated because of their ability to shorten the time to fall asleep and to increase total sleep duration[7, 8]. Due to their sedating action, the (short-term) adverse effects of BZD/Zs include decreased alertness with risk for falling and anterograde amnesia. After 4 weeks of continuous BZD/Z use most patients engage in chronic use, while the hypnotic effect decreases due to tolerance[9]. Interruption of treatment can lead to withdrawal symptoms[10], and these symptoms are often the reason to continue use.

Guidelines discourage chronic use because of both physical and psychological dependence as well as the unproven long-term effectiveness[11-13]. Moreover, it has been hypothesised that long-term use might have a detrimental effect on cognition and a potential acceleration of cognitive impairment[14]. The high prevalence of chronic BZD/Z users indicates that these guidelines are insufficiently implemented.

Long-term effectiveness is difficult to assess and requires long follow-up data[15]. Epidemiological studies of the effects of chronic BZD/Z use on sleep quality are scarce. Ohayon et al.[16] reported few distinctions in the various dimensions of sleep quality between older drug-taking insomniacs and older nontreated insomniacs. A study among 516 older adults in Berlin[17] reported a higher rate of sleep related complaints among individuals taking sleep medication. Both studies did not focus on BZD and Z-drugs, and did not use a standardised method to evaluate sleep. Polysomnography is the objective tool for examining effectiveness of sleep medication[18]. However, the patient's perception of sleep quality remains the determinant of most requests for prescribing hypnotics and is a common criterion by which the general physician and patient judge efficacy[19]. Therefore, a subjective tool such as the Pittsburgh Sleep Quality Index (PSQI)[20] has gained widespread acceptance to analyse sleep quality. It has undergone extensive psychometric evaluation and is often used in older adults[15, 21-23]. A Canadian study[15] in a large sample of community dwelling older adults that aimed to investigate the association between BZD use and overall sleep quality used this instrument and found a poorer sleep quality among BZD users. However, in this study the BZD use was self-reported, there was no focus on chronic use and there were no other interfering co-medication reported. We found no study especially designed to compare sleep parameters in a well-defined group of chronic BZD/Z users and a group of nonusers. Therefore, we set out to design a longitudinal study investigating sleep quality with the validated PSQI questionnaire. The aim of our study was to describe the sleep parameters of mentally competent nursing home residents as well as to investigate which sleep parameters are associated with self-perceived sleep quality, and which characteristics influence global sleep quality. More importantly, we compared sleep parameters between chronic BZD/Z users and nonusers.

METHODS

In this baseline assessment of a longitudinal cohort study in the Belgian nursing home setting, we investigated the sleep quality in a group of mentally competent chronic BZD/Z users and a group of mentally competent nonusers (control group).

Setting:

The Belgian long-term residential care structure consists of residential and/or nursing homes for older people, which offer a home replacement with or without nursing care. Governance of nursing homes for older people is either public (community health services) or private (predominantly non-profit) with little difference in quality. The point prevalence of dementia among residents is around 50% with considerable variation among nursing homes[24].

Design:

From a convenience sample of 10 nursing homes, all mentally competent residents were identified, screened for inclusion and exclusion criteria, and separated in an exposure group of BZD/Z users and a control group based on analysis of the medication chart. No matching procedure was applied. Both groups were evaluated at baseline (and will be re-evaluated at 1 year).

Inclusion and exclusion criteria:

We only included mentally competent residents defined as having a Mini Mental State Examination (MMSE)[25] score of at least 18. We excluded residents that only used the sedative antidepressants trazodone or mirtazapine or phytotherapy as a sleep medication. We also excluded residents that used BZDs for the indication anxiety. Residents with BZDs or Z-drugs administered at bedtime for at least 3 months were allocated to the exposure group. Residents who were free of any hypnotic medication and did not use a BZD during daytime for anxiety were allocated to the control group.

Data collection:

Demographic data were obtained from the resident's record and medication data from the medication chart in the period December 2011- January 2012. Cognitive function was scored by the MMSE test. The scores of this crude screening tool range from 0 to 30, with higher scores indicating a better global cognition. Functional characteristics were scored by the KATZ Activities of Daily Living (ADL) scale[26]. This instrument is mandatory in the Belgian nursing homes. The first part of this instrument scores six ADLs from 1 (independent) to 4 (total dependent). The second part scores disorientation in time and place ranging from 1 (no disorientation) to 4 (severe) and was used to confirm mental competence.
Based on the Anatomical Therapeutic and Chemical classification (ATC)[27], we selected the classes N05BA (anxiolytics), N05CD (hypnotics) and N05CF (Z-drugs) to define the BZD/Z group. The BZDs, tetrazepam and clonazepam, both taken by one person were in this study classified as sleep medication, though they have a different ATC nomenclature. We divided the BZDs and Z-drugs according to half-life based on a reference source[28]: triazolam, lormetazepam, loprazolam, oxazepam, lorazepam, bromazepam, alprazolam, zopliclone and zolpidem were grouped into short-acting drugs ($T_{1/2}$<24h) and tetrazepam, clonazepam, flurazepam, flunitrazepam, diazepam, prazepam and chorazepate into long-acting drugs ($T_{1/2}$>=24h). We recorded the total number of chronically used medications as well as possible interfering medication such as antidepressants (ATC N06A), antipsychotics (ATC N05A), anti-dementia

drugs (ATC N06D), anti-Parkinson (ATC N04) drugs and narcotic pain medication (ATC N02A).

Sleep evaluation:

The PSQI[20], a self-rated questionnaire that investigates global sleep quality and sleep disturbances was used (Dutch translation[29]). Because our sample was a geriatric population, the researchers assisted the resident with the recording and rating of the questionnaire. The seven components of the PSQI are scored from 0 to 3, yielding a total score ranging from 0 to 21, with a higher score indicating worse sleep quality. The component 'sleep difficulties' included nocturia and pain, both defined as waking up in the night more than once a week.
A total PSQI score of more than 5 is a widely used cut-off that indicates poor sleep quality. Because, we wanted to compare sleep quality in a group of BZD/Z users and nonusers in this study, we generated a new PSQI score (adjusted PSQI) without the component 'sleep medication'. The adjusted PSQI can range from 0 to 19 and was the variable of choice when we investigated and compared sleep quality in BZD/Z users and nonusers.

Sample size calculation:

We calculated a required sample size of at least 99 individuals per group to detect a difference of 2 points on the PSQI from 4.5 to 6.5 (SD 5) with a power of 0.80 and $P<0.05$ as the level of significance.

Statistics:

In the primary analysis, demographic, functional and medication characteristics were described for the total nursing home population and compared between the BZD/Z users and the nonusers, using Chi^2 for categorical variables and independent t-tests for continuous variables.
The internal consistency of the total PSQI was 0.66 (Cronbachs α), which was comparable with previous studies[30]. We analysed the sleep parameters in the total population and in the two parallel groups. All component scores were compared with non-parametric statistics (Mann Whitney U) and the frequencies in each component score were analysed with Chi^2.
Within the BZD/Z group, the different PSQI components were compared between users of long-acting and short-acting BZD/Z with non-parametric statistics (Mann Whitney U).
To find which components of the PSQI were related to the subjective PSQI component 'self-perceived sleep quality', we used multiple linear regression with the score on self-perceived sleep quality as the dependent variable.
Variability of different parameters among the nursing homes was analysed with non-parametric statistics (Kruskal Wallis).
Furthermore, we analysed which demographic, functional and medical characteristics were associated with global sleep quality in a multiple linear regression model with the total adjusted PSQI as dependent variable. All statistical analyses were performed using the statistical package SPSS version 20 with $p<0.05$ as the level of significance.

Ethical considerations:

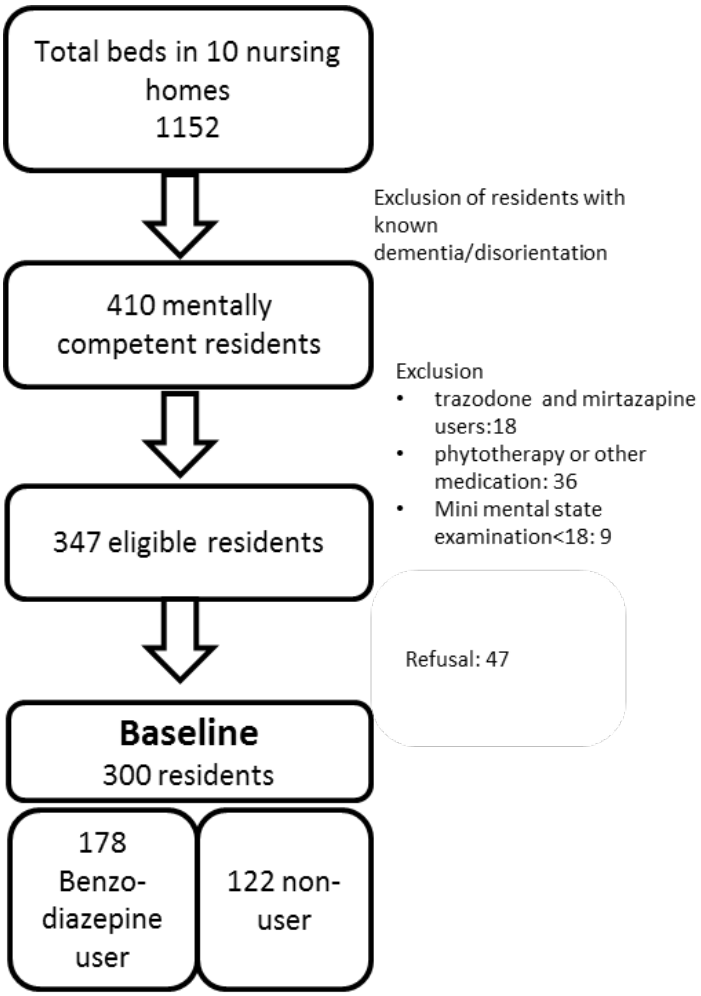
This observational cohort study was approved by the Ethics Committee of the University Hospital of Antwerp (registration number B300201112211). Each nursing home received information and gave approval to screen the nursing home population. Each included resident received oral and written information and gave consent.

RESULTS

Recruitment:

Ten nursing homes with a total of 1152 beds (located in two Flemish regions of Belgium, Antwerp and Ghent) agreed to participate. Inclusion criteria were met by 410 residents. Sixty three residents were excluded based on analysis of the medication chart. We asked 347 eligible residents to participate and 47 refused. Of the 300 enrolled residents, 178 (59%) used a BZD/z-drug and were included in the BZD/Z group and 122 nonusers in the control group (Fig 1).

Fig 1: Flowchart of prospective cohort study



Demographic and functional characteristics of the total population:

The mean age of the total population was 85.5 years (range 57-100) and the average time of institutionalisation was 40 months. Three quarters were female. Schooling age was not higher than 14 years in 59% of the residents. The mean MMSE score was 25.6 (range 18-30), and the mean ADL score was 12.1 (range 6-24), with mainly difficulties with washing and clothing. The average number of chronic medications was 8.1 (range 0-18) (Table 1).

Table 1. Description of demographic, functional and medication characteristics in total population and compared between chronic benzodiazepine users and nonusers.

	total population N=300	BZD/Z group N=178	CONTOL group N=122	p value**
Demographic characteristics				
age (mean-range)	85.5 (57-100)	85.4 (57-100)	85.7 (65-99)	0.767
gender (%female)	74.7	75.3	73.8	0.768
length of stay in months (mean-range)	39.7 (0-223)	39.7(1-191)	39.6 (0-223)	0.985
education level				
elementary (%)	14.7	17.4	10.7	0.342
high school till 14y (%)	44.7	42.1	48.4	
high school till18y (%)	33.0	32.0	34.4	
higher (%)	7.7	8.4	6.5	
Functional characteristics (mean-range)				
self-dependency score (ADL) (6-24)	12.1 (6-24)	12.3 (6-24)	11.8 (6-22)	0.382
disorientation score (2-6)	2.6 (2-6)	2.5 (2-6)	2.7 (2-6)	0.073
MMSE score (0-30)	25.6 (18-30)	25.4 (18-30)	25.7 (18-30)	0.407
Medication				
chronic medications (mean-range)	8.1 (0-18)	9.2 (1-18)	6.6 (0-17)	**<0.001**
use of Sleepmedication (%)	59.3	100.0		
ATC class				
hypnotic* (%)		43.8*		
anxiolytic* (%)		39.9*		
Z-drug* (%)		25.3*		
duration of action				
long-acting (%)		12.4*		
short-acting (%)		90.4*		
use of Psychotropics (%)	53.3	62.4	40.2	**<0.001**
antidepressant (%)	36.3	44.9	23.8	**<0.001**
antipsychotic (%)	13.0	15.7	9.0	0.089
anti-dementia (%)	4.7	3.4	6.6	0.199
anti-Parkinson (%)	6.0	5.6	6.6	0.736
use of narcotic analgesic (%)	16.7	23.0	7.4	**<0.001**

* sum of percentages >100% due to duplicate use

** p value: continuous variables with independent t-test and dichotomous variables with Chi^2

ADL: Activities of Daily Living

MMSE: Mini Mental State Examination

ATC: Anatomical Therapeutic Chemical Classification/ (hypnotic= N05CD, Z-drug= N05CF; anxiolytic= N05BA)

In the BZD/Z group, 44% used a hypnotic (ATC N05CD), 40% used an anxiolytic (ATC N05BA) and 25% a z-drug (ATC N05CF). Dual BZD use was seen in 13% (n=23). Most often (34%) lormetazepam was used. Zolpidem and lorazepam were each used by 25% of the users. Based on the half-life, 90% used a short-acting and 12% a long-acting benzodiazepine (2% overlap due to dual use).

Sleep characteristics of the total population:

The mean adjusted PSQI score (without the medication component) of the 300 residents was 4.9 (SD 2.4). This score was mainly influenced by the component sleep latency (r=0.705, p<0.001) and the self-perceived sleep quality (r=0.703, p<0.001). Additionally, the components daytime dysfunction, sleep disturbance, efficiency and duration had a significant correlation with the total PSQI of 0.566, 0.450, 0.286, and 0.231, respectively.
The number of bad sleepers (adjusted PSQI more than 5) was 36%. The mean hours of night-time sleep was 8h57min (3h25 to 13h15). The mean number of minutes before a resident fell asleep was 27 minutes (1min. to 210min.). Mean scores of the different PSQI components are shown in table 2. Nocturia occurred in more than 70% of the nursing home residents and was the most frequent night-time disturbance. Awakenings due to pain were present in 24%, of which 46% had a prescription for a narcotic analgesic.

Table 2. Sleep characteristics compared between benzodiazepine users and nonusers.

COMPONENTS of PSQI*	BZD/Z group N=178	CONTROL group N=122	p value**
SLEEP duration (0-3)	0.17	0.10	0.334
hours of sleep (mean-range)	8h56 (3h25-13h15)	8h58 (5h10-11h55)	0.818
SLEEP latency (0-3)	1.40	1.19	0.072
minutes before falling asleep (mean-range)	28 min (1-210)	25 min (1-150)	0.414
SLEEP disturbance (0-3)	**1.21**	**1.02**	**0.002**
midnight awakenings (0-3)	**2.12**	**1.68**	**0.001**
difficulties falling asleep (0-3)	**1.47**	**1.20**	**0.050**
midnight toilet awakenings (0-3)	2.08	2.07	0.804
awakenings pain (0-3)	**0.82**	**0.50**	**0.013**
Daytime dysfunction (0-3)	**1.44**	**1.16**	**0.015**
daytime sleepiness (0-3)	1.60	1.48	0.388
well rested (0-3)	**0.82**	**0.48**	**0.002**
SLEEP efficiency (0-3)	0.07	0.03	0.335
SLEEP self-perceived sleep quality(0-3)	**1.12**	**0.78**	**0.001**
total adjusted PSQI (0-19)	5.4 (1-12)	4.3 (0-11)	**<0.001**
% bad sleepers (adjusted PSQI >5)	42.1	27.0	**0.007**
total PSQI (0-21)	8.2 (1-17)	4.6 (0-11)	**<0.001**

* six components of the adjusted PSQI ; expressed as mean score, with higher scores indicating worse outcome

'Sleep duration' is categorised into more than 7 hours of sleep (score 0), between 6 and 7 hours (score 1), between 5 and 6 hours (score 2) and less than 5 hours (score 3). 'Sleep latency' consists out of 2 items; 'difficulties falling asleep' and 'minutes before falling asleep' categorised as less than 15minutes (score 0), between 16 and 30minutes (score 1), between 31 and 60minutes (score 2), and more than 60minutes (score 3). The components 'sleep disturbances', 'daytime dysfunction' and 'sleep medication' are scored from 0 to 3 (coded as not during the past month to three or more times a week. 'Sleep efficiency', composed as the ratio hours slept/ hours spent in bed is divided into 85% or more (score 0) , between 75% and 84% (score 1), between 65% and 74% (score 2), and less than 65% (score 3). The subjective component 'self-perceived sleep quality' is also scored from 0 to 3, meaning very good, fairly good, fairly bad and very bad respectively.

** scores with Mann Whitney U test,continuous variables with independent t test and percentage with Chi^2

PSQI= Pittsburgh Sleep Quality Index / adjusted PSQI= PSQI without the medication component

The mean score of the component 'self-perceived sleep quality' was 0.98 (SD 0.84). We investigated which components of the PSQI were associated with self-perceived bad sleep quality (table 3) and in univariate analysis; we found that all sleep parameters were associated. In multivariate analysis, sleep latency had the highest correlation (r=0.349), followed by pain (r= 0.161), the feeling of not being rested in the morning (r=0.146) and midnight awakenings (r=0.134).

Table 3. Sleep parameters (derived from the Pittsburgh Sleep Quality Index) associated with the component self-perceived sleep quality: Univariate and multivariate analysis.

	self-perceived sleep quality (range 0-3)				
COMPONENTS of PSQI	**UNIVARIATE**		**MULTIVARIATE****		
	r	**p value***	**B**	**ß**	**p-value**
SLEEP duration (0-3)	0.152	0.009	0.258	0.141	0.004
hours of sleep (mean-range)	-0.137	0.018			
SLEEP latency (0-3)	0.411	<0.001	0.264	0.349	<0.001
minutes before falling asleep	0.528	<0.001			
SLEEP disturbance (0-3)	0.240	<0.001			
midnight awakenings (0-3)	0.233	0.001	0.089	0.134	0.008
difficulties falling asleep (0-3)	0.439	0.001			
midnight toilet awakenings (0-3)	0.149	0.010			
awakenings pain (0-3)	0.259	<0.001	0.120	0.161	0.002
Daytime dysfunction (0-3)	0.196	0.001			
daytime sleepiness (0-3)	0.125	0.031			
well rested (0-3)	0.240	<0.001	0.133	0.146	0.004
SLEEP efficiency (0-3)	0.198	0.001			
SLEEP medication (0-3)	0.223	<0.001	0.066	0.115	0.023

*non parametric statistics (spearman rank)

** multivariate linear regression (r^2=0.32)

Factors associated with bad sleep:

With this analysis, we wanted to investigate several demographic, functional and medication characteristics associated with sleep quality (Table 4). Univariate analysis showed there was no correlation between adjusted PSQI and the use of psychotropic drugs other than BZD/Zs. Gender, MMSE score, functional status, education level, and length of stay also were not associated. Multivariate analysis showed that the adjusted PSQI had the highest association with BZD/Z use (r= 0.173). Age and the number of chronic medications also were associated (Table 4). Although the variance explained in our model remained small, it did increase from 8% to 13% when we included study centre in the model.

Table 4. Demographic, functional and medication characteristics associated with bad sleep (according to the total adjusted Pittsburgh Sleep Quality Index score).

	total adjusted PSQI(range 0-19)					
	UNIVARIATE*		MULTIVARIATE**			
Factors/Characteristics	**r**	**p-value**	**B**	**ß**	**p-value**	**R^2**
BZD/Z use	0.230	<0.001	0.850	0.173	0.003	0.053
number of chronic medications	0.185	0.001	0.077	0.126	0.030	0.067
age	0.130	0.025	0.048	0.144	0.008	0.083
disorientation	-0.107	0.066				
narcotic use	0.097	0.094				
antipsychotic use	0.073	0.210				
MMSE score	0.073	0.208				
education	-0.065	0.262				
antidepressant use	-0.021	0.719				
gender (female)	0.012	0.839				
length of stay	-0.012	0.838				
ADL	-0.011	0.846				
anti-Parkinson drugs	-0.030	0.601				
anti-dementia drugs	-0.061	0.289				
study centre effect (nursing home)	0.234	<0.001	0.205	0.229	<0.001	0.134

* Pearson correlation

**multivariate linear regression: cumulative R^2 shown

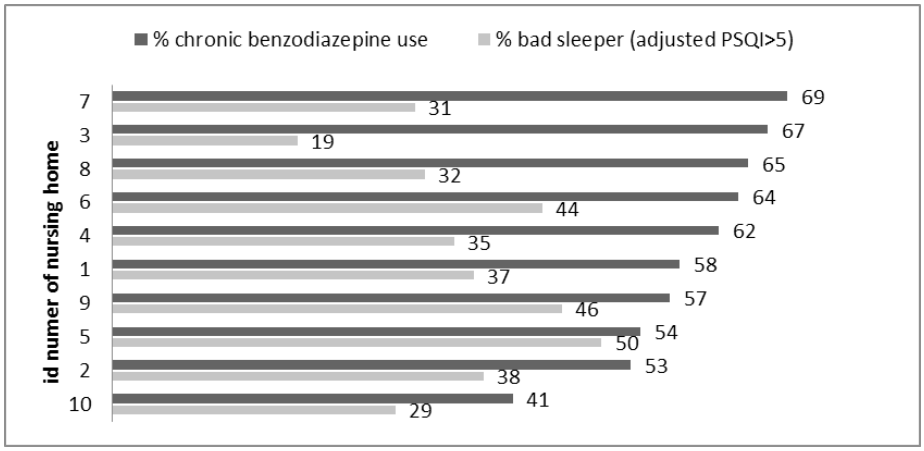
MMSE: Mini Mental State Examination

ADL: Activities of Daily Living

Variability among nursing homes:

We saw considerable variation in the adjusted PSQI score in the ten nursing homes ranging between 3.1 and 5.2 (p=0.018). The percentage of BZD/Z users per nursing home ranged from 41% to 69% while the prevalence of bad sleepers (adjusted PSQI >5) ranged from 19% to 50%. There was a negative correlation between these two parameters, but it was not significant (r=-0.231, p=0.522) (Fig 2).

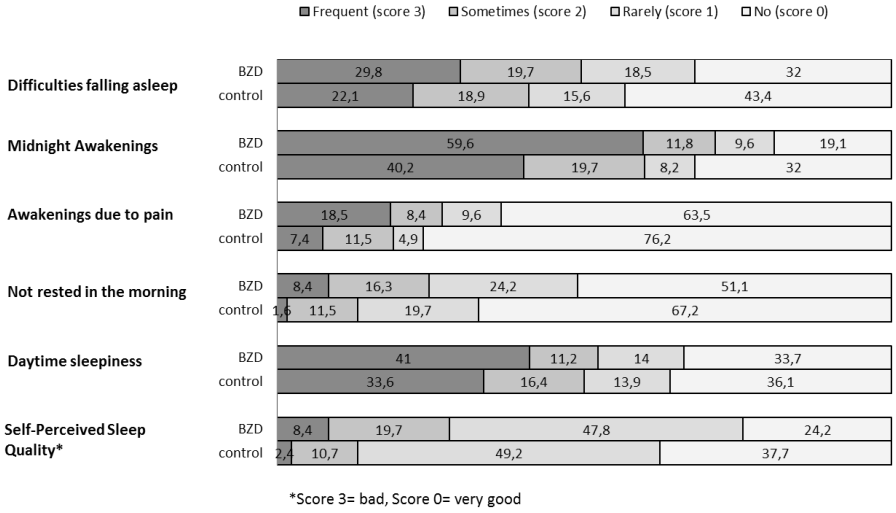
Fig 2: Percentages of chronic benzodiazepine use and bad sleepers per nursing home.



Comparison between benzodiazepine users and nonusers:

The BZD/Z users and the nonusers did not differ in demographic and functional characteristics. The average number of chronic medications differed in the two groups; 9.2 chronic medications in the BZD/Z group, and 6.6 in the control group. The use of other psychotropic drugs differed between users and nonusers, more specifically the use of antidepressants (45% vs. 24%) and narcotic analgesics (23% vs. 7%) (Table 1).
We looked at the differences in the mean scores of PSQI components (Table 2) and also at the frequency distribution of the scores in percentages (Fig 3). The total adjusted PSQI score differed between the two groups; 5.4 in the BZD/Z group and 4.3 in the control group (p<0.001).

Fig 3: Frequency distribution of the scores of the Pittsburgh Sleep Quality Index for chronic benzodiazepine users and non-users per component (score range: 0-3).



In the BZD/Z group, 8% perceived their sleep quality very bad and 20% rather bad. This percentage was at least two times higher than in the control group (2% and 11% respectively, p<0.001). Approximately 30% of the BZD/Z users had frequent difficulties with falling asleep compared to 22% in the control group. Midnight or early morning awakenings were frequent in 60% of the users compared to 40%. Sleep disturbance due to pain was frequent in 19% of the users compared to 7%. The feeling of not being well rested in the morning was present in 8% of the users compared to 2% of the nonusers. All of these differences were statistically significant (Table 2). Nocturia, the mean hours of nighttime sleep, the minutes before falling asleep and the feeling of sleepiness during the day did not significantly differ between users and nonusers.
Within the BZD/Z group, a separate analysis comparing users of long-acting (n=17) versus short-acting BZDs (n=156) showed a worse adjusted PSQI score (6.5 vs. 5.3, p=0.012), though there were no differences in sleep duration and time to fall asleep. Users of long-acting BZDs had more difficulties with falling asleep than users of short-acting (mean score 2.2 vs. 1.4 p=0.013) and perceived a poorer subjective sleep quality (1.6 vs. 1.1 p=0.02). Other sleep parameters, such as midnight awakenings, not feeling rested in the morning, and daytime sleepiness did not significantly differ.

DISCUSSION

Our study was the first study especially designed to investigate sleep quality among chronic BZD/Z users in the nursing home setting and to compare this to a well-defined control group using an adequate tool that reports several aspects of sleep quality.
The main finding of our study was that chronic users of BZD/Zs had a poorer sleep quality than nonusers, though they did not differ in terms of demographic and functional characteristics. More specifically, chronic users reported more difficulties with falling asleep, a higher frequency of midnight awakenings, and a higher frequency of not being well rested in the morning. Additionally, we found that the sleep quality considerably differed between the participating nursing homes.

Sleep characteristics of the total population:

Nursing home residents in our study needed approximately half an hour (27min) to fall asleep and had a long but disturbed night-time sleep (9 hours). Midnight toilet awakenings occurred in 70% and were the most common sleep disturbance in our study, as well as in other studies[31, 32]. Surprisingly, the self-perceived sleep quality of nursing home residents was not determined by nocturia, but was predominantly determined by difficulties falling asleep and by pain. Because pain can provoke sleep problems[33], underlying causes should be addressed and could reduce the prescribing of sleep medication. In future research, the concomitant use of a pain assessment scale could help in clarifying sleep problems.

Characteristics associated with bad sleep:

We investigated which demographic, functional and medical characteristics were associated with poorer sleep quality. Except for a weak association with age, we found no specific associations with demographic and functional characteristics such as gender, education, and ADL score. Similar to other studies[34], we found that the more intense the polypharmacy was (even when the use of psychotropic drugs was excluded), the poorer the sleep quality. Multiple pathologies and the associated medication use can influence the sleep quality[35].
The variance of our model was small, though it increased from 8% to 13% when we introduced the study centre effect. A large part remains unexplained; therefore institutional characteristics such as the type of ward and nighttime policy[31, 36] should be included in future research of sleep quality. Additionaly more psychometric properties of the older adults such as depressive symptoms should be investigated.

Sleep characteristics compared between benzodiazepine users and nonusers:

Although the main reason to initiate BZD/Zs is to shorten the time before falling asleep[7, 8], chronic users reported more difficulties with falling asleep in our study. Surprisingly, the self-reported more objective sleep parameters such as time before falling asleep and hours of sleep did not differ between the two groups. Pseudoinsomnia, a misperception of sleep in which sleep latency is overestimated, has been described in the literature[37] and could be the reason why residents using sleep medication perceive subjective sleep complaints more intensely.
The feeling of being tired in the morning was more present among chronic BZD/Z users. This confirms the risk of the hangover effect[38]. Long-acting BZDs are said to have more daytime residual effects[39]. In our study, when a long-acting BZD was used, the overall differences were accentuated, but not in daytime dysfunction.
It is known that BZD/Zs change sleep architecture at the expense of the deep restorative

stages of sleep; therefore our finding that chronic users reported more midnight awakenings is logical. Another explanation could be that the BZD/Z user had a less restorative and more fractionated sleep as a consequence of aging, and had no persistent improvement with the drug.
Furthermore, awakenings due to pain were more frequent among chronic BZD/Z users in our study, which additionally could influence the overall rate of awakenings.

Strengths and limitations:

The strength of our study compared to other studies examining the differences in sleep quality between sleep medication users[15-17], was our focus on BZD/Zs, considered the use of co-medication, used a validated questionnaire, and reported the different aspects of sleep quality. Furthermore, we enhanced data accuracy by only including mentally competent residents, and we had a participation rate of 87%. This strenght allowed us to confirm results from other studies, but in a more specific setting.
There are several limitations related to our study design. We used a convenience sample of nursing homes. However, the respondents' characteristics were comparable to the Belgian nursing home population (age-gender-chronic drug intake)[24].
Our finding that sleep quality was poorer in chronic BDZ/Z users does not support the hypothesis of the long-term effectiveness of BZD/Zs but cannot disprove it either. To make conclusions with regard to long-term effectiveness, and development of tolerance, longitudinal studies with incident users and baseline sleep parameters are necessary. Unfortunately, we do not have this information, given the cross-sectional character of our study. Further follow-up for our study (1 year) will provide evidence regarding differences in temporal evolution of sleep quality between BZD/Z users and nonusers.
Another limitation was that we used proxies for clinical data. Unfortunately, we had no information on specific sleep disorders and on specific medication other than psychotropics or narcotics that could influence sleep quality (i.e. beta blocker, thyroid medication)[3]. Furthermore, we did not collect information on fall incidents or fractures. We did not gather information regarding the length of BZD/Z use beyond the minimum requirement of 3 months and we did not record dosages.
The use of a subjective tool to evaluate the effectiveness of hypnotics, such as the PSQI, is both a limitation and strength. Self-reported time in and out of bed can be inaccurate, though there is a good correlation between self-reported sleep measurements and objective measurements such as actigraphy[41] and polysomnography[23]. Another limitation of the PSQI in our study was the presence of the medication component. Similar to other studies[15, 42], we excluded this component in analysis, leading to a lower total score and an underestimation of the percentage bad sleepers.

CONCLUSION

Our findings do not support long-term effectiveness of BZD/Zs; chronic users slept worse than nonusers (even more pronounced in users of long-acting BZDs). In future longitudinal comparative studies of sleep quality, unexplained variability needs further assessment with medical, psychological, and institutional parameters.

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CHAPTER 2.4

One-year evolution of sleep quality in older benzodiazepine users: A longitudinal cohort study in Belgian nursing home residents.

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ABSTRACT

Objectives: Chronic use of benzodiazepines and Z-drugs (BZD/Zs), the most commonly used symptomatic treatment for sleep problems is discouraged because of the unproven long-term effectiveness and potential side-effects.
In this study, we evaluated one-year evolution of subjective sleep quality of chronic BZD/Z users compared to nonusers.

Methods: All cognitively competent residents from 10 Belgian nursing homes were screened and compiled in a group of chronic BZD/Z users or nonusers, based on the medication chart. We collected demographic, functional and psychometric characteristics (depressive symptoms with the 8-item Geriatric Depression Scale), sleep parameters (with the Pittsburgh Sleep Quality Index-PSQI) and medication use. We analysed evolution of sleep quality with nonparametric statistics. Associations with worsening of sleep quality were analysed with linear regression.

Results: We collected data of 131 BZD/Z users and 95 nonusers. The mean age in both groups was 85 years and 77% was female.
Over a period of one year, the PSQI score evolved from 5.2 to 5.8 ($p=0.035$) in the BZD/Z users, and from 4.3 to 4.7 ($p=0.078$) in the nonusers. Though the mean deterioration in one year did not differ significantly between both groups, the BZD/Z users had a significantly worse sleep quality compared to nonusers at both time points.
Depressive symptoms were significantly associated with worsening sleep quality (ß=-0.243, $p<0.001$).

Conclusion: Sleep quality in chronic BZD/Z users significantly decreased over one year and was significantly worse than nonusers at the end of this period. This study suggests that using BZD/Zs chronically does not maintain or improve sleep quality. Depressive symptoms are an important factor in the deterioration of sleep quality.

INTRODUCTION

Benzodiazepines and related z-drugs (BZD/Z) are the most frequently used symptomatic treatment for sleep problems in the older population and particularly in the nursing home setting[1, 2]. Although BZD/Zs alter the sleep architecture by suppressing deep sleep stages, they are initiated because they shorten the time to fall asleep and increase total sleep duration[3]. Due to their sedating action, the (short-term) adverse effects of BZD/Zs include decreased alertness with risk of falls[4] and anterograde amnesia. Although most patients engage in chronic use, the hypnotic effect decreases due to tolerance [5]. Due to the risk of adverse drug events and drug dependence, guidelines advise short-term use of BZD/Zs Interruption of treatment can lead to withdrawal symptoms[6], and this is often the reason for continued use.

Long-term effectiveness is difficult to assess and requires long-term follow-up data. Until now, there have been no randomised controlled studies published that have investigated the long-term effectiveness of chronic BZD/Z use (max. follow-up time is 6 months[7]). Epidemiological studies of the effects of chronic BZD/Z use on sleep quality [8-11] indicate a worse sleep quality in chronic BZD/Z users. But longitudinal studies which investigate the temporal evolution of sleep quality are scarce[12], especially in older people residing in the nursing homes [13]. Moreover, most studies on benzodiazepines do not differentiate between the indication insomnia or anxiety.

Our aim was to investigate the one-year evolution of sleep quality in a well-defined group of chronic BZD and z-drug users (indicated for insomnia) and compare this to a well-defined group of nonusers. Furthermore, we investigated which demographic, functional and clinical characteristics and medications were associated with worsening sleep quality over time.

METHODS

In this longitudinal cohort study in the Belgian nursing home setting, we compared the one-year evolution of sleep quality in a group of cognitively competent chronic BZD/Z users to a group of cognitively competent nonusers. The methodology and baseline findings were previously published[11].

Design:

From a convenience sample of 10 nursing homes, all cognitively competent to respond to questionnaires (defined as having a Mini Mental State Examination (MMSE)[14] score of at least 18 out of 30[15]) residents were identified. We excluded residents which only used the antidepressants trazodone or mirtazapine or phytotherapy as a sleep medication, and residents that used BZDs for the indication anxiety (defined as daytime use of BZDs). Residents with BZDs or Z-drugs administered at bedtime for at least 3 months were allocated to the BZD/Z group. Residents free of any hypnotic medication were allocated to the nonuser group. Both groups were evaluated at baseline (December 2011-January 2012) and after one year (January 2013).

Data collection:

Demographic data were obtained from the resident's record and medication data from the medication chart. Clinical data included cognitive competence (assessed with MMSE), hearing, visual problems, and functionality (Activities of Daily Living, ADL).
Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI)[16], a self-rated questionnaire for global sleep quality and specific aspects of sleep disturbance. The 7 components of the PSQI are scored from 0 to 3, with higher scores indicating worse sleep quality. Similar to other studies[10, 17], we used an adjusted PSQI score that can range from 0 to 19 (with higher scores indicating a worse sleep quality). This adjusted score excludes the PSQI component 'sleep medication' because of its full correlation with BZD/Z use. The widely used cut-off of 5 was used to indicate poor sleep quality.
At one-year follow-up, additional items were investigated. Depressive symptoms were scored with the 8-item Geriatric Depression Scale (GDS-8)[18]. This abbreviated version of the GDS-30 was especially designed and validated for nursing home residents. A score of three or more on the GDS-8 is indicative for depression[19]. Additionally, we recorded falls by checking the medical file. We also recorded the presence of restless legs, frequent pain, the frequency of social activities, social contacts (visitors in and out the nursing home) and mental stimuli (watching TV, reading, memory games) by using a yes or no question.

Ethical considerations:

This observational cohort study was approved by the ethics committee of the University Hospital of Antwerp (registration number B300201112211). Each nursing home received information and approved the screening of residents. Each resident included in our study received oral and written information, and gave their consent.

Statistics:

The analysis and presentation of our results focused on the residents still included at one-year follow-up and was based on initial group assignment.
Demographic, functional, psychometric and medication characteristics were described and compared between the BZD/Z group and the control group, using percentages and Chi^2 for

categorical variables and means and independent t-tests for continuous variables except for scaling results where we used nonparametric statistics.
Sleep evolution was presented with mean adjusted PSQI scores and standard deviations (SD) and analysed with Wilcoxon Signed Rank test. Differences in adjusted PSQI scores between both groups were analysed with Mann Whitney U test.
Multiple linear regression was used to analyse the associations between demographical, functional, and clinical characteristics, and medication and the worsening sleep quality (difference in adjusted PSQI score between the baseline and the 12 month assessment).

RESULTS

At baseline, 300 residents met the inclusion criteria: 178 BZD/Z users and 122 nonusers (sleep characteristics are previously published [11]). After one year, we had follow-up data of 226 residents; 131 BZD/Z users and 95 nonusers.
There were no differences in characteristics between residents lost-to-follow (n=74) and residents still in the study (n=226) at one year, except for the baseline MMSE score, which was 1 point lower in the residents lost-to-follow (25.8 vs. 24.9, p=0.015). Mortality was an important cause of lost-to-follow-up in both groups (16.3% in the BZD/Z group and 11.5% in the control group, p=0.253).

Comparison of BZD/Z users' characteristics to nonusers:

The comparisons of BZD/Z users' clinical, psychometric characteristics and medication information to nonusers are presented in Table 1.
The demographic and clinical profile of the BZD/Z users and the nonusers was similar, except for depressive symptoms, which were more present among the BZD/Z users (43% vs. 27%). The BZD/Z users played less memory games compared to the control group (31% vs. 45%). The BZD/Z group took significantly more chronic medications compared to the control group (mean of 9.1 vs. mean of 7.5), with a larger intake of pain medication (41% vs. 17%).
The most frequently used BZD/Zs at baseline (n=131) were lormetazepam (34%), zolpidem (26%) and lorazepam (23%). Short/intermediate-acting BZD/Z were used in 90% (n=118) and long-acting in 14% (n=18), with 4% overlap.

Table 1. Comparison of characteristics between BZD/Z users and nonusers.

	BZD/Z users N=131	nonusers N=95	p value[d]
Demographic characteristic[a]			
age (mean-range)	85.3 (57-99)	85.0 (65-99)	0.763
gender (%female)	75.6	78.9	0.552
length of stay in months (mean-range)	40.4 (3-191)	41.1 (3-223)	0.901
education level- higher education(%)	36.6	43.2	0.322
Clinical characteristics[b]			
self-dependency score (ADL) (6-24)	12.82	12.38	0.418
disorientation score (2-6)	2.81	2.86	0.935
MMSE score (0-30)	23.9	24.2	0.301
visual problems (%)	9.2	9.5	0.936
hearing problems (%)	9.9	13.7	0.382
falls during 1 year (%)	41.2	33.7	0.249
Psychometric characteristics[b]			
frequent pain (%)	47.3	42.1	0.436
depression (GDS≥ 3) (%)	43.3	27.2	0.014
adjusted PSQI score (0-19)	5.79	4.74	0.004
bad sleeper (adjusted PSQI>5) (%)	45.8	27.7	0.006
frequent social activities (%)	48.6	43.6	0.440
frequent social contact[c] (%)	86.3	87.4	0.880
mental stimuli: reading (%)	61.8	66.3	0.489
mental stimuli: memory games (%)	31.3	45.3	0.032
mental stimuli: watching TV (%)	92.4	88.4	0.313
Medication Information[b]			
chronic medications (mean-range)	9.08	7.48	0.002
benzodiazepine/Zdrug (%)	93.1	10.5	<0.001
antidepressant (%)	42.7	30.5	0.061
antipsychotic (%)	18.3	9.5	0.063
anti-Alzheimer (%)	2.3	5.3	0.232
anti-Parkinson (%)	6.1	7.4	0.707
pain medication (%)	41.2	16.8	<0.001
narcotic analgesic (%)	22.1	6.3	0.001
non-narcotic analgesic(%)	22.9	8.4	0.004
NSAIDs(%)	4.6	4.2	0.894

[a] baseline , [b] we report the 1 year results of these parameters

[c] frequent social contacts defined as frequent visitors

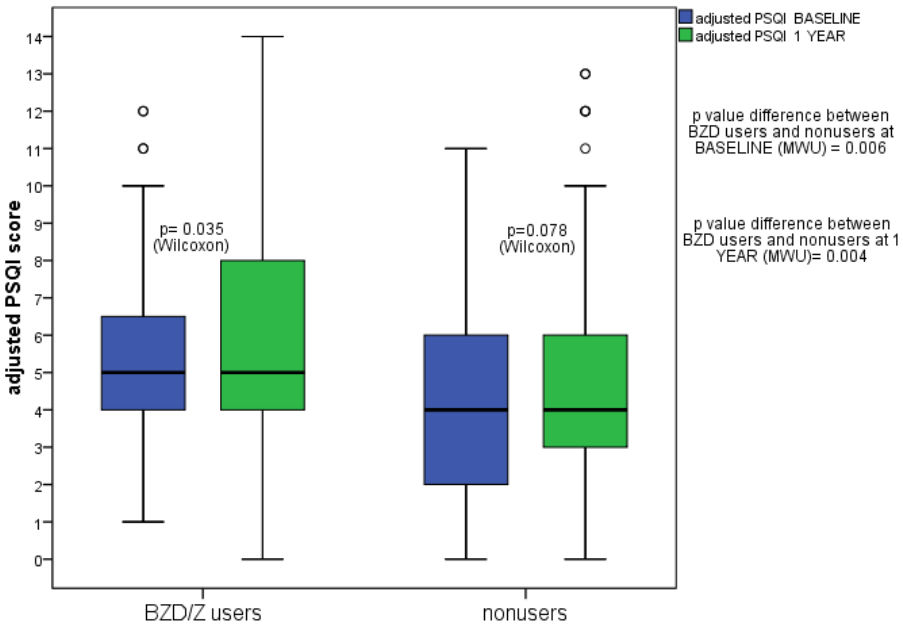
[d] pvalue: continuous variables with independent t test, percentages with Chi^2 and Mann Whitney U for scales

MMSE= Mini Mental State Examination, GDS= Geriatric Depression Scale, ADL= Activities of Daily Living, PSQI= Pittsburgh Sleep Quality Index, NSAID= non-steroidal anti-inflammatory drugs

Sleep evolution in the BZD/Z users compared to nonusers:

Over a period of one year, in the BZD/Z group, the adjusted PSQI score evolved from 5.2 (SD 2.4) to 5.8 (SD 3.1) (p=0.035) and in the nonusers from 4.3 (SD 2.3) to 4.7 (SD2.9) (p=0.078). This mean deterioration in both groups did not differ significantly (Fig. 1).

Fig 1: One-year evolution of sleep quality (adjusted PSQI score) in BZD/Z users and nonusers.



Legend:

PSQI: Pittsburgh Sleep Quality Index, MWU: Mann Whitney U test, BZD/Z user: benzodiazepine or Z-drug user

Horizontal lines indicate the median, and the small circles indicate outliers

The percentage of bad sleepers (adjusted PSQI >5) was larger in the BZD/Z group compared to the nonusers at baseline (39.7% vs. 28.4% p=0.079) and increased in one year (45.8% vs. 27.7% p=0.006). In the BZD/Z group 19.5% became a new bad sleeper compared to 11.7% nonusers (NS).

Associations with sleep quality worsening:

In the univariate analysis, we did not find correlations between worsening sleep quality and any demographic (age, gender, educational level), any (number of) medication or any functional or any clinical characteristic except for depressive symptoms (ß=-0.235, p<0.001) (Table 2). In multivariate analysis controlled for age, gender and BZD/Z use, depressive symptoms were significantly associated with worsening sleep quality (ß=-0.243, p<0.001) (Table 2).

Table 2. Factors related to the observed difference in sleep quality between the baseline and the 12-month assessment using the adjusted PSQI: Univariate and multivariate linear regression model.

	worsening sleep quality (delta PSQI adjusted) [a]					
factors	**UNIVARIATE**			**MULTIVARIATE [b]**		
	B	**beta**	**p-value**	**B**	**beta**	**p-value**
Age	-0.012	-0.032	0.631	0.007	0.020	0.779
Gender	-0.307	-0.046	0.495	-0.394	-0.058	0.396
BZD/Z use	-0.124	-0.022	0.745	0.044	0.008	0.908
Education	-0.310	-0.091	0.173			
Number of medications	0.011	0.015	0.825			
Antidepressant use	0.375	0.065	0.333			
Pain medication	0.447	0.074	0.270			
Antipsychotic	0.642	0.080	0.232			
ADLscore	0.038	0.066	0.326			
MMSEscore	-0.050	-0.084	0.209			
Pain	0.004	0.001	0.992			
GDSscore	-0.277	-0.235	<0.001	-0.286	-0.243	<0.001
Social activities	0.409	0.072	0.284			

[a] dependant variable is delta PSQI = PSQIadjusted baseline minus PSQIadjusted 12 months, worsening sleep quality is indicated by a negative score

[b] R^2 of the model was 0.041

MMSE= Mini Mental State Examination, GDS= Geriatric Depression Scale, ADL= Activities of Daily Living,

DISCUSSION

During the one-year follow-up, the sleep quality of the BZD/Z users deteriorated significantly, while in nonusers there was also a deterioration of the sleep quality, but not significant. The rate at which this deterioration occurred did not differ significantly between BZD/Z users and nonusers, which could indicate a questionable clinical impact. However, the sleep quality in chronic BZD/Z users was significantly worse compared to nonusers both at baseline and at one-year follow-up.

In both groups the sleep quality deteriorated, which can be partly explained due to aging[20] or comorbidities[21]. The comorbidity 'depression' was in this study a significant factor in worsening sleep quality. Depression and sleep problems are often linked together[22, 23] (e.g. sleep problems are often included in depressive symptoms). In this study, depressive symptoms were also more prevalent in chronic BZD/Z users compared to nonusers. There is a complex relationship between sleep and depression that needs further investigation. Moreover, residents with BZD/Zs take more chronic medication, especially psychotropic medication. Polypharmacy and psychotropic drugs could influence sleep quality and its evolution. Although we did not find explicit factors besides depressive symptoms related to worsening sleep quality, other influences such as pain and other comorbidities cannot be ruled out.

Our study shows that chronic use of BZD/Z does not maintain or improve sleep quality. We now know that the sleep quality of chronic BZD/Z users is worse than nonusers and it does not improve (over 1 year). A study in community dwelling older adults also found a worse sleep quality in long-term BZD/Z users[10] and reported a negative impact on evolution compared to nonusers[12].

This was the first study especially designed to investigate sleep quality and its temporal evolution among a well-defined group of chronic BZD/Z users in the nursing home setting and

compare it to a well-defined control group (free of any hypnotic) using an adequate tool that reports several aspects of sleep quality. In order to reduce indication bias, we included residents who used BZD/Zs only at bedtime as a proxy for the indication insomnia. Nevertheless indication bias cannot be completely ruled out because we did not ask the GP for confirmation of this indication. Another strength was the inclusion of several risk factors such as functionality, social status, depressive symptoms and medication use. Several limitations are inherent to the study design. We used a convenience rather than a representative sample of nursing homes. However, the respondents' characteristics were comparable to the Belgian nursing home population (age-gender-chronic drug intake)[24]. Although there were no noticeable differences between residents lost-to follow up and residents in the study, selection bias cannot be excluded. Unfortunately, we had no information about specific sleep disorders, specific medications other than psychotropics or narcotics that could influence sleep quality, or 'past BZD/Z use' and duration of use. However, in most residents the BZD/Z is already present at nursing home admission and remains on the medication list for a long period of time [25-27]. Although the study adds to the knowledge that chronic continuation is not recommended in terms of sleep quality, we did not investigate incident users and baseline sleep parameters. Longitudinal studies with incident BZD/Z users followed over a longer period of time (i.e. more than 6 months) are lacking. In future research, it is recommended to monitor the evolution of sleep quality in incident users and to investigate the consequences of BZD/Z discontinuation on sleep.

CONCLUSION

Sleep quality in chronic BZD/Z users significantly decreased over one year and was significantly worse than nonusers at the end of this period. This study suggests that using BZD/Zs chronically does not maintain or improve sleep quality. Depressive symptoms are an important factor in the deterioration of sleep quality.

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CHAPTER 2.5

The impact of chronic benzodiazepine use on cognitive evolution in nursing home residents.

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ABSTRACT

Background & objectives: Chronic use of benzodiazepines and Z drugs (BZD/Zs) has been linked to cognitive decline. In this one year prospective cohort study, we aim to investigate the association between users of chronic BZD/Zs for insomnia, and cognitive evolution in comparison to nonusers.

Methods: Cognitively capable residents of 10 Belgian nursing homes were divided in BZD/Z users and nonusers, based on medication charts. We assessed cognition with the Mini Mental State Examination test (MMSE) at baseline and 12 months later. A decrease of ≥4 points on the MMSE (clinically relevant decrease) was used in multiple logistic regression. We collected baseline demographics, functional, psychometric and social characteristics potentially influencing cognition.

Results: We collected data of 131 BZD/Z users and 95 nonusers (in both groups: mean age 85 year, 77% female). In both groups the cognition decreased significantly over time, but without significant difference between the groups. Clinically relevant decrease was present in 34% BZD/Z users and 27% nonusers (NS). Controlled for age, gender, education and BZD/Z use, the strong, significant risk factors for clinically relevant cognitive decline were depression (OR 2.77, 95%CI 1.39-5.52), hearing (OR 3.83, 95%CI 1.45-10.13) and functional impairment (OR 1.18, 95%CI 1.10-1.27). Frequent reading was associated with less MMSE decrease (OR 0.46, 95%CI 0.23-0.91).

Conclusions: Our findings could not demonstrate with statistical significance that BZD/Z use was associated with fast cognitive decline. The strong risk factors for fast decline were depression, hearing and functional impairment, and the absence of a reading attitude. In addition, BZD/Z users had a higher prevalence of depression and depression influenced cognitive decline, which indicates a complex relationship between cognitive impairment, depression and BZD/Z use.

INTRODUCTION

Benzodiazepines and related Z-drugs (BZD/Zs) are indicated for the short-term treatment of sleep disorders (and benzodiazepines also for anxiety). However, these medications are often prescribed for longer periods, particularly in older adults. Because of the unproven long-term effectiveness [1], possibly caused by tolerance [2] and because of both physical and psychological dependence [3], international guidelines warn against chronic use [4, 5]. Nevertheless, the consumption of BZD/Zs among community dwelling older adults is high and even higher (range 20%-55%) among European nursing home residents [6-8]. It has been hypothesized that chronic use might have a detrimental effect on cognition and might cause acceleration of cognitive impairment [9, 10]. Still, the literature is inconclusive whether or not there is a negative impact of chronic BZD/Z use on cognitive decline [11-13]. Due to the abundant chronic use of BZD/Zs and the major impact of cognitive decline on society, this research domain remains important.

In a review of six large-scale (varying between n=242 and n=3309) epidemiological observational studies, conflicting results were found with regard to the association of chronic BZD/Z use and cognitive decline/onset of dementia [11]. A later nested-case control study suggested increased risk for dementia among long-term users of BZD/Zs [14]. The Caerphilly Prospective Study in Wales [15] provided long-term prospective evidence of an adverse effect of BZD/Zs on the development of dementia, but included only males. A recent prospective study [16] in community dwelling older adults found a significant increased risk of dementia in incident BZD/Zs users compared to nonusers. Mura et al. [17] found a poorer cognitive performance in chronic BZD/Z users, but no association with accelerated cognitive decline. Most of these studies had no differentiation between BZD/Z use for sleep problems or anxiety and most of the observational cohort studies were not specifically set up to investigate the use of chronic BZD/Z use on cognition.
Our study focuses on the evolution of cognition and on the benzodiazepines (BZDs) and Z drugs used for sleep problems in the nursing home setting.
The objectives of our study were to describe the one year evolution of cognition in a group of chronic BZD/Z users compared to a control group of nonusers, both cognitive capable at baseline, and to investigate whether chronic BZD/Z use was associated with a differential decrease in cognition. Furthermore, in addition to other possible risk factors, we aimed to explore the impact of BZD/Zs on a clinically relevant decrease in cognition.

METHODS

In this prospective cohort study in the Belgian nursing home setting, we assessed cognition in a group of chronic BZD/Z users (BZD/Z group) and compared this to a group of nonusers (control group) at baseline (December 2011 and January 2012) and at 12 months (January 2013).

Setting:

The Belgian long-term residential care structure consists of residential or nursing homes for older people, which offers a home replacement with or without nursing care. Governance of nursing homes for older people is either public (community health services) or private (predominantly non-profit) with little difference in quality of care. The point prevalence of dementia among residents is approximately 50% with considerable variation among nursing homes [18].

Design:

In a convenience sample of 10 Belgian nursing homes, all cognitively capable residents were screened for inclusion and divided in an exposure group of BZD/Z users and a control group based on the medication chart. No matching procedure was applied. Study design and baseline findings were published elsewhere[1]. Only residents with baseline and 12 month follow-up data were included in the analysis.

Inclusion and exclusion criteria:

At baseline, we only included cognitively capable residents defined as having a Mini Mental State Examination (MMSE)[19] score of at least 18 out of 30. We excluded residents who only used sedative antidepressants trazodone or mirtazapine or phytotherapy as a sleep medication. We also excluded residents who used BZDs for the indication of anxiety (daytime use of BZD). Residents with BZDs or Z drugs daily administered at bedtime for at least 3 months were allocated to the chronic BZD/Z group. Residents who were free of any hypnotic medication were allocated to the control group. This analysis was based on the initial group assignment.

Data collection:

Demographic data were obtained from the resident's record and medication data were obtained from the medication chart. Functional characteristics, as a proxy for functional independence, were scored by the nurse with the Katz scale [20]. The first part of this instrument scores six Activities of Daily Living scale (ADL) from 1 (independent) to 4 (totally dependent). The second part scores disorientation in time and place ranging from 1 (no disorientation) to 4 (severe) and was used to confirm cognitive competence.
Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI) [21, 22], a self-rated questionnaire for global sleep quality and specific aspects of sleep disturbance. The 7 components of the PSQI yield a total score ranging from 0 to 21, with higher scores indicating poorer sleep quality. A total PSQI score of more than 5 is a widely used cut-off that indicates poor sleep quality.
Medication data were obtained from the medication chart. We recorded the total number of chronic medications (used for more than 3 months). Medication was coded with the Anatomical Therapeutic and Chemical (ATC) classification [23]. We considered the classes N05BA (anxiolytic), N05CD (hypnotic) and N05CF (Z drugs) as benzodiazepines. The BZD 'clonazepam' and 'tetrazepam' were classified as sleep medication in this study, though they have a different ATC nomenclature. Based on half-life, we categorised the BZD/Zs into short-acting

(T1/2 < 24h) and long-acting (T1/2 ≥24h) [24].

Depressive feelings were scored with the 8-item Geriatric Depression Scale (GDS) [25]. The 30 item GDS [26] was designed for older adults. An abbreviated version of the GDS (8 item) was especially designed and validated for nursing home residents. A score of three or more on the GDS-8 is indicative for depression [25, 27]. Additionally, we recorded falls by checking the medical file. We also recorded other possible risk factors of cognitive decline such as hearing and visual impairment, frequent pain, and the frequency of social activities, social contacts (visitors in and out the nursing home) and mental stimuli (watching TV, reading, memory games) by using a yes or no question.

Cognitive evaluation:

The cognitive screening as well as the evolution was investigated with the MMSE test [19]. This widely used and validated instrument has a maximum score of 30. Five different domains of cognition are investigated: (1) Orientation, contributing a maximum of 10 points, (2) Memory, contributing a maximum of 6 points, (3) Attention and calculation, as a measure of working memory, contributing a maximum of 5 points, (4) Language, contributing a maximum of 8 points, and (5) Design copying, contributing a maximum of 1 point. Internal consistency of the MMSE was evaluated with Cronbach's alpha (and was in our study 0.70).

Ethical considerations:

This observational cohort study was approved by the ethics committee of the University Hospital of Antwerp (registration number B300201112211). Each nursing home received information and gave approval to screen the nursing home population. Each resident, included in our study, received oral and written information and gave consent.

Statistics:

The analysis and presentation of our results was focused on the residents still included at 12 months follow-up (n=226).
In a primary analysis, demographic, functional, psychometric and medication characteristics were described and compared between the BZD/Z group and the control group, using percentages and Chi^2 for categorical variables and means and independent t-tests for continuous variables except for scaling results where we used nonparametric statistics.
Cognitive evolution was presented with mean MMSE scores and standard deviations (SD) and analysed with Wilcoxon Signed Rank test. Differences in MMSE scores between both groups were analysed with Mann Whitney U test.
Clinically relevant decrease in cognition was defined as a MMSE decrease of 4 or more points [28-31]. We analysed which factors were associated with this MMSE decrease and particularly whether chronic BZD/Z use, controlled for other variables, had an influence on it. Multiple logistic regression was used to indicate the determinants of this decrease.

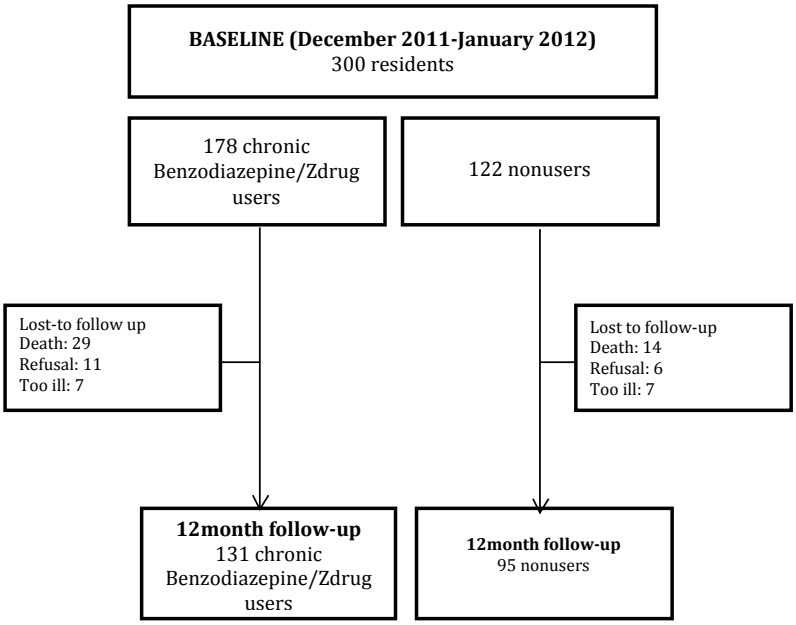
RESULTS

Study flow:

At baseline, 300 residents met the inclusion criteria; 178 in the BZD/Z group and 122 in the control group. As illustrated by the flowchart (Fig. 1), we had 12 month follow-up data of 226 residents; 131 in the BZD/Z group and 95 in the control group. We observed no difference in characteristics between residents lost-to-follow (n=74) and residents still in the

study (n=226), only the baseline MMSE score was 1 point lower in the residents lost-to-follow (25.8 vs. 24.9, p=0.015). Mortality was an important cause of lost-to-follow-up in both groups (16.3% in the BZD/Z group and 11.5% in the control group, p=0.253).
At 12 months follow-up, we observed retrospectively that 10 residents in the control group initiated a BZD/Z and 9 BZD/Z users had stopped. We analysed the 226 residents based on the initial group assignment.

Fig 1: Flowchart



Comparison of demographic and clinical characteristics in the BZD/Z and control group:

As shown in Table 1, the baseline demographic profile of the BZD/Z users and the nonusers was similar: the mean age was 85 year, 77% was female and 60% attended school till the age of 14.
Clinical characteristics such as the ADL score, disorientation score, the prevalence of hearing and sight impairment were similar in both the BZD/Z group and the control group. Falls during the last year (41% vs. 34%) and the prevalence of reported pain (47% vs. 42%) did not differ significantly (Table 1).
The amount of bad sleepers was 46% in the BZD/Z group and significantly larger than the 28% in the control group (p=0.006). The presence of depressive symptoms differed significantly between the BZD/Z group and control group (43% vs. 27% p=0.014). The combined presence of depression and sleep problems was predominantly present in the BZD/Z group (29% vs. 8% p<0.001).
Regularly attending social activities, as well as frequent reading, watching TV and social contacts was similar in both groups. The BZD/Z group did less memory games compared to the control group (31% vs.45% p=0.032).
The BZD/Z group took significantly more chronic medications compared to the control group (mean of 9.1 vs. mean of 7.5) in particular pain medication (41% vs. 17%) including narcotic (22% vs. 6%) as well as non-narcotic analgesics (23% vs. 9%). In the BZD/Z group, 52% of the residents with pain medication reported pain. In the control group, this was 56% of the

residents.

In the BZD/Z group (n=131), lormetazepam (34%), zolpidem (26%) and lorazepam (23%) were the most frequently used. Short-acting BZD/Z were used in 90% (n=118) and long-acting in 14% (n=18), with some overlap due to duplicate use.

The residents that switched medication during the one-year follow-up (n=19) were similar on al demographical and clinical characteristics. They did not differ in MMSE score at baseline (25.8 vs. 25.6, p=0.825).

Table 1. Demographic, Clinical, Psychometric characteristics and Medication information of the benzodiazepine group (BZD/Z) and the control group.

	BZD/Z group N=131	**CONTROL group N=95**	**p value[d]**
Demographic characteristic[a]			
age (mean-range)	85.3 (57-99)	85.0 (65-99)	0.763
gender (%female)	75.6	78.9	0.552
length of stay in months (mean-range)	40.4 (3-191)	41.1 (3-223)	0.901
education level- higher education(%)	36.6	43.2	0.322
Clinical characteristics[b]			
self-dependency score (ADL) (6-24)	12.82	12.38	0.418
disorientation score (2-6)	2.81	2.86	0.935
MMSE score (0-30)	23.9	24.2	0.301
visual problems (%)	9.2	9.5	0.936
hearing problems (%)	9.9	13.7	0.382
falls during 1 year (%)	41.2	33.7	0.249
Psychometric characteristics[b]			
frequent pain (%)	47.3	42.1	0.436
depressive symptoms (GDS≥ 3) (%)	43.3	27.2	0.014
adjusted PSQI score (0-19)	5.79	4.74	0.004
bad sleeper (adjusted PSQI>5) (%)	45.8	27.7	0.006
frequent social activities (%)	48.6	43.6	0.440
frequent social contact[c] (%)	86.3	87.4	0.880
mental stimuli: reading (%)	61.8	66.3	0.489
mental stimuli: memory games (%)	31.3	45.3	0.032
mental stimuli: watching TV (%)	92.4	88.4	0.313
Medication Information[b]			
chronic medications (mean-range)	9.08	7.48	0.002
benzodiazepine/Zdrug (%)	93.1	10.5	<0.001
antidepressant (%)	42.7	30.5	0.061
antipsychotic (%)	18.3	9.5	0.063
anti-Alzheimer (%)	2.3	5.3	0.232
anti-Parkinson (%)	6.1	7.4	0.707
pain medication (%)	41.2	16.8	<0.001
narcotic analgesic (%)	22.1	6.3	0.001
non-narcotic analgesic(%)	22.9	8.4	0.004
NSAIDs(%)	4.6	4.2	0.894

[a] baseline , [b] we report the 1 year results of these parameters

[c] frequent social contacts defined as frequent visitors

[d] pvalue: continuous variables with independent t test, percentages with Chi^2 and Mann Whitney U for scales

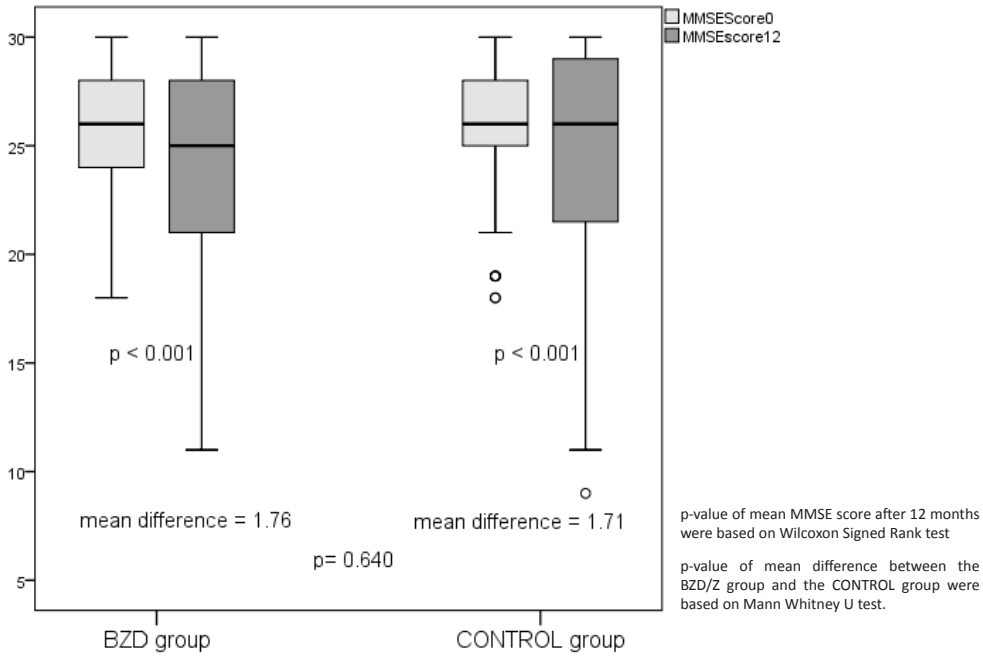
MMSE= Mini Mental State Examination, GDS= Geriatric Depression Scale, ADL= Activities of Daily Living,

PSQI= Pittsburgh Sleep Quality Index, NSAID= non-steroidal anti-inflammatory drugs

Comparison of evolution of cognition over 12 months:

In the BZD/Z group the total MMSE decreased from 25.7 (SD 3.0) to 23.9 (SD 4.5), and in the control group the total MMSE decreased from 25.9 (SD 2.9) to 24.2 (SD 5.2). The baseline scores did not differ in both groups as well as the mean differences (Fig. 2), respectively 1.76 (SD 3.9) in the BZD/Z group and 1.71 (SD 3.9) in the control (p=0.640).

Fig 2: EVOLUTION OF COGNITION (as measured by the MMSE)



p-value of mean MMSE score after 12 months were based on Wilcoxon Signed Rank test

p-value of mean difference between the BZD/Z group and the CONTROL group were based on Mann Whitney U test.

A closer analysis of the different elements of the MMSE showed that in both groups 'orientation (spatial and temporal)', 'memory', 'attention' and 'language' significantly decreased, while 'constructional praxis' increased over 12 months. In the BZD group, we observed a trend showing that MMSE scores on 'orientation', 'memory', and 'language' decreased more in 12 months compared to the control group (NS).
In the BZD/Z group, 33.6% of the residents decreased 4 or more points (clinically relevant) on the MMSE test compared to 27.4% in the control group (p=0.318).

Risk factors of a clinically relevant MMSE decrease:

With this analysis on the total 226 residents, we wanted to investigate the risk factors for clinically relevant MMSE decrease and whether chronic BZD/Z use was a risk factor controlled for other related factors.
Univariate analysis (Table 2) of variables influencing a MMSE decrease of 4 or more points showed that age, functionality (ADL score), depression (GDS score), hearing problems, and antidepressant use were associated with a decrease in the MMSE score. A higher educational level, social activities, memory games and frequent reading were associated with a reduced risk of MMSE decrease.

Multivariate analysis (Table 2) controlled for age, gender and educational level failed to show an impact of chronic BZD/Z use (OR 1.29, 95% CI 0.64-2.58) on MMSE decrease. Hearing impairment (OR 3.83, 95%CI 1.45-10.13), depression (OR 2.77, 95%CI 1.39-5.52) and a higher functional dependency (ADL score) (OR 1.18, 95%CI 1.10-1.27) were significantly associated with MMSE decrease. There was a reduced risk of MMSE decrease when the resident read frequently (OR 0.46, 95%CI 0.23-0.91). The variance explained by the model was 31% (Nagelkerke R^2=0.312).

Table 2. Factors associated with clinically relevant decrease: univariate and multivariate analysis.

	MMSE decrease ≥4 points					
	yes	**no**	**UNIVARIATE**		**MULTIVARIATE[b]**	
	n= 70	**n= 156**	**OR[a]**	**95%CI**	**ORa**	**95%CI**
Benzodiazepine/ Z-drug use	62.9%	55.8%	1.34	0.75-2.39	1.29	0.64-2.58
Age (mean-range)	86.8	84.4	1.05	1.00-1.096	1.03	0.98-1.08
Gender %female	80.0%	75.6%	1.29	0.65-2.57	1.58	0.66-3.77
Education longer than the age of 14	28.6%	44.2%	0.50	0.28-0.93	0.73	0.48-1.21
Hearing impairment	18.6%	8.3%	2.51	1.1-5.74	3.83	1.45-10.13
Sight impairment	14.3%	7.1%	2.20	0.89-5.45		
Falls in the last 12 months	40.0%	37.2%	1.13	0.6-2.01		
Activities of Daily Living (ADL) (mean)	15.1	11.5	1.17	1.10-1.25	1.18	1.10-1.27
Depressive symptoms (% GDS≥3)	53.0%	29.4%	2.71	1.49-4.92	2.77	1.39-5.52
Bad sleeper (% PSQadj >5)	40.6%	37.2%	1.15	0.65-2.06		
adjusted PSQI score (mean)	5.57	5.26	1.03	0.94-1.13		
Frequent reading	51.4%	69.2%	0.47	0.26-0.84	0.46	0.23-0.91
Frequent social activities	34.8%	51.9%	0.49	0.27-0.89		
Frequent mind games	21.4%	44.2%	0.34	0.18-0.66		
Frequent social contacts	84.3%	87.8%	0.74	0.33-1.66		
Number of chronic medications (mean)	8.5	8.4	1.01	0.93-1.08		
Antidepressant use	48.6%	32.7%	1.94	1.09-3.46		
Pain medication	38.6%	27.6%	1.65	0.91-2.99		

[a] Odds Ratio: risk of a decrease of 4 or more points on the Mini Mental State Examination

[b] Multiple logistic regression, R^2 of this model = 0.312

DISCUSSION

Main findings:

In this prospective observational controlled study we found that the general cognition of nursing home residents (as measured by the MMSE) decreased significantly in 12 months, both in the group of BZD/Z users and in the nonusers, but there was no significant difference in mean MMSE decrease between those two groups. When focusing on clinically relevant cognitive decrease, there were more residents in the BZD group with severe deterioration (MMSE decrease of 4 or more points), but this difference was not significant (34% vs. 27%). We found the following risk factors of accelerated cognitive decline: depressive feelings, hearing impairment and functional impairment. Additionally, we found that frequent reading was significantly associated with less cognitive decline.

Strenghts and limitations:

Discovering risk factors of cognitive decline is an important research topic. In this regard, the use of BZDs has been subject of numerous studies [11-13], but not always in a prospective research design and with inconsistent findings.

The first strength of this study lies in its sampling; a well-defined group of chronic (more than 3 months) BZD and Z-drug users as sleep medication and a group of nonusers, free of any hypnotic, followed prospectively for one year. In order to reduce indication bias, our results focus on BZD/Z use for sleep problems.

The second strength was the inclusion of a wide range of possible risk factors (associated in the literature with cognitive decline) such as depressive symptoms [32, 33], sleep problems [34], functionality [35], social status [36], pain [37] and medication [38].

The third strength was our stringent definition of cognitive decline. Small changes in MMSE should be interpreted with care due to measurement error, learning effects and regression to the mean. We did not focus on mean change, but enhanced clinical relevance by using a cut-off. Comparable to other studies, we defined clinically relevant decrease as a 12 month decrease of 4 points or more on the MMSE[28, 31, 39].

However, an important limitation, not only in our study but in many other studies trying to investigate cognition in older adults, was the use of the MMSE. The MMSE has been criticised for being insufficiently sensitive for cognitively capable older adults and for not taking enough into account patients' characteristics such as visual and hearing impairment and level of education. We tackled this by including all these covariates in our multivariate analysis and using a cut-off. Unfortunately, we did not have sufficient medical information to analyse the impact of comorbidity. We focused on psychotropic medication and the total number of medication, as a proxy for co-morbidity. We acknowledge the existence of other medication classes (for example anticholinergic drugs [40, 41]) as a possible risk factor for cognitive decline. In order to reduce indication bias, we included residents who used BZD/Zs only at bedtime as a proxy for the indication insomnia. Nevertheless indication bias cannot be completely ruled out because we did not ask the GP for confirmation of this indication. We had no information on 'past BZD/Z use' and length of use. But in most residents the BZD/Z is fixed on the medication list for a long period of time [42, 43]. We did not omit the residents that stopped or started a BZD/Z and we performed an intention-to-treat analysis on this cohort. We acknowledge the possible bias. However, there were no differences on baseline characteristics between those 19 residents and the cohort. Since the effects on cognition are subtle, larger studies with more than 226 residents are necessary. In this study, the residents for whom we had no 12 month follow-up data (due to refusal, illness or death), had a one point lower baseline MMSE score (survivorship bias). In addition, the BZD/Z users had a non-significantly higher mortality.

Comparison of demographic and clinical characteristics in the BZD/Z and control group:

The BZD/Z group and control group were similar in all demographic and most clinical characteristics. The risk of falling is a major concern in older adults, and in several studies associated with psychotropic medication use, in particular with BZD/Z use [44]. However, in our study we did not find a significant impact of BZD/Z use on fall risk..
We observed differences in medication use and psychometric properties. The BZD/Z group used more chronic medications, especially more analgesics, though they did not indicate to have pain more frequently.
Similarly to our baseline findings in a former article on sleep quality in this cohort [45], we also found at 12 months a worse sleep quality in chronic BZD/Z users compared to nonusers. This finding does not support effectiveness of chronic hypnotic use [46].
Depression was more prevalent in the group of chronic BZD/Z users compared to the nonusers [12]. A possible hypothesis might be that the high prevalence of depressive symptoms, sleep problems and the higher intake of medication among BZD/Z users are related to a greater tendency of these users to feel and to express complaints and to a prompt pharmaco-therapeutic response from the prescriber. Furthermore, depression and sleep problems are often linked together[47]: diagnostic instruments for depression (Hamilton depression rating scale [48], "DSM IV criteria") include sleep difficulties, which makes it difficult to differentiate between pure insomnia symptoms and depressive symptoms. Initiating a BZD/Z which often evolves into chronic use does not resolve the depressive symptoms. Instead, non-pharmacological treatment and appropriate antidepressants for major depression are advised [49].

Comparison of evolution of cognition over 12 months:

When focusing on the evolution of cognition, we found that in cognitively capable nursing home residents, the cognition declined significantly in 12 months' time as well in the BZD/Z group as in the control group. When looking at clinically relevant cognitive deterioration (MMSE decrease of 4 or more points), one third of our sample had a fast decline. After 12 months the mean decline did not differ between BZD/Z group and control group.
A closer analysis of the MMSE components revealed that all components decreased, except the 'constructional praxis'. In this component the resident was asked to copy a complex figure. It is possible that recognition occurs for this aspect [31, 50].

Risk factors of a clinically relevant MMSE decrease:

Due to methodological limitations in the research on cognitive deterioration, it is not possible to determine causality. Is it because of the risk factors that older adults develop cognitive impairment or is it because of the cognitive impairment that they behave and feel differently? This analysis only reveals associations.
Residents with social activities, residents who read frequently and play memory games had a lower risk of a fast cognitive deterioration. In multivariate analysis these factors were lost, except for frequent reading. This suggests the importance of stimulating and training the mind [36, 51]. A low ADL score was associated with cognitive decline [35]. An important finding, similar to another observational study in older adults [52], was the impact of hearing impairment on cognitive decline. Possible hypotheses are: the social deprivation associated with hearing loss, or a shared neuropathological origin of hearing loss and cognitive decline [52].
In some studies [34, 53] insomnia and sleep problems were associated with cognitive impairment. Our study was especially designed to measure cognitive evolution and sleep quality. We used the validated PSQI to measure sleep parameters and difficulties, but we found no association with cognitive decline.
Furthermore, we found that residents with depression had 2.8 higher risk of a rapid MMSE

decline. This association was also observed in other studies [12, 54, 55], but the mechanisms behind the association have not been elucidated [55, 56]. Is depression an early-phase symptom of cognitive impairment, is it a risk factor, or is it a reaction on cognitive decline. As mentioned above, depression was in our study more common in BZD/Z users and was also linked with bad sleep among the BZD/Z users. The complex relationships between cognitive impairment and depression and BZD/Z use need to be further investigated. Meanwhile, current guidelines advocating prudent use of BZD/Zs in older adults prevail.

Implications for research:

Our findings could not demonstrate with statistical significance that BZD/Z use was associated with fast cognitive decline. In concordance with other research on the association of BZD/Z and cognition, we conclude that the expected effects of chronic BZD/Z use on cognitive decline were subtle. Therefore large observational studies and more sensitive instruments are necessary. Moreover, there is a complex relationship between BZD use and depression, and depression and cognitive decline, which needs to be further investigated. In future research, we need adequately funded larger prospective cohort studies, together with a full collection of data on medication use and (psychometric) comorbidities.

Implication for practice:

Because of the extensive BZD/Z use in the older nursing home population, and the possible detrimental effect on cognitive evolution, the current advice to limit chronic BZD/Z use prevails.

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RESULTS: The impact of chronic benzodiazepine use on cognitive evolution in nursing home residents.

CHAPTER 2.6

Barriers to discontinuation of chronic benzodiazepine use in nursing home residents: perceptions of general practitioners and nurses

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ABSTRACT

Background & objectives: Prescription guidelines caution against chronic benzodiazepine and Z-drug (BZD/Z) use. Nevertheless, chronic use among older adults, especially in nursing homes is widespread. We wanted to explore why it is difficult to implement discontinuation. We focused on individual residents that used BZD/Zs and explored benefit and harm of chronic BZD/Z use, willingness to try and barriers against the discontinuation of chronic BZD/Z use.

Methods: In this cross-sectional study, we selected nursing home residents with at least 3 months of BZD/Z use. A resident-specific questionnaire was addressed to the GP and to the responsible nurse and questioned effectiveness, side effects, initiation and willingness to stop. For every resident, the GP and nurse had to score 8 barrier statements on a 10 point Likert scale. Additionally, we collected 10 general attitudes scored by GPs and nurses.

Results: We received data for 109 chronic BZD/Z users. GPs and nurses indicated that the BZD/Z still had the desired effect in respectively 87% and 83% of the 109 residents and in 75% and 70% they observed no side-effect. Dependence was seen in respectively 41% and 28%. Overall, the GPs had higher barriers than the nurses but indicated a higher willingness to stop (33% vs. 21%). Both caregivers were willing to stop in 13% of the residents.

Conclusion: The perceived effectiveness, the absence of side-effects and the presence of dependence in most residents on chronic BZD/Z use resulted in a low willingness to stop. Future discontinuation guidelines should consider all caregivers' perceptions and promote a multidisciplinary approach.

INTRODUCTION

Benzodiazepines (BZDs) are indicated for the short-term treatment of insomnia and anxiety. They are the most commonly prescribed psychotropic drugs, especially among the nursing home population [1, 2]. In most patients, their use becomes chronic. In Belgium, half of the nursing home population takes BZD/Zs (including Z-drugs) chronically [3]. Prescribing guidelines caution prescribers and patients against this chronic use [4-8]. Several research units launched a protocol to tackle chronic BZD/Z prescribing and to investigate discontinuation [9-12]. Two studies reported success rates of 57% and 59%, respectively 2 and 10 years after discontinuation [13, 14]. Nevertheless, chronic BZD/Z use outside the research context remains high. Possible reasons for this discrepancy are the perceived dependence of BZD/Zs [15] and the risk of withdrawal effects with temporary worsening of insomnia and anxiety [16, 17]. Moreover, the perception among prescribers and patients of BZD/Zs as harmless drugs [18] hinder discontinuation efforts.

Long-term BZD/Z use is of particular concern because of the lack of proven continuous effectiveness [19] because of adverse effects such as sedation and hang-over effects [20], because of the risk of dependence, and because of potential acceleration of cognitive impairment [21]. Withdrawal attempts are recommended for long-term users. In the nursing home setting, both prescribers and nurses are important in the initiation and the discontinuation of BZD/Zs. Therefore, it is crucial to understand the perceptions of prescribing general practitioners and nurses towards BZD/Zs before engaging in efforts to obtain sustained change in chronic BZD/Z use.

Qualitative studies have investigated the general perceptions of BZD/Z use among patients [22], among physicians [23-25] and among nurses [26]. There are some quantitative studies [27-29], but these did not focus on possible discontinuation in an individual resident. The objective of this study was to investigate initiation, indications, previous stop attempts and perceived benefit and harm of BZD/Zs as well as the willingness to stop chronic BZD/Z use in individual nursing home residents. By focussing on perceptions pertaining to an individual resident, we hope to obtain a more realistic view on the feasibility to discontinue chronic BZD/Z use. We wanted to capture resident-specific barriers and also general attitudes towards discontinuation of chronic BZD/Z use among the two key care givers in the nursing home setting (the general practitioner and the nurse).

METHODS

This was a cross-sectional study based on a resident-specific questionnaire addressed to the general practitioner (GP) and to the nurse.

Development of the questionnaire:

As we did not find examples in literature specific to the nursing home setting, we developed a questionnaire based on an expert meeting. The expert meeting included different representatives of geriatric care (GPs, nurses, nurse assistants, pharmacists and clinical pharmacologists) and focussed on the discontinuation of BZD/Z use. Based on what was discussed in the expert meeting, we developed a questionnaire intended for GPs and nurses and designed to be filled in for each individual resident in order to avoid global impressions. The questionnaire was developed with the expertise of an epidemiological researcher, GP, pharmacist and nurse. The preliminary version of the questionnaire was pretested among GPs and nurses for 5 residents.
As shown in Table 2, the resident-specific questionnaire examined indications (insomnia, anxiety, depression, agitation), where and when the BZD/Z was initiated (before entering the nursing home, in the nursing home, during hospital admission, unknown), whether the BZD/Z still showed benefit, whether there were any side-effects (listed by the Belgian farmacotherapeutic information centre[30]: sedation during the day, confusion, muscle weakness, concentration problems, apathy, memory problems, dizziness, physical and psychological dependence) or previous stop-attempts and the willingness to stop chronic BZD/Z use in each individual resident. Furthermore, we wanted to identify possible barriers against discontinuation. We formulated eight resident-specific barriers to be scored on a 10 point Likert scale, with a higher score indicating agreement with the barrier statement.
Additionally, we collected ten general attitudes (not resident specific) towards BZD/Z discontinuation of the GPs and nurses. These were also scored on a 10 point Likert scale.

Inclusion of nursing home residents:

In a convenience sample of five nursing homes in the region of Antwerp, Belgium, we screened medication charts and included those residents that used BZD/Zs daily for at least three months (chronic). The Anatomical Therapeutic and Chemical Classification (WHO 2012) was used to define BZD/Z use including the classes N05BA (anxiolytics), N05CD (hypnotics), N05CF (Z-drugs) and clonazepam (N03AE01). Tetrazepam (M03BX07) was included in our analysis but is withdrawn from the Belgian market since September 2013.

Data collection:

After selecting the residents with chronic BZD/Z use, the questionnaires were delivered to the medical coordinator of the nursing home, who handed them over to the head nurse and to the GP responsible for the specific resident. In Belgian nursing homes, residents are supervised by their own GP, with an average of 32 GPs per nursing home (Elseviers et al 2010). Data collection was performed between November 2011 and March 2012. Data collection included demographic and functional information of the resident. Functional characteristics were scored by the KATZ scale [31]. This instrument is mandatory in the Belgian nursing homes. The first part of this instrument scores six activities of daily living (ADL) from 1 (independent) to 4 (total dependent) and the sum score can range from min. 6 to max. 24. The second part scores disorientation in time and place, each ranging from 1 (no disorientation) to 4 (severe disorientation) and was used as a proxy to estimate the cognitive competence. A disorienta-

tion sum score of more than 4 was considered as impaired cognitive competence.

Statistical analysis:

All statistical analyses were performed using the statistical package IBM SPSS statistics version 20 with $p<0.05$ as the level of significance. Level of agreement between GP and nurse was assessed using kappa coefficients and descriptive percentages of positive agreement. The barrier statements as well as the general attitudes, both scored on a 10 point Likert scale, were described using medians and ranges. Differences between GP and nurse were assessed using non-parametric statistics: the barrier statements with Wilcoxon Signed Rank test for paired observations and the general attitudes with Mann Whitney U test. The internal consistency (cronbach's alfa) of the general barriers was 0.80 for the GPs and 0.76 for the nurses, and of the resident-specific barriers, this was 0.76 and 0.83, respectively.

Ethical consideration:

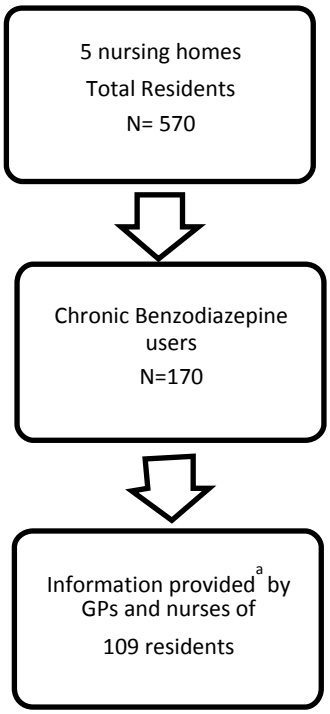
This study was approved by the Ethics committee of the University Hospital Antwerp (approval number B300201112279). The participating nursing home management, nurses and GPs all gave approval. All information of the resident was coded. We communicated with the GPs and nurses through the coordinating physician of the nursing home.

RESULTS

Study population:

In the five participating nursing homes (total of 570 beds), 170 (30%) residents took BZD/Zs chronically. In this study, we only included those residents for whom we received completed questionnaires from both the GP and the nurse. We received completed questionnaires for 109 residents (response rate of 64%); 25 GPs and 16 nurses filled in the questionnaires (Fig. 1).

Fig 1: FLOWCHART



[a] 16/16 nurses responded for 170/170 residents (100% response rate)
25/51 GPs responded for 109/170 residents (64% response rate)

Of the 109 residents, the mean age was 86 years (range 60-100) and 81% was female. The mean time spent in the nursing home was 40 months. The mean activities of daily living score was 15, with mainly problems with washing and clothing. Around one third (30%) of this population was considered to have dementia (Table 1).
The most prescribed BZD/Z was zolpidem (28%), followed by lorazepam (27%) and lormetazepam (20%). Concomitant BZD/Z use was seen in 8% of the residents (Table 1).

Table 1. Characteristics of chronic benzodiazepine users in Belgian nursing homes

CHARACTERISTICS of Chronic BZD/Z users	**n= 109**
Demographic	
Age (years-range)	85.9 (60-100)
Gender (% female)	80.7%
ADL score (mean-SD)	15.4 (5.5)
Dementia (% disorientation)	30.3%
Institutional	
Stay in months (median-range)	40.3 (1-186)
Medication Information	
duplicate BZD/Z use	8.3%
substance name (ATC code)*	
zolpidem (N05CF02)	28.4%
lorazepam (N05BA06)	26.6%
lormetazepam (N05CD06)	20.2%
tetrazepam (N03BX07)	7.3%
prazepam (N05BA11)	6.4%
bromazepam (N05BA08)	6.4%
alprazolam (N05BA12)	5.5%
clonazepam (N03AE01)	1.8%
zopiclone (N05CF01)	1.8%

BZD/Z= benzodiazepine or Z-drug use

ATC= Anatomical Therapeutic Chemical classification

*percentages exceed 100% due to double use; Additionally to this list: clorazepate, cloxazolam, flurazepam, flunitrazepam, brotizolam were all used by 1 resident

Initiation, indication and previous attempts to stop chronic benzodiazepine use:

GPs and nurses did not know where the BZD/Z was initiated in respectively 15% and 26% of the residents. According to the GPs, 62% of the chronic BZD/Z users started before entering the nursing home, 22% in the nursing home itself and less than 1% in the hospital. According to the nurses, 46% of the residents started BZD/Z use before entering the nursing home, 27% in the nursing home itself and only 2% in the hospital (Table2).
GPs and nurses could not estimate the duration of BZD/Z use in respectively 65% and 62% of the residents. In the other residents, the GPs estimated an average duration of 66 months (SD 82, n=38) and the nurses estimated 29 months (SD40, n=42).
The most common indication for chronic BZD/Z use was insomnia (69% and 68%). Other indications are shown in table 2. The GPs and the nurses indicated that they already attempted a withdrawal in the past in respectively 26% and 12% of the residents (Table 2).

Benefit and harm of benzodiazepine use:

GPs and nurses indicated that the BZD/Z still had the desired effect in respectively 87% and 83% of the chronic BZD/Z users (Table 2).
GPs and nurses noted dependence (psychological or physical) in respectively 41% and 28% of the residents. Apart from dependence problems, no other side-effects were observed by the GPs and the nurses in respectively 75% and in 70% of the residents. Daytime sleepiness was noted by the GP and nurse in respectively 17% and in 22% of the residents.

Willingness to stop chronic benzodiazepine use:

GPs indicated that in 33% of the residents they were willing to stop chronic BZD/Z use. We did not find a difference in willingness to stop when there was a previous stop attempt. Nurses considered a stop possible in 21% of the chronic BZD/Z users. Only in 13% of the residents, the GP and the nurse were both willing to stop (Table 2).

Table 2. Initiation, indications, previous stop attempts, side effects, perceived effectiveness and willingness to stop in 109 chronic BZD/Z users as indicated by the GPs and nurses.

INITIATION of BZD/Z in 109 residents as indicated by				
	GPs	**Nurses**		
WHERE?				
before entering nursing home	62.4%	45.7%		
in nursing home	22.0%	26.7%		
during hospital admission	0.9%	1.9%		
unknown	14.7%	25.7%		
HOW LONG?				
median number of months (range)	66.4 (3-240)	28.7 (3-240)		
unknown	65.1%	61.5%		
INDICATIONS[a] of BZD/Zs in 109 residents as indicated by				
	GPs	**Nurses**	**agreement[b]**	**kappa[c]**
insomnia	69.4%	67.6%	56.5%	0.442
anxiety	28.4%	15.7%	9.3%	0.268
acute agitation	11.0%	21.3%	8.3%	0.431
muscle relaxation	5.5%	6.5%	4.6%	0.775
depression	7.3%	9.3%	4.6%	0.516
unknown	4.6%	13.0%	2.8%	0.266
other	8.3%	2.8%	0.9%	0.130
STOP ATTEMPTS in 109 residents as indicated by				
	GPs	**Nurses**	**agreement[b]**	**kappa[c]**
previous stop attempts	25.8%	11.8%	6.5%	0.216
PERCEPTION of BENEFIT of BZD/Zs in 109 residents as observed by				
	GPs	**Nurses**	**agreement[b]**	**kappa[c]**
BZD still has desired effect	87.0%	82.7%	74.8%	0.262
PERCEPTION of HARM[a] of BZD/Zs in 109 residents as observed by				
	GPs	**Nurses**	**agreement[b]**	**kappa[c]**
no side effects	40.4%	44.9%	28.3%	0.386
psychological dependence	38.9%	23.4%	18.9%	0.462
physical dependence	21.3%	16.8%	11.3%	0.510
daytime sleepiness	17.0%	22.6%	7.5%	0.232
memory problems	8.5%	0.9%	0.9%	0.186
muscle weakness	4.6%	4.6%	1.9%	0.370
dizziness	2.8%	1.9%	0.9%	0.386
WILLINGNESS to STOP BZD/Z use in 109 residents as indicated by				
	GPs	**Nurses**	**agreement[b]**	**kappa[c]**
willingness to stop	33.3%	21.2%	13.1%	0.300

[a] sum of percentages exceeds 100% due to multiple indications or side effects

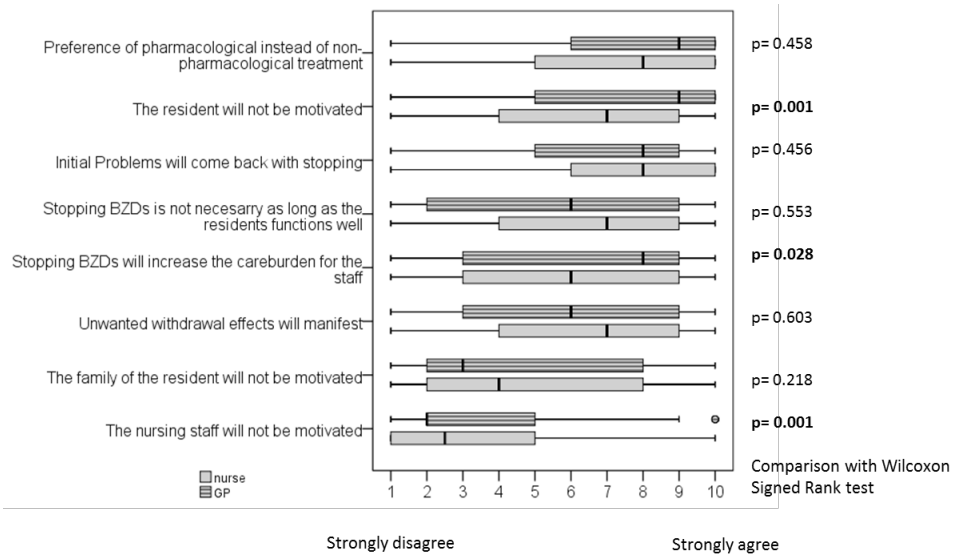
[b] percentage of positive agreement between the GP and the nurse

[c] *kappa= (observed agreement-the probability of random agreement) / (1-the probability of random agreement)*

Resident-specific barriers against discontinuation:

Of all eight resident-specific barriers (Fig. 2), most common among the GPs were the fear of resistance from the resident (median 9 on 10 point Likert scale), the preference of a pharmacological treatment above a non-pharmacological treatment (median 9), the fear that in this resident initial problems will come back (median 9), the fear of an increase of the care burden for the staff (median 8), the perception that change is not necessary as long as the resident functions well (median 8) and the fear of withdrawal effects (median 7).
Among the nurses, the most common barrier was the fear that in this resident initial problems will come back (median 8), the preference of a pharmacological treatment (median 8) and the conviction that change is not necessary as long as the resident functions well (median 7).
Among both caregivers, resistance of family or care staff was presumed to be low (Fig. 2).
The GPs perceived the resident's motivation as a larger barrier than the nurses (median 9 vs. 7, p = 0.001). The GPs, more than the nurses, indicated that discontinuation of BZD/Zs can lead to an increase in care burden (median 8 vs. 6, p = 0.028).

Fig 2: boxplots of barrier statements of 109 residents compared between GP and nurse.

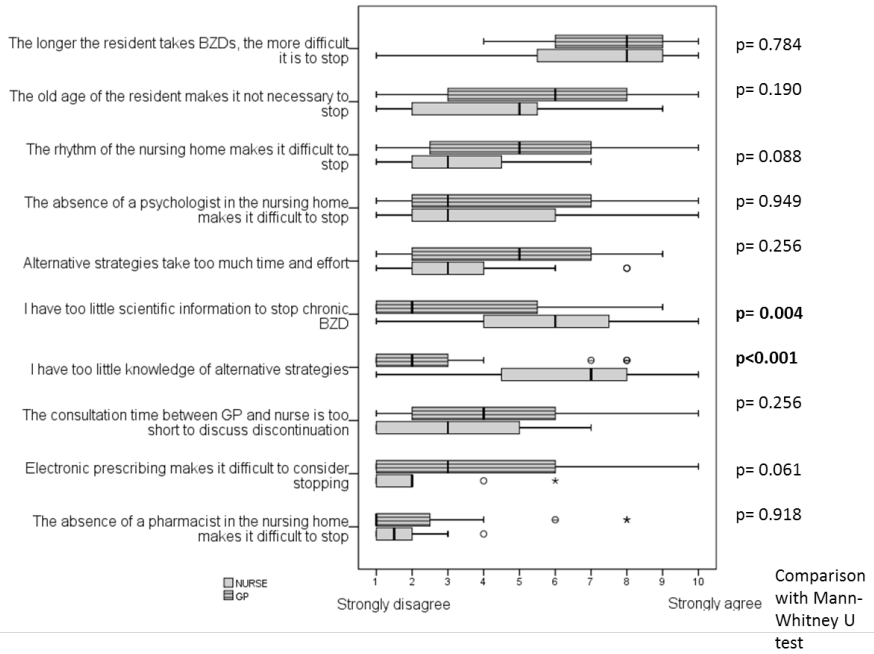


General attitudes of GPs and nurses towards stopping chronic benzodiazepine use:

Of all ten general statements (Fig. 3), the most common attitude among both GPs and nurses was that the longer the resident takes the medication, the more difficult it is to stop (median 8). GPs and nurses agreed on the statement that old age of a resident makes it difficult and unnecessary to stop (median 6 vs.5, NS). According to both GPs and nurses, the help of other care professions such as a psychologist (median 3) and a pharmacist (median 1 vs. 2, NS) was not really perceived to be necessary. Electronic prescribing was not perceived to be a barrier (median 3 vs. 2, NS).
The GPs and nurses perceived that alternative strategies are more time consuming (median 5 vs.3, NS) and that the rhythm of a nursing home with strict bedtimes also limits possibilities for discontinuation (median 5 vs. 3, NS). Nurses agreed and GPs disagreed on the statements that there is little knowledge on alternative strategies to cope with problems when stopping

BZDs (median 7 vs. 2, p< 0.001) and that there is little scientific information available for stopping (medians 6 vs. 2, p =0.004).

Fig. 3: Boxplot of general attitudes of GP and nurses towards stopping chronic BZD use



DISCUSSION

This study on perceptions of benefit and harm, the willingness to stop and perceptions towards barriers against discontinuation of BZD/Zs in the nursing home setting elucidates reasons why the discontinuation of chronic BZD/Z use is difficult.
We found that both GPs and nurses perceived that the BZD/Z still had the desired effect in respectively 87% and 83%; and that except for dependence, there were no observed side-effects in 75% and 70% of the residents. The GPs were willing to stop this chronic use in one out of three residents and the nurses in one out of five. Surprisingly, in only 13% of the residents they were both willing to stop. Overall, there was a low agreement between GP and nurse.

Strenghts and limitations:

The major strength of our study design is that we focused on perceptions pertaining to an individual resident. Therefore, we had a more realistic representation of the possibility to discontinue chronic BZD/Z use. Other studies on the perceptions of GPs and nurses towards BZD use [24-26] were often qualitative and did not focus on discontinuation. Our response rate of 64% was quite high. All nurses participated and non-response was exclusively caused by 26 GPs who did not return their questionnaires. This discrepancy can be explained because the medical coordinator gave questionnaires directly to the responsible nurse, whereas the GPs received it through mail. Although this was a convenience sample, demographics and functionality (ADL) were comparable with a representative sample of Belgian nursing homes residents in 2006[32]. Content validity was assured (expert meeting). Because this questionnaire

was not developed to be used as a scoring instrument, we did no further construct validation. As to limitations, we collected information of 109 residents through only 16 different nurses and 25 GPs, so our observations could be biased by the consecutive completion of the questionnaire by nurse and GP for several residents. Although we focused on the perceptions of GPs and nurses, the patient's perspective on BZD/Z use is important and his motivation is necessary in order to discontinue BZD/Zs successfully. We collected data for several demographic parameters, but we did not collect data on co-medication and co-morbidities. Recall bias is possible, because time between the BZD/Z initiation and the questionnaire completion could be lengthy. Although there is an important link between BZD/Z use and risk of falls in literature[33, 34], we did not collect specific data on falls.

Discussion of the main findings:

For this study, the main selection criterion was chronic use for at least 3 months. But when we asked the GPs about the duration of use, they indicated that more than 50% started before entering the nursing home and very often the GPs could not indicate for how long the BZD/Z was used. Hence, chronic use of at least 3 months was in most cases permanent use.
Similar to another study of our research group [3], 'insomnia' was the main indication for the chronic BZD/Z use. Therefore, the results and conclusions of this study are predominantly relevant for sleep problems.
GPs as well as nurses considered the chronic use of BZDs to be still effective. This can be a socially desirable response, because GPs are still responsible for prescribing these drugs. Nevertheless, long-term BZD effectiveness is doubtful[35, 36]. Longitudinal studies of incident users with validated instruments are necessary to evaluate long-term effectiveness.
The most commonly reported side-effect was psychological and physical dependence. As reported in other studies[8, 37], GPs and nurses also pointed out that the expected resistance from the resident is a high barrier to try discontinuation. Prescribers are often confronted with patients' demands to continue these drugs [25]. Nevertheless, some patients are susceptible to change, therefore routinely raising the issue, negotiating dose reduction schedules should be advised [25, 29]. Together with the perception of the effectiveness of chronic BZD/Z use and the lack of other side-effects, these notable addiction problems [8] lead to the chronic continuation of these drugs. There should be a shift in the caregivers general acceptance of chronic BZD/Z use to an holistic addiction management approach that aims to discontinue BZD/Z use in the best interest of the patient.
The scores for the resident-specific barriers were higher (more agreement with the barrier) than for the general statements. This finding confirms that this study with resident-specific information provides realistic views towards discontinuation compared to general opinions of the caregivers.
A common barrier for both the GPs and the nurses was the preference for pharmacological instead of non-pharmacological approaches. Nurses indicated that they had too little scientific information and knowledge on that matter. Training programs should focus on medication reassessment and on implementation of non-pharmacological approaches. GPs, more than nurses, indicated that the non-pharmacological treatment options take more time and effort. However, in a nursing home there is more care support (occupational therapist, physical therapist,…) available to try non-pharmacological approaches than in primary care. Nevertheless, in our study, the help of a psychologist or pharmacist to assist with the discontinuation was not perceived to be important.
The fear that the initial problems will come back is also a barrier that was scored high among GPs and nurses. During withdrawal it is known that rebound insomnia or anxiety is possible [16]. But patients as well as prescribers should focus on the long-term outcome. For the indication 'insomnia', there is evidence that sleep quality improves after the BZD/Z is withdrawn [19]. Informing the patient on possible, but temporarily withdrawal symptoms and on sleep quality

improvement can help the patient's motivation on discontinuing sleep medication.
The prolonged use of the BZD/Zs and the old age of nursing home residents affect the willingness to discontinue BZD/Zs [25]. Most people enter a nursing home as a final step in life, and for the sake of convenience, care staff as well as patients can be more resistant towards prescribing guidelines urging them to stop. In this older, more vulnerable population with co-morbidities and polypharmacy (including other psychotropic drugs), caregivers should be stimulated to discontinue chronic BZD/Z use, because of side-effects such as sedation, the risk of falling, the deterioration of cognitive functions, and poor sleep quality.
Although the GPs indicated higher resident-specific barriers, they were more willing to try discontinuation compared to the nurses. Maybe the prescribers are aware that discontinuation is advised and although they report higher barriers, they feel more obliged to follow guidelines. The level of agreement between the GP and the nurse was low, showing that both caregivers, with different responsibilities towards patients, do not share the same opinion on the same individual patient. Consequently, this finding illustrates the need for more structured interdisciplinary contacts between caregivers in order to optimise medication use.
In conclusion, the caregivers in our study reported a low willingness to discontinue chronic BZD/Z use in individual patients due to the caregivers' perceptions about the chronic effectiveness of, the residents' dependence on and the absence of side-effects of BZD/Zs. Barriers towards discontinuation were higher among GPs than nurses. On the other hand, GPs were willing to try discontinuation in one out of three residents while nurses only wanted to try in one out of five. Overall, there was a low level of agreement between GP and nurse indicating the need for interdisciplinary contacts.

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CHAPTER 2.7

Feasibility of discontinuing chronic benzodiazepine use in nursing home residents: A pilot study

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ABSTRACT

Background & objectives: Although guidelines discourage the chronic use of benzodiazepines and related Z-drugs (BZD/Zs) for sleep problems, the prevalence among older adults residing in nursing homes remains high. Discontinuing these drugs is widely recommended, but seems difficult to implement.
The aim of our study was to evaluate the overall feasibility in the nursing home, in terms of willingness towards discontinuation and success rate at 8 months in willing patients, together with the impact on withdrawal symptoms, change in sleep quality, quality of life and medication use.

Methods: In a convenience sample of 5 Belgian nursing homes (823 residents), we included cognitively competent residents with chronic BZD/Z use for insomnia. Sleep quality was investigated with the Pittsburgh Sleep Quality Index (PSQI), quality of life with the EQ-5D, and withdrawal symptoms with the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ). The (not) willingness to initiate a discontinuation was analysed with descriptive statistics, and the success rate with survival analysis.

Results: Of the 135 eligible residents, both GP and resident were willing to initiate discontinuation in 38 residents. The most indicated reason for refusing to initiate discontinuation among GPs was the 'unmotivated patient' and among residents the 'reluctance towards change'. At 8 months, 66.0% were successful in completely discontinuing BZD/Z use. In these successful discontinuers (n=25) the subjective PSQI component evolved favourably (p=0.013) and the number of midnight awakenings decreased (p=0.041). In the relapse group (n=13), the quality of life decreased (p=0.012), with mainly an increase of problems with activities and pain/discomfort. In both groups, the withdrawal symptoms, functionality and medication use did not change.

Conclusion: Discontinuation of chronic BZD/Z use is feasible in the nursing home setting without noticeable withdrawal symptoms, without a switch in medication use, without detrimental effect on quality of life and with a positive effect on the self-perceived sleep quality.

INTRODUCTION

Benzodiazepines and related Z-drugs (BZD/Zs) are the most frequently used symptomatic treatment for sleep difficulties in older adults [1]. International guidelines discourage the chronic use of these BZD/Zs, because of the lack of long-term effectiveness, the risk of dependence, tolerance and withdrawal syndromes [2-4]. Though there were several campaigns and guidelines issued (the UK report in 1988 [5], US reconciliation act in 1987[6] and a more recent report in Belgium [7]), the prevalence of chronic BZD/Z use remains high, particularly in the nursing home setting (prevalence ranges in European nursing homes from 28% to more than 50%[8-11]).

Due to the BZD/Z's sedating action, the acute adverse effects include decreased alertness with risk of falling[12] and anterograde amnesia[13]. It has been suggested that chronic BZD/Z use has also been associated with increased risk on cognitive decline [14] and mortality [15]. With increasing age, pharmacokinetics change and central nervous system sensitivity increases [16, 17]. Together with comorbidities and associated (in particular psychotropic) polypharmacy, older people are more at risk for the adverse effects. A meta-analysis of risks and benefits in older people [1] showed an increased risk and marginal benefit of acute hypnotic use. However, this meta-analysis did not take into account the dependency problems associated with chronic use. Most of the nursing home residents have established chronic use, long before entering the nursing home [18, 19].

Discontinuing BZD/Zs is widely advised, but seems difficult to implement [20, 21]. There is no consensus on the optimal tapering strategy [20, 22], with options varying from abrupt discontinuation [23, 24] to tapering schedules of more than a year [25]. Several meta-analysis tried to evaluate strategies for BZD/Z discontinuation [22, 26] and concluded that a minimal intervention (for example: sending a letter from physician to patient), followed by gradual tapering (led by a physician or psychologist, and sometimes augmented with psychotherapy or pharmacotherapy), is effective in reducing BZD/Z use. Most studies included in this meta-analysis did not focus on older adults, and were performed in primary care or in psychiatric clinics (and are not representative for low dose users). Often, the BZD/Z initiation followed by chronic continuation is established in primary care. Therefore, this setting is an important research domain. However, it can be valuable to guide BZD/Z discontinuation in this older population in a more controlled setting such as hospitals and nursing homes.

A recent meta-analyse on reducing BZD/Zs in older people [27] , included 16 studies, in primary care [28], in geriatric wards [29, 30] and in nursing homes [31, 32] and pointed at the effect of consultations, education of both prescribers and patients, both followed by a supervised withdrawal. In general, the studies in this analysis had a limited follow-up (3 studies with follow up of max 12 months, and none in the nursing home) resulting in a lack of knowledge on long-term effectiveness (of specific interventions). The discontinuation of BZD/Zs in community dwelling older people (aged 85+years), appears to be possible [33]. The question remains whether BZD/Z discontinuation is feasible in the nursing home setting.

Some (non-randomised) studies have investigated BZD/Z withdrawal in the nursing home setting and reported success rates of 87% after 8 weeks [34], a 50% reduction in BZD/Z use after 3 months [35], and 60% after 1 year [36]. In those studies there was a focus on the success rate (focus on residents already willing to discontinue). However, health policy makers should have an idea of the extent of the target population and the overall feasibility, including the willingness towards discontinuation in this setting.

Therefore, we designed a study in the nursing home setting to analyse both the feasibility in terms of willingness towards discontinuation and the success rate at 8 months follow-up. We focused on cognitively capable residents with chronic BZD/Z use for sleep problems. Second-

ary, we investigated possible withdrawal symptoms, the impact on sleep quality and on the quality of life.

METHODS

Design:

This pilot study with a follow-up of 8 months investigated the overall feasibility of a discontinuation process of chronically used BZD/Zs in cognitively competent nursing home residents. The analysis of overall feasibility was divided into the willingness to initiate a discontinuation both among general physicians (GPs) and residents, and into the success rate in those residents who started discontinuation. We focused on BZD/Z use for sleep problems and explored possible withdrawal symptoms and the evolution of sleep quality and quality of life.

Setting:

The Belgian long-term residential care structure consists of residential or nursing homes for older people, which offers a home replacement with or without nursing care. Governance of nursing homes for older people is either public (community health services) or private (predominantly non-profit) with little difference in quality of care. Often, the resident retains his/her own GP, resulting in an average of 32 consulting GPs per nursing home. The point prevalence of dementia among residents is approximately 50% with considerable variation between nursing homes [37].

Inclusion and exclusion criteria:

In a convenience sample of 5 Belgian nursing homes, all cognitively competent residents were screened for inclusion (September 2012 till July 2013).
Eligible residents had established chronic use of benzodiazepines or Z-drugs for insomnia (daily administered at bedtime for at least 3 months) and were cognitively competent, which was confirmed with a KATZ disorientation score of 1 or 2 (disorientation in time and place ranging from 1-no disorientation to 4-severe))[38].
We excluded residents who were critically ill, or had a fatal diagnosis with short life expectancy; residents who used a benzodiazepine during the day (for the indication anxiety) or used a sedative antidepressant (trazodone, amitriptyline, mirtazapine) or phytotherapy as co-medication.

Willingness to initiate discontinuation in chronic BZD/Z use (GP and resident):

One part of the overall feasibility focused on investigating how many GPs and residents were willing to initiate discontinuation.
The general physician (GP) of the eligible resident received a recruitment letter. In this letter, the GP saw the name of his patient and the prescribed BZD/Z with the dose. In this recruitment letter we asked the GP for the duration of BZD/Z use and whether he/she was willing to initiate a discontinuation in this particular resident. In case the GP did not want to initiate discontinuation, he/she could indicate the reason(s) among the following options: 'psychiatric problems or major depression; specific sleep disorders; specific medication inducing insomnia (e.g.psychotropic drugs, thyroids); BZD/Z used as anxiolytic or muscle relaxant; not feasible because of failed prior attempt(s); not feasible because of the lack of the resident's motivation; and other reasons.'
All residents, whose GP agreed to initiate discontinuation, were informed and asked for their willingness to discontinue their BZD/Z (informed consent).

Success Rate of discontinuation process:

In cases where both the GP and resident agreed, the discontinuation was initiated. Because of our naturalistic study design, we did not implement a strict discontinuation schedule and used no substitution or alternatives. The GP was responsible for the discontinuation but we proposed a possible discontinuation schedule to the GP in the recruitment letter (25% reduction per week or per 2 weeks).
The successful discontinuation rate 8 months after inclusion was our main outcome parameter. We documented relapse and its reason (sleep problems during or after withdrawal; loss of motivation; and other).

Data collection- outcome:

We performed data collection at baseline, 2 months and 8 months after baseline, except for withdrawal symptoms (at baseline and after discontinuation). As our sample was a geriatric population, the researcher (J.B.) assisted residents with the recording and rating of the questionnaires.
Demographic data was obtained from the resident's record and medication data from the medication chart. Based on the Anatomical Therapeutic and Chemical classification (ATC) [39], we selected the classes N05BA (anxiolytics), N05CD (hypnotics) and N05CF (Z-drugs) as BZD/Z use. We divided the BZDs and Z-drugs according to half-life in short/intermediate (T1/2<24h) and long-acting (T1/2>=24h) based on a reference source [40]. We also used the Defined Daily Dose (DDD) to compare dosages. The total number of chronically used medications as well as possible interfering medication such as antidepressants (ATC N06A), antipsychotics (ATC N05A), anti-dementia drugs (ATC N06D), anti-Parkinson (ATC N04) drugs and pain medication (ATC N02) were recorded. Functional characteristics were scored by the KATZ scale [38]. This instrument is mandatory in the Belgian nursing homes. The first part of this instrument scores six Activities of Daily Living (ADL) from 1 (independent) to 4 (totally dependent). The second part scores disorientation in time and place ranging from 1 (no disorientation) to 4 (severe) and was used in the inclusion of eligible residents (residents with score 1 or 2). Depressive feelings were scored with the 8-item Geriatric Depression Scale (GDS), which is an abbreviated version of the GDS 30 [41] and especially designed and validated for nursing home residents [42, 43]. A score of three or more on the GDS-8 is indicative for depressive symptoms. Additionally, we recorded hospital admissions and falls by checking the medical file and recorded hearing and visual impairment, and frequent pain (by using a yes or no question).
The validated Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) was used [44] to detect withdrawal symptoms. This self-report questionnaire measures 20 symptoms. The three answer possibilities (no-moderate-severe) are linked to a rating of 0, 1 or 2, with higher scores indicating more withdrawal symptoms (maximum score is 40).
The sleep quality was analysed with the Pittsburgh sleep quality index (PSQI) [45], a self-rated questionnaire which investigates global sleep quality and sleep disturbances (Dutch translation [46]). The seven components of the PSQI are scored from 0 to 3, yielding a total score ranging from 0 to 21, where higher scores indicate worse sleep quality. A total PSQI score of more than 5 is a widely used cut-off that indicates poor sleep quality. Because in this study, we wanted to compare sleep quality before and after discontinuation, we left out the PSQI component 'sleep medication' in the total PSQI score (adjusted PSQI, with a score ranging between 0 and 19). We also reported the component 'subjective sleep quality' as perceived by the resident himself (scored from 0 to 3).
Quality of life was assessed with the descriptive part of the EQ-5D-3L, which is a standardised measure of health status developed by the EuroQol Group [47] and also validated in nursing home residents [48]. The EQ-5D-3L descriptive system comprises the following dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, which can be

scored from 1 (no problems), 2 (some problems) till 3 (extreme problems). The descriptive profile score is converted into the EQ-5D index [49], with higher sores indicating better health.

Ethical considerations:

This observational study was approved by the ethics committee of the University Hospital of Ghent (registration number B670201213943). Each nursing home received information and gave approval to screen the nursing home population. The GP had to approve the resident's inclusion. Each resident, included in our study, received oral and written information and gave consent.

Statistics:

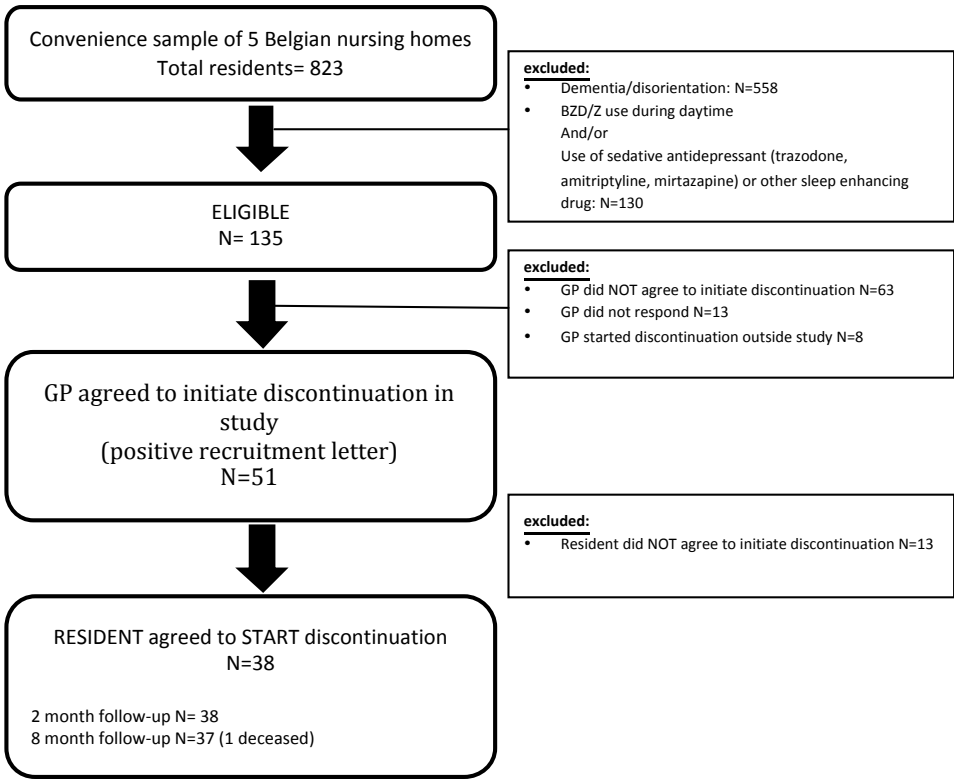
We used descriptive statistics to analyse the feasibility of discontinuation and survival analysis to analyse the success rate of discontinuation during an 8 month period. The outcome parameters, i.e. withdrawal symptoms, sleep quality, quality of life, functionality and medication use were described and compared between the discontinuers and the controls, and also between the successful discontinuers and the relapse group. Because of the small number of residents in each group, we used nonparametric statistics (Mann Whitney U for the comparison of categorical variables between groups and Kruskal Wallis for paired analysis).

RESULTS

Willingness to stop:

In the five nursing homes with a total of 823 residents, our exclusion of residents with known dementia or disorientation (n= 558) and of residents with BZD use for anxiety or other sleep enhancing medication (n=130), resulted in 135 eligible residents (16%) (Fig 1).

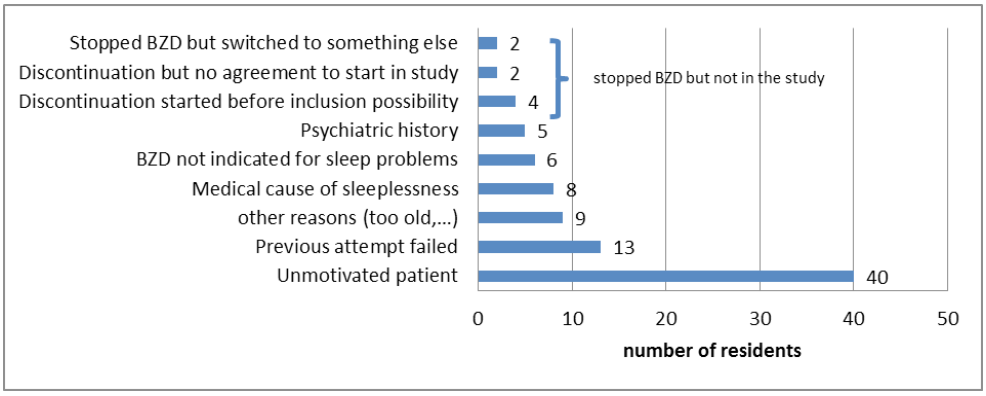
Fig 1: Flowchart of the willingness to discontinue chronic benzodiazepine/Z-drug use.



The GPs of those 135 residents indicated that a discontinuation was feasible in 51 residents by returning a positive recruitment letter. For 13 residents, the GP did not respond to the recruitment letter. The reasons why GPs (n=71) were not willing to initiate a discontinuation are summed in Figure 2. More than half of the GPs indicated that there was a lack of motivation of the resident himself (56%). In 18%, the failure of a previous attempt was the reason not to initiate a discontinuation.

Of those 51 residents, where the GP agreed, 13 residents refused to start the discontinuation of their BZD/Z. The main reason (12/13) was the reluctance towards change (too old, I sleep well). In total, 38 residents gave informed consent and were included in the discontinuation study. The most frequently used BZD/Zs in the 38 discontinuers were lormetazepam (36.8%) and lorazepam (21.1%), 37 residents used a short acting BZD/Z and the median prescribed dose was 1 DDD (range 0.10-2.00).

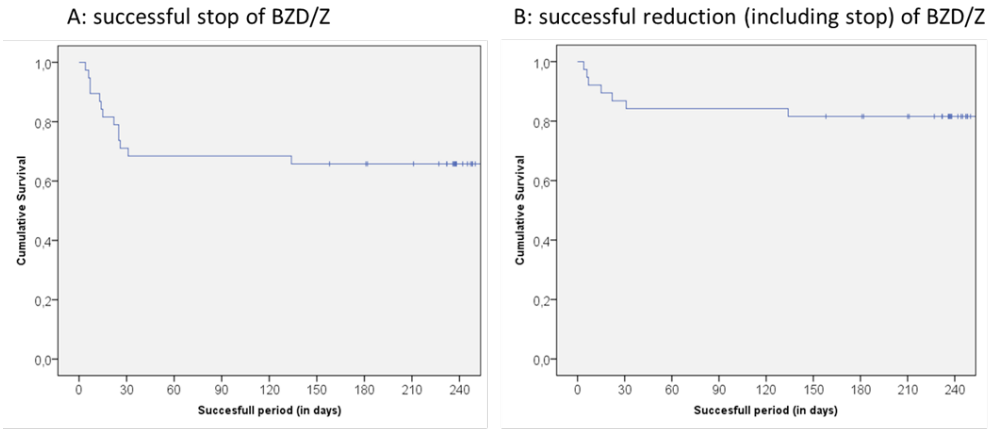
Fig 2: General Physicians' reasons for not initiating discontinuation in a resident in the study (n= 71).



Success rate (survival analyse):

After 2 months, 25/38 residents were BZD/Z free, 7/38 residents reduced their dose and 6/38 residents relapsed. After 8 months, one resident of the 25 successful discontinuers relapsed, one deceased and one additional resident stopped BZD/Z. The median duration of the discontinuation process was 21 days (range 7 days to 88 days). The reasons why residents 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). Real increase in withdrawal symptoms (as scored by the BWSQ) was not observed. Of the 24 residents who were successfully weaned after 8 months, one person took placebo, and one person used an antihistaminic (hydroxyzine) as needed.
The survival analysis revealed that 66.0% were successful in completely discontinuing BZD/Z use at 8 months. If we also considered the residents who decreased their BZD/Z dose as successful, the success rate increased to 82.0% (Fig. 3).

Fig 3: Survival Analysis of the 38 residents who initiated discontinuation (Kaplan Meier).



*Lost of follow-up: 1 deceased during observation period

Baseline comparison between successful discontinuation group and relapse group:

At baseline, the successful discontinuers (n=25) and relapse group (n=13) were comparable on all demographic, clinical, institutional and medication characteristics (Table 1) as well as for baseline outcome parameters (sleep quality components, quality of life).

Table 1. Baseline characteristics of included residents with a comparison between Successful discontinuation (n=25) and Relapse (n=13).

		BASELINE COMPARISON		
	TOTAL	**SUCCESSFUL**	**RELAPSE**	**p-value[a]**
	n= 38	**n= 25**	**n=13**	
Demographic characteristics				
Age in years (mean-range)	84.3 (65-97)	84.3 (65-97)	84.3 (72-93)	0.987
Gender (% female)	71.1%	79.2%	53.8%	0.108
Length of stay in months (mean-range)	34.1 (3-128)	37.9 (3-128)	26.9 (3-107)	0.426
Education (%higher education >14y)	36.8%	37.5%	38.5%	0.867
Clinical characteristics				
ADL score (mean-range) (0-24)	14.1 (6-23)	15.4 (6-23)	11.6 (6-22)	0.051
Disorientation score (mean-range) (0-8)	2.7 (2-4)	2.8 (2-4)	2.5 (2-4)	0.377
Sight impairment (not blind)	23.7%	16.7%	38.5%	0.140
Hearing impairment (not deaf)	39.5%	41.7%	30.8%	0.514
Fall<12months	31.6%	29.2%	38.5%	0.564
Chronic pain	15.8%	12.5%	23.1%	0.405
Depressive symptoms (%GDS≥3)	27.0%	20.8%	38.5%	0.249
Medication Information				
Total number of chronic medication (mean-range)	8.2 (1-18)	8.6 (4-13)	7.5 (1-18)	0.168
Benzodiazepine/Zdrug[b] DDD	0.9 (0.1-2.0)	1.0 (0.1-2.0)	0.8 (0.1-2.0)	0.437
long-acting[c]	2.6%	0.0%	7.7%	0.160
Antidepressant medication	26.3%	29.2%	23.1%	0.690
Antipsychotic medication	13.2%	8.3%	15.4%	0.510
Anti-Epileptic medication	7.9%	8.3%	7.7%	0.946
Pain medication	26.3%	37.5%	7.7%	0.051
narcotic	18.4%	25.0%	7.7%	0.199
nonnarcotic	13.2%	20.8%	0.0%	0.077

[a] p-value of difference between successful and relapse with nonparametric statistics (Chi^2 for categorical variables and Mann Whitney U for continuous)

[b] BZD/Zs: lormetazepam was used by 14, lorazepam by 8, zolpidem by 7, bromazepam by 4 and alprazolam by 3 residents;flurazepam and triazolam by 1 resident.

[c] long acting was defined as a BZD/Z with a half-life of ≥24h; in our study only flurazepam was recorded

ADL= Activities of Daily Living, GDS=Geriatric Depression Scale, DDD= defined daily dose

Impact of discontinuation on withdrawal symptoms:

The mean BWSQ score among the 38 discontinuers evolved from 3.9 (SD 2.8, range 0-11) at baseline to 4.1 (SD 2.6, range 0-12) after discontinuation (p=0.865), indicating that there were no excess symptoms noticeable during withdrawal. Both in the successful (n=25) and the relapse group (n=13), the withdrawal symptoms did not differ at baseline and did not change over time (p=0.175).

Among the 38 discontinuers, the most commonly reported symptoms incorporated in the BWSQ were muscle pain (baseline 49% and 63% afterwards), muscle twitching (41% and

37%), loss of memory (41% and 32%), pins and needles (35% and 39%) and feeling depressed (32% and 37%).

Impact of discontinuation on sleep quality:

The total adjusted PSQI score in the successful discontinuers (n=24) was the same over the three time points 5.3 (SD 2.9), 5.1 (SD 2.6) and 5.3 (SD 3.3) at baseline, 2 months and after 8 months, respectively (difference between baseline and 8 months p= 0.880). In the relapse group, this adjusted PSQI score evolved from 5.8 (SD 2.8) at baseline to 5.5 (SD 2.3) at 2 months and increased to 7.9 (SD 4.8) at 8 months (difference between baseline and 8 months p=0.075) (Table 2).
The subjective component in the PSQI questionnaire showed an overall improvement of the sleep quality in the successful discontinuers (from 1.25 at baseline to 0.88 at 8 months, p=0.013). In the relapse group the subjective sleep quality evolved from 1.23 at baseline to 1.15 at 8 months, p=0.739).
The total "hours of sleep" decreased over 8 months, in the successful discontinuers from 8h44min at baseline to 8h01min at 8 months (p=0.031); in the relapse group from 8h24min to 7h01min (p=0.019). The "sleep latency" increased over 8 months; from 27min to 42min (p=0.304) in the successful group, and from 26min to 41min (p=0.107) in the relapse group.
The number of midnight awakenings decreased significantly among the successful discontinuers (1.56 at baseline to 0.83 at 8 months, p=0.041). All other components of the PSQI did not change significantly.

Impact of discontinuation on other outcome parameters:

The functionality (ADL score) or the number of chronic medications (BZD/Z not included) did not change in both groups over 8 months (p value= 0.280) (Table 2).
The EQ-5D-3L index score did not evolve significantly in the successful discontinuers (from 0.439 to 0.456, p=0.879) (Table 2). In the relapse group, quality of life decreased from 0.676 to 0.556 (p=0.012), with mainly an increase of problems with activities and pain/discomfort.

Table 2. Evolution of outcome parameters during 8 month follow-up.

	SUCCESSFUL N=24			RELAPSE N=13		
	BASELINE	8 MONTHS	p-value[b]	BASELINE	8 MONTHS	p-value[b]
Sleep quality						
adjusted PSQI (mean-range)	5.3 (1-13)	5.3 (1-13)	0.880	5.8 (1-15)	7.9 (2-12)	0.075
Hours of sleep (mean-range)	8:44 (5:50-11:55)	8:01 (4:45-11:40)	0.031	8:24 (5:40-10:00)	7:01 (2:50-9:15)	0.019
Sleep latency in hours (mean-range)	0:27 (0:02-2:00)	0:42 (0:10-4:00)	0.304	0:26 (0:10-1:00)	0:41 (0:05-2:00)	0.107
Subjective sleep quality (mean) [a]	1.25	0.88	0.013	1.23	1.15	0.739
Sleep disturbance[a]	0.96	0.96	1.000	1.15	1.00	0.157
midnight awakenings[a]	1.56	0.83	0.041	1.46	1.08	0.334
difficulties falling asleep[a]	1.60	1.54	0.751	1.85	1.85	1.000
midnight toilet awakenings [a]	2.04	2.09	0.831	2.00	2.15	0.680
awakenings pain[a]	0.52	0.25	0.070	0.69	0.46	0.496
Daytime dysfunction[a]	0.92	0.83	0.802	1.31	1.61	0.248
Quality of life						
EQ-5D index (mean, SD)	0.44 (-0.17-1)	0.46 (-0.30-1.00)	0.879	0.68 (0.03-1)	0.56 (-0.10-1.00)	0.012
Functionality						
ADL score (mean, SD)	15.4 (6-23)	15.4 (6-24)	0.838	11.6 (6-22)	11.9 (6-22)	0.593
Medication use						
total number (mean, range)	7.46 (3-12)	7.50 (3-14)	0.751	6.46 (0-17)	7.31 (2-18)	0.142

[a] score can range from 0 (no) to maximum 3 (frequent)

[b] p value of difference between baseline and after 8 months with nonparametric statistics (Wilcoxon Signed Rank test)

adjusted PSQI: Pittsburgh Sleep Quality Index Questionnaire whithout the component 'sleep medication'; ADL: Activities of Daily Living

DISCUSSION

This discontinuation study in the nursing home setting showed that discontinuation of chronic BZD/Z use is feasible without noticeable withdrawal symptoms, without a switch in medication use, without a detrimental effect on quality of life and with a positive effect on the sleep quality. Our analysis at 8 month follow-up showed that 66% succeeded in stopping their BZD/Z use. The success rate was enhanced to 82% when we included everyone who decreased their dose. Nevertheless, the proportion of eligible residents was low and the recruitment was difficult. Our inclusion criteria provided a small sample of eligible residents (135/823). Recruiting residents of which both GP and resident agreed to initiate discontinuation reduced our sample further to 38/135. The most frequently indicated reason for refusing discontinuation among GPs was an 'unmotivated patient' and among residents the 'reluctance towards change'.

Strenghts and limitations:

Rational medication use also includes the discontinuation of drugs which are not really necessary or can cause harm [21, 50]. This concept is in accordance with the concept of quaternary prevention, which is the avoidance of unnecessary medical activity [51]. Because discontinuing medication in older adults is not yet a routine procedure and is especially difficult when it concerns chronic BZD/Zs for insomnia problems [20], our study on the feasibility of discontinuing chronic BZD/Z use in the nursing home setting appears to be very relevant.
The major strength is our focus on the overall feasibility. Some studies investigated the general perceptions of chronic BZD/Z use among physicians [52-54] and among patients [55-57]. Other studies focused on the discontinuation process [34, 58]. Our study combines those two important research topics in order to represent the overall feasibility; the willingness to initiate a discontinuation and whether this discontinuation can be successful for a longer period (8 months). This study was not intended to find the optimal tapering strategy; the GP was free to tailor the withdrawal to the needs of his/her patient as suggested in the literature [20].
Another strength of this study lies in its pragmatic approach and easy translation to the real-life setting. However, several exclusion criteria limit the total generalizability. We excluded residents with dementia/disorientation because of the controversy towards medication withdrawal and because of the difficulty of monitoring study outcomes (withdrawal symptoms, sleep quality…) in this patient group. This ethical hindrance has led to a paucity of valuable information, with no specific studies on BZD/Z withdrawal in this patient group [59]. From a previous study in the Belgian nursing homes [19], we knew that 59% of the chronic BZD/Z use is intended to treat the sole indication 'insomnia'. All guidelines agree on the time-limited use for this indication. Because there is uncertainty on the appropriateness of long-term use of BZD/Z for anxiety disorder [60] and other indications (such as epilepsy, muscle spasm,…) and because we were not able to offer alternative (non-)pharmacological therapy, we excluded residents that used the BZD/Z for anxiety. Because our focus on BZD/Z use, we excluded residents that used other hypnotic medication, such as trazodone or other antidepressants and phytotherapy.
Though inherent to a pilot study, our small sample size is an important limitation. Moreover, we had no control group which limits the interpretations towards differences in outcome parameters. Although it would be of great value to have a comparable group of residents who do not stop their BZD/Z and serve as controls, no study has been able to include this because of recruitment difficulties. Our large cascade limits the possibilities of comparison and forces us to use nonparametric statistics. However, we had a very small number of lost-to-follow-up. We did collect the number of chronic medication and focused on psychotropic medication, but we had no information on comorbidities. Recall bias could not be avoided, as we ques-

tioned the withdrawal symptoms after the completion of the discontinuation process.

Main discussion:

Overall feasibility: willingness and success rate

Of the total sample of 135 eligible residents, only 28% were willing to initiate a discontinuation. This finding confirmed the results of a previous survey among GPs and nurses investigating willingness to stop [19]. This older population with years (even decades) of daily BZD/Z use [18] and with limited prospects for clinical improvement, expresses a lack of motivation and even reluctance towards discontinuation [53, 61]. Because we were ethically obliged to first ask the GP for agreement to initiate withdrawal, we could not know whether the GP had discussed discontinuation with his/her patient or he just assumed a lack of motivation. Nevertheless, some patients are susceptible to change. Therefore it is advised to routinely raising the issue and negotiating dose reduction [62, 63].
Of the residents who initiated withdrawal, 66% succeeded in withdrawing their BZD/Z fully at 8 months, and an additional 16% decreased their dose. This percentage is similar to another study in this setting [36] (60% still BZD/Z free at 1 year).

Outcome parameters

In our study, the residents with chronic BZD/Z for sleep problems used low dosages and there was no increase in withdrawal symptoms noticeable. The BWSQ is intended to detect change in different symptoms. We found an already high frequency of several symptoms at baseline (muscle pain, muscle twitching,…), but we did not find a change during withdrawal. However, there were some residents who relapsed due to sleep problems during or after withdrawal (n=6/13), indicating possible rebound insomnia [64].
We saw that residents with successful discontinuation reported a better sleep quality than before the discontinuation and the number of midnight awakenings was significantly reduced. We found a significant reduction of the total 'hours of sleep'. Whether this is a positive or a negative effect depends on the amount of restorative sleep and impact on daytime functioning. It is known that BZD/Zs shorten the sleep latency and change sleep architecture at the expense of the deep restorative stages of sleep [65]. Stopping the chronic BZD/Z use could imply that the sleep rehabilitates, becomes less fractionated and less vulnerable to pain, noise, and other potential distractions.
There was no change in quality of life and functionality among the successful discontinuers. The quality of life index (EQ-5D-3L) did decrease significantly in the relapse group, but was still higher than in the success group.
Medication substitution is a common concern [66-68], but in our study, there was no increase in medication use or switch towards other (psychotropic/sedative) medication (except for intermittent use of a placebo or antihistaminic in 2 residents).

Implications for research:

More research is needed to decide whether a discontinuation campaign in this subpopulation is cost-effective, and which interventions can lift barriers and increase the willingness to engage in discontinuation, both in patients and in physicians.
In order to confirm with sufficient power that discontinuation of BZD/Z leads to better sleep quality, prospective studies with sufficient sample size and a random or matched control group should be set up.
Finally, the feasibility, success rate and outcome should also be investigated in residents with dementia/disorientation and in people with BZD/Zs used for the indication anxiety, not only in the nursing home setting, but also in ambulatory care.

Implications for practice:

The approach to discontinuation in our study can be implemented on a larger scale. Nursing homes may be a protected environment where GPs (and other care personnel) can familiarize with discontinuation efforts, gain confidence and even extend these efforts to the large community of home dwelling older adults. Informing all prescribers, caregivers and patients of the negative effects of chronic BZD/Z use and the positive prospects of discontinuation together with educating prescribers in motivational techniques could impact the overall willingness.
When taking care of the oldest old, especially in the nursing home, multiple actors are responsible for the medication use so it is important to include nurses, physicians, pharmacists and management, taking into account powerful barriers towards willingness to change.

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3

CHAPTER
DISCUSSION

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DISCUSSION

A discrepancy exists between current guidelines cautioning against chronic benzodiazepine and Z-drug (BZD/Z) use and its high prevalence among older nursing home residents in Belgium. Major gaps in BZD/Z research are the lack of data on long-term efficacy, and inconsistent findings on long-term risk, such as cognitive deterioration.
With this thesis we wanted to contribute to the knowledge on the benefits and risks of chronic BZD/Z use and focus on the largest consumer group of these drugs, the older nursing home residents. Furthermore, we investigated whether discontinuation was feasible in this setting. A clear cut differentiation between BZD/Z use for insomnia and use for anxiety or other indications has not been made in many studies. This thesis focused on the main indication, insomnia.

1. ANSWERS TO THE RESEARCH QUESTIONS

What are the indications of the benzodiazepines and Z-drugs used in the nursing home and at which dosages (chapter 2.1)?

We found that half (50%) of the nursing home residents in Belgium used BZD/Z drugs on a daily base and for at least 3 months. This indicates chronic use, generally considered to be inappropriate. The main indication of chronic BZD/Z use was insomnia (59%), followed by anxiety (17%). For anxiety, multiple dosing per day resulted in a higher daily BZD dosage compared to insomnia. For insomnia, BZD/Zs were taken once in the evening, in dosages equal to the DDD but higher than recommended for the geriatric population.

What is the proportion of antidepressants used for insomnia and anxiety in the nursing home and what are the dosages (chapter 2.2)?

In our exploration of antidepressant use for the overlapping indications with BZD/Zs, we found that sedative antidepressants (mainly trazodone) were prescribed at dosages below the DDD for the off-label indication insomnia without concomitant depressive symptoms. For the indication anxiety, guidelines recommend antidepressants as first-line treatment. However, in our study, we found that the Belgian physicians preferred to prescribe BZDs above the recommended SSRIs for long-term treatment of anxiety.

What is the sleep quality of chronic BZD/Z use in nursing home residents and does it differ from nonusers (chapters 2.3 and 2.4)?

In our cohort of cognitively competent nursing home residents, we found at baseline that chronic BZD/Z users had a worse sleep quality than nonusers. More specifically, chronic users reported more difficulties with falling asleep, reported a higher frequency of midnight awakenings, and a higher frequency of not being well rested in the morning. The one-year follow-up results of this observational cohort study revealed that the sleep quality of the BZD/Z users deteriorated significantly, while in nonusers, there was also a deterioration of the sleep quality, but not significantly.
The comorbidity 'depression' was in this study a significant factor in worsening sleep quality, and also in this study, depressive symptoms were more prevalent in chronic BZD/Z users.

What is the relationship between chronic BZD/Z use and cognitive deterioration in nursing home residents? (chapter 2.5).

We explored the risk of chronic BZD/Z use on cognitive deterioration in the same cohort. The general cognition of nursing home residents (as measured by the MMSE) decreased significantly in one year, both in the group of BZD/Z users and in the nonusers, but there was no significant difference in mean MMSE decrease between those two groups. When focusing on clinically relevant cognitive decrease, there were 34% BZD/Z users with severe deterioration (decrease of 4 or more points in one year) compared to 27% nonusers, but this small difference was not significant. A strong risk factor for clinically relevant cognitive decline was depression. Social activities and cognitive stimuli (such as reading, memory games) were associated with less cognitive decline.

Is it feasible to implement discontinuation in the nursing home (chapter 2.6 and 2.7)?

First, we explored perceptions of benefit and harm, the willingness to stop BZD/Z and barriers against discontinuation by performing a survey addressed to the two main caregivers in the nursing home, the GP and nurse. In more than 60% of the residents, the GP could not indicate the duration of BZD/Z use. In those who had a defined duration, it was 66 months, which illustrates chronic use. GPs as well as nurses considered the chronic use of BZD/Zs to be still effective and did not report many noticeable side-effects, except for dependence. Together with the expected resistance from the resident, all these factors contribute to the low willingness to discontinue BZD/Zs; GPs were willing in one third, while nurses were willing in one fifth of the residents with chronic BZD/Z use. Overall, there was a low agreement between GP and nurse.

Finally, we investigated overall feasibility, incorporating both the willingness towards discontinuation and also the success rate of discontinuing chronic BZD/Z use.

Our focus on cognitively competent residents, using BZD/Z only for insomnia led to a small sample of 135 on a total of 823 residents. Only for 38 residents both GP and resident were willing to discontinue. Lack of motivation was the main barrier to refuse discontinuation. Nevertheless, we learned that in this pilot group of 5 nursing homes, discontinuation of chronic BZD/Z use is feasible without noticeable withdrawal symptoms, without a switch to other medication, without a detrimental effect on quality of life, and with a positive effect on the sleep quality. Our analysis at 8 month follow-up showed that 66% succeeded in stopping their BZD/Z use. The success rate was enhanced to 82% when we included everyone that decreased their dose.

2. STRENGTHS AND LIMITATIONS

This thesis has contributed to the understanding of the high prevalence of chronic BZD/Z use in the Belgian nursing home setting, with an exploration of its indications and optimal dosages (chapter 2.1). This thesis has contributed to the much needed information on chronic effectiveness of BZD/Zs in term of sleep quality (chapter 2.3 and 2.4), and also explored the worrisome link with cognitive decline (chapter 2.5). In this thesis, we did not limit ourselves to observational studies, but we also set up a pilot discontinuation study to enhance the clinical relevance of our work (chapter 2.7).

An overall strength of this thesis was our focus on BZD/Z use for sleep problems, whereas most studies do not differentiate between BZD/Z use for insomnia, for anxiety, or for other indications. The strength of the descriptive studies with data from the PHEBE database (chapter 2.1 and 2.2) was the large representative sample of residents and the data collection from primary sources (GP and medication chart). Although the indications were gathered retrospectively, this clinical information was essential to differentiate between insomnia, anxiety and other indications, thus limiting indication bias. Strength of the first chapter was our exploration of "optimal geriatric dosing" and the confrontation with actual prescribed dosages in clinical practice, which can guide clinicians in installing a dosing regimen.

The strength of our observational cohort study (chapter 2.3, 2.4 and 2.5) was that it was the first study especially designed to investigate sleep quality, cognition and its temporal evolution among cognitively competent long-term users of BZD/Z for insomnia in the nursing home setting, and with a comparison to a well-defined control group using an adequate tool for sleep quality (PSQI) and global cognition (MMSE). Although evidence to determine the benefit/risk ratio should come from randomised controlled trials (RCTs) with incident users, we were not able to perform such a study because most of the time the chronic BZD/Z use is already established before admission to the nursing home. Moreover, continuing a long-term BZD/Z therapy is not concordant with the guidelines. By implementing several exclusion criteria, we assembled a well-defined cohort of users, and a comparator group with similar demographical and clinical characteristics. In our attempt to minimise indication bias and focus on BZD/Z for insomnia, we excluded residents with BZD/Z use for anxiety, and excluded residents with sedative antidepressants or phytotherapy. Nevertheless, we managed to select a relatively large sample of nursing home residents (n=300 at baseline, n=226 at one-year follow-up). The power was sufficient to detect differences in sleep quality. However, for the detection of subtle changes in cognition, a larger sample and a more sensitive cognitive measurement tool were required.

Strength of our discontinuation study (chapter 2.7) lies in its pragmatic approach, which encourages an easy translation from research into real-life. However, the sample in our pilot study was small and we did not include a control group, thus limiting the interpretations towards differences in outcome measurements. A limitation in our cohort study and discontinuation study was our lack of information on comorbidities. We focused on interfering (psychotropic) medication and the impact of depressive symptoms. Both in our observational cohort study and pilot study, we excluded residents with known dementia and disorientation, which diminished our sample of eligible residents and consequently limited generalizability. On the other hand, this strong focus leads clear interpretation of results in a specific population.

3. SPECIFIC POINTS OF DISCUSSION

As put forward in many guidelines [1, 2] and explicit criteria for inappropriate prescribing [3-5], long-term use of BZD/Z is discouraged. However, in our two cross-sectional studies on BZD/Z use in the nursing home setting (PHEBE and barriers study), we saw that chronic use was very prevalent. This finding is in accordance with previous studies in this setting [6, 7].

Focus on the indication insomnia

A general characteristic of BZDs is its broad range of physiological effects which results in various treatment possibilities. This is also the main obstacle for comparing BZD studies. When investigating (inappropriate and) off-label prescribing, information on the reasons to initiate BZD/Zs together with dosing information is necessary [8]. In most research [9, 10], indication analysis is done by linking possible clinical diagnoses, classified with the International Classification of Diseases (ICD) or Diagnostic and Statistical Manual of Mental Disorders (DSM), with the individual medications. However, this does not automatically provide information on the reason or the indication for which each medication was prescribed. To register this information automatically in a database, improved software tools are needed to allow the prescriber to easily record the indication [11].

Optimal geriatric dosing

In our attempt to make an easy guidance for optimal geriatric dosing, we reviewed several international pharmaceutical sources with dose recommendations for older adults (international formulary[12-14] and explicit criteria for inappropriate prescribing[3, 15, 16]). Overall, there is an under-representation of older adults in pharmacokinetic and -dynamic studies leading to a lack on dosing information [17]. Most sources stay vague and issue a general dose reduction of 50%. Therefore, it is not surprising that most prescribed dosages in older nursing home residents exceed recommendations. This finding pinpoints that the prescribing physicians are not aware of geriatric dosing regimens, and that the criteria for optimal geriatric dosing for BZD/Z use are not well investigated and communicated.

Insomnia and sleep problems in older adults

As mentioned in the introduction, insomnia and sleep problems are, strictly speaking, not the same. Daytime impairment is a required item in several insomnia classifications (DSM-V[18], ICSD-2[19]). Moreover, subjective exaggeration of sleep difficulties is common and may be related to a general tendency to overestimate severity of symptoms [20]. Because it is difficult to differentiate between sleep complaints and insomnia, and also because of the elaborate aetiological possibilities of insomnia (such as pain, medication use, environmental factors, specific sleep disorders-sleep apnoea, somatic and psychiatric comorbidities) a thorough diagnostic assessment is necessary before installing a treatment (National guideline Domus Medica[21])[22, 23]. This diagnostic assessment should include detailed medical, medication, and psychiatric history. The sleep history should cover pre-sleep conditions, sleep-wake patterns, other sleep-related symptoms, and daytime consequences, which can help to establish the type and evolution of insomnia, perpetuating factors, and identification of comorbid medical, substance, and/or psychiatric conditions [24]. Knowing possible precipitating factors for the sleep problems could result in a different treatment strategy, such as an adequate pain management, alleviation of depression or a referral to specialist care/sleep clinic for sleep apnoea. While a sleep evaluation scale such as a sleep diary is an ideal tool to evaluate sleep problems, a more research oriented instrument such as the PSQI could also be useful. In view of a good therapeutic adherence it is important to know the expectations of the patient [25, 26].

An extra impeding factor in aging adults is the physiological change of the sleep architecture. The fragmentation with less slow wave sleep (deep sleep) makes the sleep of these older adults more vulnerable for interfering comorbidities (such as pain, restless legs,…)[27] and disrupting factors (noise, care routines, nocturia). Moreover, the age-related circadian changes are noticeable by the tendency of older adults to go to bed earlier, which also results in earlier awakenings [28, 29]. The habit of napping (in the afternoon, or in the early evening-when watching television) is also prevalent among older adults, and can disrupt the night-time sleep pattern. Discussing sleep patterns and informing patients on sleep hygiene are the initial steps in a stepped care approach to treat insomnia. Evaluation of this non-pharmacological approach is necessary in order to decide whether there is need for further steps, such as cognitive behavioural therapy. As these non-pharmacological treatment strategies imply a well-trained GP or psychologist, more time and resources are required for implementation[21, 30].

Alternative pharmacological agents for sleep problems in older adults

Both the BZDs and the Z-drugs have received criticism during the last 30 years, which encouraged the search for alternative drugs. Melatonin (licensed in both the US and Europe for primary insomnia)[31], a hormone which regulates the circadian rhythm, and a melatonin receptor agonist (ramelteon, approved in the US and Japan) [32] have entered the market. Though they appear to have a good tolerability, their effect sizes are small [33, 34]. Antihistaminic drugs (diphenhydramine and doxylamine) are an over-the-counter sedative alternative. They bind non-selectively to other neurotransmitter sites which results in their undesirable anticholinergic side-effects [35]. Antidepressants, antipsychotics and anticonvulsants with sedative properties are often prescribed for patients with insomnia despite having no FDA/EMA approved indication to treat insomnia. Although these drug classes might be useful for patients with comorbid insomnia, evidence on efficacy and tolerability is lacking and they are definitely not recommended as first-line treatment [35]. Nowadays, the sedative antidepressants, mainly trazodone, are increasingly prescribed for insomnia problems [36, 37]. Till now, there is little research available on trazodone's effects and side-effects, which results in the absence of official labelling for primary insomnia [38]. Clearly, the poor evidence base for these products does not justify their widespread use.

BDZ/Z use and its relationship with depression

Another finding, which surfaced in almost all chapters, was the clear association between BZD/Z use and depressive symptoms. Not only in our studies focusing on BZD/Z use for sleep problems, but also in our study analysing antidepressant use for the overlapping indications, we saw an association between antidepressant use and BZD/Z use [39, 40].

For the indication anxiety, we observed that Belgian physicians preferred BZDs above the recommended SSRIs. In recent guidelines, BZDs are relegated for anxiety treatment only as a short-term measure during crises or can be co-administered for a short period to overcome the delayed pharmacological effect of the antidepressant. But in order to avoid dual therapy, the BZD should be tapered (after a maximum of 4 weeks) [1, 41].

We also observed an association between BZD/Z use, bad sleep and depressive symptoms. Insomnia and depression can be considered as separate disorders and co-exist, but insomnia can also be seen as a risk factor for depression [42], or even perpetuate the development of depression [43]. Moreover, sleep problems can be seen as a symptom of depression and are often integrated in the diagnostic criteria of screening for depression (Hamilton depression rating scale[44]), which makes it difficult to differentiate between pure insomnia symptoms and depressive symptoms. Moreover, depression often has an atypical presentation in older

adults, which makes a correct diagnosis difficult [45, 46]. The bidirectional relationship between insomnia and depression is complex. BZD/Zs which should in fact lessen sleep problems were linked to bad sleep and depressive symptoms, in our study as well as in other studies[39, 40]. Not treating sleep problems could provoke and worsen the depressive symptoms, although it is not well researched whether treating insomnia or depression will automatically impact the other[47]. Studies showed that non pharmacological treatments (such as patient-education and CBT) reduce sleep problems and positively affect depressive symptoms[48, 49].

Next to the BZD/Z's relationship with depression, our studies showed an association between BZD/Z use and pain and psychotropic co-mediation. Another study showed that BZD/Z use is linked to a poorer life satisfaction and more somatic and psychological symptoms [50, 51] . Are BZD/Z users more psycho-socially vulnerable? Or do they have a greater tendency to express complaints? Or both?

BZD/Z use and the risk on cognitive impairment

The link between chronic BZD/Z use and cognitive impairment has shown up in several studies [52-55]. The acute effects of BZD/Z use on memory, attention [56] and postural sway [57] have been demonstrated. The impaired attentional processes together with the sedative effects which impair reaction time and problems with balance/equilibrium lead to impaired driving and (car)accidents[58]. The effects of chronic BZD/Z use on the long-term evolution of cognition are less conclusive [59, 60]. Chronic BZD/Z users perform worse on neurocognitive testing, despite the assumed development of tolerance to the acute sedation and impaired attention[56]. However, most clinical data do not support the existence of tolerance to the BZDs' induced cognitive impairments (memory impairment) [59-61]. Studies investigating cognition upon BZD/Z withdrawal showed subtle improvements in cognitive areas [62-64], indicating a reversible cognitive impairment. However, a history of long-term daily BZD/Z use shows a persistent worse cognition compared to nonusers, even after withdrawal, indicating a persistent influence and incomplete restitution of cognitive function[65].

In our study, we measured global cognition with the MMSE, which is a much used and validated instrument to screen cognitive dysfunction in nursing home residents. However, small changes in MMSE should be interpreted with care due to measurement error, learning effects, diurnal fluctuation in alertness and regression to the mean [66, 67]. Therefore we did not focus on mean change but enhanced clinical relevance by using a cut-off (a 12 month decrease of 4 points or more on the MMSE [68, 69]. Nevertheless, this tool was too crude to detect subtle changes in cognition. The importance of cognitive testing with a sensitive cognitive testing battery at baseline and at several follow-up times should give a better idea of the impact on cognitive evolution [52]. Another strategy is to concentrate on a relevant distant outcome such as severe cognitive decline/dementia. Indeed, dementia has also been linked to BZD/Z use [70-73]. However, not controlling for the BZD/Z's indication (the reason of the initiation), and not taking into account co-morbidities, co-medications and psychological background have forced critics to question possible causality [74]. Anxiety and sleep problems (indications for BZD/Z use), but also depression are possible prodromal effects of early dementia [75]. Moreover, depression, anxiety and sleep problems can influence motivation and result in suboptimal performance (effort) on neurocognitive tests [76, 77].

In addition to our observed association between BZD/Z use, sleep problems and depression, we found a strong relationship between depression and cognitive impairment. Other studies found similar links [78, 79], indicating the existence of a complex psychopathological relationship. Moreover, depression can mimic a dementia state with cognitive deficits leading to the functional impairment of depression (pseudo-dementia). This also indicates that the overlap

between symptoms of depression and of dementia imposes a diagnostic intricacy. The influence of depression on cognitive decline is an important topic with a clinical impact, but which is difficult to research. Is depression an early-phase symptom of cognitive impairment, is it a risk factor, or is it a reaction to cognitive decline?

BZD/Z's benefit: effectiveness

Tolerance and the consequential loss of efficacy undermine the benefit of chronic BZD/Z use. There are several hypotheses on the neuro-adaptive mechanism that underlie tolerance, although there is no consensus [59]. Tolerance implies that a dose escalation is necessary in order to maintain the effects. However, we did not see dosages exceeding the DDD, suggesting that patients do not ask for a dose escalation, maybe due to the presence of a strong placebo effect.

Several meta-analysis showed that placebo treatment also improves the sleep significantly [80, 81]. Together with the publication bias[82] and the limited effect sizes[83], one may argue the additional benefit of BZD/Zs.

An ideal way to investigate effectiveness of BZD/Zs in clinical studies is to combine objective sleep recordings with a subjective sleep scale (sleep diary, sleep questionnaire). Objectifying sleep with polysomnography (PSG), which is an in-laboratory (sleep clinics) recording tool, is not feasible for long-term follow-up data. Wrist actigraphy is currently the most appropriate measure available to objectively record general sleep patterns in the non-laboratory setting, although the interpretation should be combined with sleep diaries [84]. The development and further validation of other non-invasive, inexpensive and user-friendly objective sleep measures (e.g. bed sensors and the non-contact biomotion sensor) could provide additional alternatives for the evaluation of disordered sleep [85]. Because, the patient's perception of sleep quality remains the determinant of most requests for prescribing hypnotics and is a common criterion by which the GP and patient judge efficacy, assessing subjective sleep quality is important. In 2005, Devine et al. [86] published a review on subjective measures in sleep medicine and concluded that the PSQI, a self-administered questionnaire, which we used in our studies, was an ideal patient-reported outcome instrument investigating all relevant sleep domains.

Several studies that assessed short-term effectiveness of BZD/Zs have shown significant improvements in both subjective and objective parameters in placebo arms in placebo controlled trials [81], concluding that there is a strong, clinically effective placebo response [87]. BZD and Z-drugs were always assumed to be effective on the short-term, but the existence of clinical effective placebo response, together with the existence of publication bias and sponsorship bias, indicated that the hypnotic drug effects might be overestimated [82].

Long-term effectiveness (is even more difficult to assess and) requires long-term follow-up data [88], which is not concordant with the guidelines. Till now, there is one RCT evaluating eszopicone for 6 months [89] and one study of a 1-year open-label extension phase of two RCTs of zaleplon [90], though in general, the mean duration of BZD/Z use extends the duration of these follow-up. A more feasible approach could be to follow new BZD/Z users, evaluate their sleep, both objectively and subjectively, at baseline and at fixed time points. However, in the nursing home setting, the initiation of BZD/Z is limited. In our study, the sleep quality of chronic BZD/Z users was worse compared to nonusers and more importantly, it decreased further in the one-year follow-up. This finding highlights the uncertainty regarding long-term effectiveness.

The nursing home and its impact on sleep quality: organisational influences and policy

Another finding of our observational cohort was the variation in BZD/Z use and sleep quality among the participating nursing homes. We did not collect institutional characteristics that could explain the variation among nursing homes[91]. Structure-related aspects such as ownership (private non-profit, private for profit, public), number of beds, number of GPs, and organisational-related aspects such as a pharmacist inside the nursing home, electronic prescribing (database), regular re-assessment of prescriptions could influence BZD/Z use [92]. It would be helpful to detect possible organisation-related indicators of BZD/Z use, as these are probably more easily modifiable than subject-related indicators [92]. In general, the quality of care improves when a nursing home gives appropriate attention to the different aspects of care including medication management[93, 94]. Some nursing homes and staff are aware of the abundant psychotropic medication use which could explain the difference in knowledge on and attitude towards psychotropic medication. A general knowledge of the pathophysiology of sleep by the care personnel could result in the understanding of altered sleep patterns of older adults, and deliberation of possible solutions. Shortage of staff is a barrier for promoting training and implementation of nonpharmacologic interventions to reduce BZD consumption [95]. Organisation-related aspects that can also impact sleep quality are environmental factors, such as noise and light in the homes' care routines [96, 97]. Commonly perceived subject-related causes of nocturnal wakefulness in a nursing home are nocturia and pain. Although nocturia is difficult to treat [98], some care routines could influence the sleep of the residents. Pain was in our study a defining factor of worse sleep quality. A good pain detection and management could result in better sleep [99, 100].

Approaches to discontinuation

While there is an abundance of literature about starting medications, there is a scarcity of data about discontinuation [101, 102]. In most cases, initiating a BZD/Z consequently leads to long-term continuation, and is the reason why BZD/Z use is highly prevalent among nursing home residents. Perceived effectiveness, unrecognized side-effects, and psychological and physical dependence make it more difficult for a physician to persuade their patient to try discontinuation. Moreover, physicians are not familiar with withdrawal and it has not been sufficiently implemented in daily practice.

Most older BZD/Z users for the indication insomnia are low-dose users. Gradual tapering is recommended (25% dose reduction every week or bi-weekly)[103], though abrupt discontinuation of long-term low-dose treatment seems feasible [104]. The best strategy is to remain flexible without prolonging the process [103]. Although there is not much research done on which BZD/Z is more resistant to weaning, generally, short-acting BZD/Zs are more likely to cause withdrawal symptoms upon discontinuation than long-acting BZDs. Therefore, substitution with a long-acting BZD (diazepam) can lessen (and delay) withdrawal symptoms[103]. However, it is not appropriate to use long-acting BZD/Zs in older adults (cfr. all explicit criteria). The long half-life can result in accumulation. Therefore, substitution with an intermediate working BZD/Z (lorazepam/lormetazepam) or simply stay with the same product when discontinuing is advised. Substitution with other medications is not firmly established (Lader et al 2009). Psychological interventions which aid withdrawal, such as Cognitive Behavioural Therapy (CBT), have shown to be effective [105, 106], also in older adults [107]. These psychological techniques are intended to facilitate withdrawal and motivate patients to maintain abstinent over time (relapse prevention). More importantly, they may treat any underlying psychological disorder [103, 107]. CBT includes psycho-education (advantages and disadvantages of chronic BZD/Z use), cognitive restructuring techniques (tackling unrealistic expectations, apprehension and misattribution of withdrawal symptoms) and behavioural techniques (such

as relaxation, sleep deprivation, stimulus control).

Discontinuation in the nursing home setting

In our thesis, we wanted to focus on discontinuation which is feasible in the nursing home. A meta-analysis focusing on older adults showed that the best strategy for discontinuing BZD/Z in older adults was the combination of supervised withdrawal with psychotherapy [107]. Supervising the withdrawal in a setting with supporting care personnel is possible, but delivering psychotherapy seems more difficult to implement. A promising strategy for reducing BZD/Zs in the nursing home, next to other inappropriate prescriptions, was the implementation of a (clinical) pharmacist medication review [108, 109]. Often, the pharmacists gave recommendations or feedback to the nursing staff and delivered "an educational message". Also a programme led by a psychologist which educated prescribers and caregivers, offered health education and relaxation training to the residents, reduced the overall prevalence of BZD/Z use (from 70% to 35%) in this setting [110]. The educational tools used in long-term care facilities varied from prescribing algorithms and bulletins to staff meetings and lectures [111]. But educational interventions alone cannot be expected to change behaviour when health care providers do not perceive it to be important, or when the change is complex and dependent on the interaction of many stakeholders. The nursing home is an environment where several disciplines are involved in the treatment decisions (patient, GP, specialist, geriatrician, nurse, family, pharmacists), and influence prescribing [112]. Moreover, there are several visiting GPs per nursing home and there is a large equip of nursing staff (day and night team), which makes clear straightforward communication difficult. However, a good communication is necessary to avoid contradiction and to ensure seamless care. Therefore, the educational interventions should be multi-faceted and targeting this variety of people, rather than just targeting GPs. The nursing home should invest in a well-structured medication management. There should be a periodic reassessment of the medication chart, taking into account the perception of the GP, nurse and patient. The pharmacist with his specific medication expertise could also be involved in the multidisciplinary communication between nurses and prescribers. They can monitor (chronic) consumption and advise withdrawal schemes.
Several studies have investigated BZD/Z withdrawal in the nursing home setting and focused on the success rate (focus on residents already willing to discontinue) [63, 64, 110, 113]. However, health policy makers should have an idea of the extent of the target population and the overall feasibility, including the willingness towards discontinuation in this setting. Therefore, GP, nurse, but more importantly, the patient has to be susceptible towards change. In our studies (barrier study and feasibility study), the lack of motivation seemed a strong barrier which impacts willingness. Moreover, a lack of knowledge on non-pharmacological treatments and a lack of time to administer, make it difficult for health providers to offer alternatives when withdrawal or rebound symptoms emerge. Some studies show that patients are susceptible towards change. Therefore it is advised to routinely raise the issue of discontinuation and negotiate dose reduction [26, 114]. Nevertheless, 'reluctance towards change' in this older population is expected because their sleeping pill has become a daily routine and because this frail population has limited prospects for clinical improvement.

However, discontinuing BZD/Zs has been linked to positive effects on sleep quality, cognition and quality of life [62-64]. Also in our pilot study, we saw that the residents with successful discontinuation had less midnight awakenings and perceived a better sleep quality than before the discontinuation. This can be persuasive to try discontinuation but should be further explored. An overall conclusion of our pilot study was that the willingness towards discontinuation was low, but in case the GP and resident approved, the success rate was satisfactory (66%). Moreover, if we included the residents with a dose reduction, which is an acceptable second option in older adults, the success rate was 82%. This finding indicates that for several

people the last step in a discontinuation i.e. stopping the BZD/Z is the most difficult in terms of psychological dependence.

Because of the controversy towards medication withdrawal (ethical) and because of the difficulty of monitoring study outcomes (withdrawal symptoms, sleep quality…) in residents with disorientation/dementia, we only included cognitively capable residents in our studies (observational cohort study and discontinuation study). However, there are many residents in nursing homes with dementia. The question remains whether these residents would benefit from discontinuing BZD/Zs.

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4 CHAPTER
CONCLUSION

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CONCLUSION

Based on the results in this thesis and the experiences gained during the practical realisation of this work, we present our ideas and vision for future research and possible improvement of the practice.

1. IMPLICATIONS FOR RESEARCH

Although many studies have investigated BZD/Z use, several items remain unexplored territory or should be researched more into detail.

Basic-Clinical-Pharmacological research

- The evidence base for dosing recommendations for specific indications, and for the geriatric population needs to be strengthened by including older adults in pharmacological research.

- In order to strengthen the evidence that BZDs and the newer, chemical different, Z-drugs are similar in benefits and risks, there is a need for more research which directly compares those 2 groups.

- Discontinuation schedules should be explored with specific reports for each of the BZD or Z-drug in their specific indication.

- There is a need for screening and diagnostic tools which could help prescribers to differentiate between sleep problems and several insomnia types (comorbid insomnia).

-The complex psychopathological pathways of insomnia, depression and its influence on cognitive decline need to be further investigated.

- There is a need for valuable instruments which can measure subtle cognitive evolution in nursing home residents.

- In order to investigate the effectiveness of BZD/Z use in the short-term, research which directly compares placebo groups and untreated groups are necessary to unmask the placebo effect.

- In order to investigate the long-term effectiveness, RCTs with incident users and follow-up time that exceeds 6 months are essential.

- Research on effectiveness should combine objective sleep evaluation with subjective parameters (sleep questionnaires, sleep diaries). The development and further validation of non-invasive, inexpensive and user-friendly objective sleep measures are necessary for implementation in the real-life setting.

- Further research should decide whether BZDs are effective when used chronically for anxiety problems, and whether discontinuation is possible in this indication.

- The effectiveness of trazodone for sleep problems in older adults, together with its discontinuation possibilities should be investigated.

Implementation research

- Further research should validate the improvements of psychological and behavioural treatments on sleep and should concentrate on the clinical applicability and economic feasibility of non-pharmacological approaches.

- Studies with a long follow-up, with inclusion of comorbidities, and with a sensitive cognitive testing battery at baseline and at several follow-up times should give robust findings on the impact of BZD/Zs on cognitive evolution.

- In order to corroborate the finding of improving the sleep quality upon BZD/Z discontinuation, future research should perform our pilot study on a larger scale with a matched control group, and with objective measurement tools.

- More research is needed to decide whether a discontinuation campaign in the nursing home setting is cost-effective in both cognitively competent and impaired residents and whether an expansion to the home-dwelling older adults is feasible.

2. IMPLICATIONS FOR PRACTICE

The studies and findings of this thesis have led to specific recommendations towards BZD/Z use and its discontinuation in older nursing home residents.

When we want to reduce chronic BZD/Z prescribing, we should prioritize insomnia, given its high prevalence as a primary indication. Guidelines on insomnia treatment promote investigating the cause of insomnia together with non-pharmacological treatments, such as psychotherapy, CBT and psycho-education, because they have better durability as manifested by stable gains at follow-ups. However, before treating insomnia and its possible cause, diagnostic evaluation is important. Screening for depressive symptoms should be performed routinely as they are often associated with bad sleep. Sleep diaries could help GPs in evaluating and objectifying the subjective sleep complaint of their patient. Though insomnia is a disabling disease which needs treatment, establishing a pharmacological treatment too quickly, eventually leading to chronic continuation is not favourable for the patient in the long run. Therefore, efforts to reduce initiation are fundamental. Sleep quality and possibly cognitive function are negatively affected by this medication. Good communication on time-limited use and a trade-off between benefits and risks on an individual basis can diminish the patient's request for sleeping pills and makes a proposal to discontinue more acceptable.

In the nursing home setting, where the BZD/Z use is chronic, discontinuation is feasible. However, there is a lack of willingness and a reluctance towards change which seems difficult but not impossible to overcome. Frequently perceived barriers among GPs and nurses towards discontinuation are the emerging of dependence and the persistent perception that BZD/Zs are effective, even in chronic use. As our study showed, a good sleep quality is not associated with the BZD/Z use. Informing and educating all involved actors such as prescribers, caregivers, patients and also family, on the negative effects of chronic BZD/Z use and the positive prospects of discontinuation should help to reach a consensus. Assessing the need to discontinue medication in older adults is not yet a routine procedure and is especially difficult when it concerns chronic BZD/Zs for insomnia problems, as there is a general lack of confidence in the successful outcome of BZD/Z discontinuation. Although it was not the intention of our pilot study to investigate the optimal strategy to implement discontinuation in a nursing home, our recruitment letter to the GP was a reminder of the chronic BZD/Z use of their

patients and was the trigger to question this chronic use and even try to stop. An extra visit to the resident to discuss and verify discontinuation was also supportive. In order to achieve a better quality of medication management, a regular reassessment of the medication chart is necessary. In the nursing home, both the expertise and information of the nurse and GP are necessary in this communication, but the pharmacist could contribute to this multidisciplinary consultation and even guide the medication discontinuation (withdrawal scheme). It is not sufficient that only the caregivers consider a possible discontinuation, the patient's motivation remains the determinant for success. In order to convince patients in changing their chronic therapy, GPs should be educated in motivational techniques. Moreover, non-pharmacological alternatives, manageable in the nursing homes, could support the discontinuation. Therefore GPs, nurses, but also psychologists could be educated for the guidance of the discontinuation.

In our study, we showed that once there is agreement on initiating discontinuation, the success rate is high (66% succeeded in remaining BZD/Z free for at least 8 months). Additionally, a small group discontinued to half the dose, as a full stop was not possible due to possible rebound insomnia or psychological dependence. Considering a dose reduction (even when a full BZD/Z stop does not seem feasible) is a good second option in this frail population with psychotropic polypharmacy. Our approach towards discontinuation is scalable and a commendable candidate for larger implementation programs. The nursing home may be a protected environment where GPs (and other care personnel) can familiarize with discontinuation efforts, gain confidence and even gradually extend these efforts to the large community of home dwelling older adults.

5

CHAPTER

SUMMARY / SAMENVATTING

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1. SUMMARY

With this thesis we add to the debate on the discrepancy between the existing guidelines cautioning against chronic benzodiazepine and Z-drug (BZD/Z) use and its high prevalence, especially among older nursing home residents in Belgium. In order to understand and tackle this highly prevalent BZD/Z use, we contributed to the research on the benefit/risk ratio, and on possible discontinuation in this setting.

Because most studies on BZD/Zs do not differentiate between use for insomnia or for anxiety or other indications and because guidelines on optimal geriatric dosing are vague, we explored indications and dosages of chronic BZD/Z use in a representative sample of Belgian nursing home residents (PHEBE database 2006) (Chapter 2.1). The main indication of chronic BZD use was insomnia (59%). In order to guide clinicians, we listed most of the existing dose recommendations and retrieved a pragmatic threshold, the "geriatric upper limit". Overall, BZD/Zs were used at low dosages (in terms of defined daily dosages and diazepam equivalents), but were not adapted to the geriatric population, especially in the indication insomnia. Before further focussing on BZD/Zs for insomnia, we also explored the use of antidepressants for the overlapping indications of insomnia and anxiety in the PHEBE database (Chapter 2.2). Despite the absence of clear evidence and despite the absence of official labelling, in Belgium, Europe, and the US, sedative antidepressants (mainly trazodone) are increasingly prescribed for primary insomnia without concomitant depressive symptoms (13% of all antidepressant prescribing is for the sole indication of insomnia). Although, antidepressants are advised for chronic anxiety, only 14 % of the residents with this indication received an antidepressant (mostly a Selective Serotonin Reuptake Inhibitor), and the remaining received a BZD.

In an observational cohort study (convenience sample of 10 nursing homes) of cognitively competent residents, we investigated the chronic effectiveness of BZD/Z use in terms of sleep quality (Chapter 2.3 and 2.4), and also explored the worrisome link with cognitive decline (Chapter 2.5). By implementing several exclusion criteria, we composed a well-defined cohort of chronic BZD/Z users for the indication insomnia, and a comparator group of nonusers, free of any hypnotic medication (also excluding sedative antidepressants). These two groups had similar demographical and clinical characteristics and were followed for one year. We used a self-administered questionnaire, the Pittsburgh Sleep Quality Index (PSQI), to evaluate sleep quality as perceived by the resident. The sleep quality in chronic BZD/Z users was significantly worse compared to nonusers both at baseline and at one-year follow-up. More specifically, chronic BZD/Z users reported more difficulties with falling asleep, reported a higher frequency of midnight awakenings, and a higher frequency of not being well rested in the morning. The one-year follow-up results revealed that the sleep quality of the BZD/Z users deteriorated significantly. The comorbidity 'depression' was in this study a significant factor in worsening sleep quality.

In addition to other possible risk factors, we wanted to explore the impact of BZD/Zs on a clinically relevant decrease in cognition (Chapter 2.5). We measured global cognition with the Mini Mental State Examination (MMSE). We found that the general cognition of nursing home residents decreased significantly in one year, both in the group of BZD/Z users and in the nonusers, but there was no significant difference in mean MMSE decrease between those two groups. When focusing on clinically relevant cognitive decrease, there were 34% BZD/Z users with severe deterioration (decrease of 4 or more points in one year) compared to 27% nonusers, but this small difference was not significant. The strong risk factor for fast cognitive decline was 'depression'.

An interesting finding in our five studies was the appearance of a relationship between BZD/Z use, depression, sleep problems and cognitive impairment, indicating the existence of a complex relationship.

In order to tackle the highly prevalent BZD/Z use among nursing homes residents, the focus should be on discontinuation, since for most residents the use is already established before their admission to the nursing home (Chapters 2.6 and 2.7). The nursing home, which is a more controlled setting, can be valuable to guide BZD/Z discontinuation in this older population. Moreover, GPs and other care personnel can familiarize with discontinuation efforts, and possibly extend these efforts to the large community of home dwelling older adults.

First, we performed a cross-sectional survey on perceptions of benefit and harm, the willingness to stop and perceptions towards barriers against discontinuation of BZD/Zs among the two main caregivers in the nursing home setting, the GP and nurse (Chapter 2.6). We approximated the real-life setting by focusing on perceptions pertaining to an individual resident. GPs as well as nurses considered the chronic use of BZD/Zs to be still effective and did not report many noticeable side-effects, except for dependence. Together with the expected resistance from the resident, all these factors contributed to the low willingness to discontinue BZD/Zs; GPs were willing in one third, while nurses were willing in one fifth of their residents. Overall, the level of agreement between GP and nurse was low, which illustrates the need for more structured interdisciplinary contacts.

Finally, in a pilot study in 5 nursing homes, we assessed the overall feasibility, incorporating both the willingness towards discontinuation and also the success rate of discontinuation, with a follow-up of 8 months (Chapter 2.7). Our focus on cognitively competent residents, using BZD/Z only for insomnia led to a small sample of 135 eligible residents on a total of 823. Our minimal intervention, sending a recruitment letter to the GP of each BZD/Z user and obtaining informed consent in those residents where the GP agreed, showed that in only 38 residents both GP and resident were willing to discontinue. Lack of motivation was the main barrier to refuse discontinuation. Nevertheless, discontinuation of chronic BZD/Z use in those 38 nursing home residents was feasible without noticeable withdrawal symptoms, without a switch to other medication, without a detrimental effect on quality of life, and with a positive effect on the sleep quality. Our analysis at 8 month follow-up showed that 66% succeeded in stopping their BZD/Z use. Moreover, if we included also the residents with a dose reduction, which is an acceptable second option in this frail population with psychotropic polypharmacy, the success rate was 82%. Our approach towards discontinuation is scalable and a commendable candidate for larger implementation programs.

2. SAMENVATTING

Met deze doctoraatsthesis willen wij een bijdrage leveren aan het onderzoek naar het hoge gebruik van benzodiazepines en gerelateerde Z-medicatie (BZD/Z) en de betwistbare risico-baten balans van dit chronisch gebruik. We concentreerden ons op de grootste gebruikersgroep, de oudere rusthuisresidenten, en focusten op het gebruik voor slaapproblemen. Met deze thesis onderzochten we naast het hoge gebruik, ook de mogelijke stopzetting van chronisch BZD/Z gebruik in deze setting.

Omdat de meeste studies geen onderscheid maken tussen BZD/Z gebruik voor slaapproblemen, voor angst, of voor andere indicaties, en omdat richtlijnen over doseringen bij ouderen vaag zijn, hebben wij de indicaties en gerelateerde dosissen van BZD/Z gebruik in een representatieve steekproef van Belgische rusthuisresidenten (PHEBE database 2006) onderzocht (Hoofdstuk 2.1). De meest voorkomende indicatie voor chronisch BZD/Z gebruik was slaapproblemen (59%). Om een leidraad te bieden aan clinici hebben we bestaande doseringsaanbevelingen geanalyseerd en samengevat in een pragmatische "geriatrische maximale dosis". De gerapporteerde dosissen waren voor alle indicaties niet echt hoog, maar waren niet aangepast aan de geriatrische populatie.

Alvorens we ons verder hebben toegespitst op BZD/Z gebruik voor slaapproblemen, onderzochten we in dezelfde PHEBE databank het antidepressiva gebruik voor de overlappende indicaties (slaapproblemen en angst) (Hoofdstuk 2.2). Ondanks het ontbreken van bewijs van effectiviteit én het uitblijven van officiële registratie worden sederende antidepressiva (voornamelijk trazodon) steeds meer voorgeschreven voor insomnia, zonder dat er depressieve symptomen aanwezig zijn. Wij vonden dat voor de indicatie chronische angst, er slechts in 14% een antidepressivum werd voorgeschreven, en voor het overgrote deel een BZD. Nochtans stellen richtlijnen bepaalde antidepressiva (selectieve serotonine heropname remmers) voor als eerste keuze.

In een observationele cohort studie van cognitief bekwame rusthuisbewoners onderzochten we het langdurig effect van BZD/Z gebruik op de slaapkwaliteit (Hoofdstuk 2.3 en 2.4) en het risico van chronisch BZD/Z gebruik op de cognitieve achteruitgang (Hoofdstuk 2.5). In een willekeurige steekproef van 10 rusthuizen, groepeerden we chronische gebruikers van BZD/Zs voor de indicatie slaapproblemen en een controle groep van niet-gebruikers, vrij van allerhande slaapmedicatie. Deze twee gedefinieerde groepen volgden we gedurende 1 jaar. Omdat de slaapperceptie van de patiënt de bepalende factor is voor het beoordelen van de slaapkwaliteit, gebruikten we een vragenlijst die de patiënt zelf moest invullen, namelijk de gevalideerde Pittsburgh Sleep Quality Index (PSQI). Aan de hand van dit instrument konden we besluiten dat de slaapkwaliteit van chronische BZD/Z gebruikers slechter was dan deze van de niet-gebruikers, zowel bij baseline als na 1 jaar follow-up. Meer in detail, de BZD/Z gebruikers hadden meer moeite met inslapen, rapporteerden meer nachtelijke ontwakingen en waren niet voldoende uitgerust 's morgens. Tijdens de 1-jaar follow-up werd de slaapkwaliteit significant slechter in de BZD/Z groep, waar dit in de controle groep niet significant was. Een grote invloed op de slechter wordende slaap was de co-morbiditeit 'depressie'.

Naast andere beïnvloedende factoren onderzochten we of chronisch BZD/Z gebruik een impact had op de klinisch relevante cognitieve achteruitgang. We gebruikten het gevalideerde Mini Mental State Examination instrument om de globale cognitie te screenen. We vonden dat de algemene cognitie significant daalde tijdens de 1-jaar follow-up, zowel in de groep van chronische BZD/Z gebruikers als in de controle groep van niet-gebruikers. Wanneer we

focusten op klinisch relevante cognitieve achteruitgang, zagen we procentueel meer BZD/Z gebruikers met een grotere achteruitgang (MMSE daling van minstens 4 punten op een totaal van max 30 punten), hoewel dit kleine verschil niet significant was (34% vs. 27%). De meest bepalende risicofactor voor snelle cognitieve achteruitgang was depressie.

Een interessante bevinding in ons onderzoek die zeker verder onderzocht moet worden was het opduiken van de relatie tussen BZD/Z gebruik, slechte slaap, depressie, en cognitieve achteruitgang.

Indien we het chronisch BZD/Z gebruik in de rusthuissetting willen aanpakken, zullen we ons moeten richten op afbouw en stopzetting, omdat deze medicatie gewoonlijk opgestart werd voor opname in het rusthuis. De rusthuissetting is een waardevolle gecontroleerde setting om BZD/Z afbouw te monitoren in de oudere populatie.

Een eerste exploratie van de percepties over afbouw van BZD/Zs verkregen we in een cross-sectionele studie bij huisartsen en verpleegkundigen (Hoofdstuk 2.6). Aan de hand van een vragenlijst onderzochten we percepties tegenover de risico-baten verhouding, de bereidheid tot stoppen en eventuele barrières tegenover stoppen. We benaderden de real-life situatie door steeds te focussen op een specifieke resident met chronisch BZD/Z gebruik. De huisartsen en verpleegkundigen beschouwden het gebruik van BZD/Zs nog steeds als effectief en ze rapporteerden buiten afhankelijkheidsproblemen, nauwelijks bijwerkingen. Samen met de verwachte weerstand bij de patiënt, zorgden deze factoren voor een algemene lage bereidheid tot afbouw: huisartsen waren bereid bij 1 op 3, en verpleegkundigen bij 1 op 5 bewoners. Over het algemeen was de onderlinge overeenstemming tussen huisartsen en verpleegkundigen laag, wat er op wijst dat gestructureerde overlegmomenten noodzakelijk zijn.

In onze pilootstudie in 5 rusthuizen onderzochten we de algehele haalbaarheid van afbouw in deze setting. We onderzochten zowel de bereidheid tot afbouw, alsook het slaagpercentage van afbouw in een pilootstudie met 8 maand follow-up (Hoofdstuk 2.7). Onze focus op cognitief gave bewoners met chronisch BZD/Z gebruik voor slaapproblemen leidde tot een kleine sample van 135 geschikte bewoners (op een totaal bewonersaantal van 823). Onze minimale interventie bestond uit het versturen van een rekruteringsbrief naar de huisarts van de chronisch BZD/Z gebruiker en, bij akkoord van de huisarts, het vragen van medewerking aan de resident. In slechts 38 bewoners waren zowel huisarts als bewoner bereid tot afbouw. Een tekort aan motivering was de voornaamste barrière tegenover afbouw. We konden aantonen dat na 8 maand 66% erin slaagde te stoppen, zonder afbouwsymptomen, zonder een switch naar andere medicatie, zonder een negatieve invloed op de levenskwaliteit, én met een positief effect op de slaap. Daarbovenop waren er ook enkele bewoners die hun BZD/Z dosis halveerden, wat ook een wenselijk gevolg is bij ouderen. Deze aanpak kan toegepast worden op grotere schaal, het maakt de huisarts (en verpleegkundigen) vertrouwd met afbouw, en kan eventueel leiden tot een uitbreiding naar de thuiswonende ouderen.

6 CHAPTER
ADDENDUM (questionnaires)

1. ADL / Katz schaal

reference: Katz & Akpom, 1976

CRITERIUM	Baseline Score	Score 2	1	2	3	4
WASSEN			kan zichzelf helemaal wassen zonder enige hulp	heeft gedeeltelijke hulp nodig om zich te wassen boven of onder de gordel	heeft gedeeltelijk hulp nodig om zich te wassen zowel boven als onder de gordel	moet volledig worden geholpen om zich te wassen zowel boven als onder de gordel
KLEDEN			kan zich helemaal aan- en uitkleden zonder enige hulp	heeft gedeeltelijke hulp nodig om zich te kleden boven of onder de gordel (zonder rekening te houden met de veters)	heeft gedeeltelijke hulp nodig om zich te kleden zowel boven als onder de gordel	moet volledig worden geholpen om zich te kleden zowel boven als onder de gordel
VERPLAAT SINGEN			is zelfstandig voor de transfer en kan zich volledig zelfstandig verplaatsen zonder mechanisch(e) hulpmiddel(en) of hulp van derden	is zelfstandig voor de transfer en voor zijn verplaatsingen, mits het gebruik van mechanisch(e) hulpmiddel(en) (kruk(ken), rolstoel,...)	heeft volstrekte hulp van derden nodig voor minstens één van de transfers en/of zijn verplaatsingen	is bedlegerig of zit in een rolstoel en is volledig afhankelijk van anderen om zich te verplaatsen
TOILET BEZOEK			kan alleen naar het toilet gaan, zich kleden en zich reinigen	heeft hulp nodig voor één van de 3 items: zich verplaatsen of zich kleden of zich reinigen	heeft hulp nodig voor twee van de 3 items: zich verplaatsen en/of zich kleden en/of zich reinigen	heeft hulp nodig voor de 3 items: zich verplaatsen en zich kleden en zich reinigen
CONTINEN TIE			is continent voor urine en faeces	is accidenteel incontinent voor urine of faeces (inclusief blaassonde of kunstaars)	is incontinent voor urine (inclusief mictietraining) of voor faeces	is incontinent voor urine en faeces
ETEN			kan alleen eten en drinken	heeft vooraf hulp nodig om te eten of te drinken	heeft gedeeltelijk hulp nodig tijdens het eten of drinken	de patiënt is volledig afhankelijk om te eten of te drinken

CRITERIUM			1	2	3	4
TIJD			geen probleem	nu en dan, zelden probleem	bijna elke dag probleem	volledig gedesoriënteerd of onmogelijk te evalueren
PLAATS			geen probleem	nu en dan, zelden probleem	bijna elke dag probleem	volledig gedesoriënteerd of onmogelijk te evalueren

2. MINI MENTAL STATE EXAMINATION -MMSE

reference: Folstein 1975

Mini-Mental State Examination (MMSE)

Patiënt:	Datum:
Onderzoeker:	Score: /30

1. Oriëntatie in tijd en ruimte

- **Wat is de volledige datum van vandaag?**

1.1. Tijd: Ken 1 punt per correct antwoord toe (score: 0-5)

• **In welk jaartal zijn we?**	Jaartal	☐
• **In welk seizoen zijn we?**	Seizoen	☐
• **In welke maand zijn we?**	Maand	☐
• **Welke dag is het vandaag?**	Dag	☐
• **De hoeveelste is het vandaag?**	Datum	☐

1.2. Ruimte: (score 0-5)

• **In welk land leven wij?**	Land	☐
• **In welke provincie zijn we?**	Provincie	☐
• **In welk(e) stad/dorp zijn we?**	Stad	☐
• **In welk hospitaal/centrum bent u?** *of* **Hoe is mijn naam?**	Centrum	☐
• **Op welke verdieping bent u?**	Verdieping	☐

2. Inprentingsvermogen

- **Ik noem drie woorden. Als ik ze gezegd heb, moet u ze alle drie herhalen.**
  Lees de woorden voor aan 1 woord per seconde. Laat ze daarna herhalen en noteer elk correct woord. (1 punt voor elk correct antwoord – score 0-3)

• **Sigaar**	Sigaar	☐
• **Bloem**	Bloem	☐
• **Deur**	Deur	☐

Als de patiënt ze niet correct herhaalt, zeg ze dan opnieuw voor en herhaal tot 6 maal.
Tel hier echter géén punten voor. Aantal pogingen: ☐
Onthoud deze woorden goed, want ik ga ze u straks nog eens vragen.

3. Aandacht

A. **Wilt u van het getal 100, 7 aftrekken?**
Van de uitkomst trekt u dan telkens weer 7 af en zo verder tot ik "stop" zeg.
Elke juiste aftrekking levert 1 punt op (vb. 93, 87, 80, 72, 65 geeft een score van 3).
Wanneer de eerste berekening foutief is, wordt dit als foutief aangerekend maar wel gecorrigeerd.
Daarna vraagt u: "Hoeveel is 93 min 7?" Vanaf dan vraagt u: "En verder?"

	(93)	☐
	(86) of -7	☐
	(79) of -7	☐
	(72) of -7	☐
	(65) of -7	☐

B. **Wilt u het woord "dorst" van achteren naar voren spellen?**

(1 punt voor elke correcte letter op de juiste plaats)	T	☐
	S	☐
	R	☐
	O	☐
	D	☐

Zowel test 3A als 3B worden afgenomen.
Vergelijk de scores van test A en test B en weerhoud enkel de hoogste score.
Schrap de andere en tel die niet mee in de eindscore.

Hoogste score: ☐

4. Geheugen

- **Welk waren de drie woorden die u moest onthouden?**

(score 0-3)

	Sigaar ☐
	Bloem ☐
	Deur ☐

5. Taal

5.1. Benoemen

• **Wat is dit?** Wijs een horloge aan.	Horloge ☐
• **Wat is dit?** Wijs een potlood aan.	Potlood ☐

5.2. Herhalen

• **Wilt u de volgende zin herhalen: "Geen als, en of maar".**	Correct ☐

5.3. Begrip

- **Neem dit papier met uw rechterhand, vouw het in twee en leg het op de grond.**

(1 punt voor elke goede handeling)	Neemt papier ☐
	Vouwt papier ☐
	Legt op grond ☐

5.4. Lezen

- **Lees wat op dit papier staat en doe wat gevraagd wordt.**

Hou het papier omhoog, waarop staat 'SLUIT UW OGEN'	Sluit ogen ☐

5.5. Schrijven

- **Kan u voor mij een zin opschrijven?**

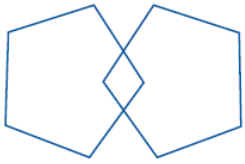
De zin moet een onderwerp en werkwoord bevatten en betekenis hebben. Fouten in de spelling en grammatica worden niet beoordeeld.	Zin ☐

6. Constructieve vaardigheid

- **Kan u deze figuur natekenen?**

Toon de twee vijfhoeken.
Voor een correct antwoord moeten er tien hoeken zijn, waarvan er twee mekaar kruisen.

Figuur ☐



Totaalscore

Tel alle goede antwoorden op (let op bij test 3A en 3B) en noteer het totaal in de rechterbovenhoek (maximumscore = 30)

3. PITTSBURGH SLEEP QUALITY INDEX-PSQI

reference: Buysse 1989 & Verster 2008 (Dutch translation)

DEEL 1: ***Vul het gepaste antwoord in de kadertjes in.***

Vraag 1: Om hoe laat wou je gewoonlijk gedurende de afgelopen maand 's avonds gaan slapen?

- Gebruikelijke bedtijd:

Vraag 2: Hoeveel minuten duurde het de voorbije maand gewoonlijk elke nacht vooraleer je in slaap viel?

- Aantal minuten:

Vraag 3: Hoe laat werd je gedurende de afgelopen maand 's ochtends gewekt?

- Gebruikelijk tijdstip van opstaan:

Vraag 4: Aan hoeveel uren SLAAP kwam je gemiddeld per nacht tijdens de voorbije maand? (Dit aantal kan verschillen van de het aantal uren dat je in bed doorbracht)

- Aantal uren ECHTE SLAAP per nacht:

DEEL 2: ***Zet bij de volgende vragen een kruisje in het vakje onder het antwoord dat op u van toepassing is. Sla geen vragen over.***

Vraag 5: Hoe vaak had je tijdens de voorbije maand moeilijkheden met slapen, omdat je…
(zie stellingen: a - j)

	Niet tijdens de voorbije maand (0)	Minder dan 1x per week (1)	1 of 2x per week (2)	3 of meer keer per week (3)
a. niet in slaap kon vallen binnen de 30 minuten				
b. midden in de nacht of in de vroege morgen wakker werd				
c. naar het toilet moest gaan				
d. niet makkelijk kon ademhalen				
e. luid hoestte of snurkte				
f. het te koud had?				
g. het te warm had?				
h. nachtmerries had?				
i. pijn had?				
j. (een) andere reden(en) had?				
Omschrijf je probleem:	…….....			

DEEL 3 : ***Zet een kruisje in het vakje bij het antwoord dat voor jou het meeste van toepassing is. Sla geen vragen over.***

Vraag 6 Wat vind je van je slaapkwaliteit de afgelopen maand?	ik slaap zeer goed (0)	ik slaap redelijk goed (1)	ik slaap eerder slecht (2)	ik slaap zeer slecht (3)
Vraag 7 Neem je 's avonds medicatie om te slapen?	niet tijdens de voorbije maand (0)	minder dan 1x per week (1)	1 of 2 maal per week (2)	3 of meer maals per week (3)
Vraag 8 Hoe vaak had je het de voorbije maand moeilijk om wakker te blijven tijdens je dagelijkse activiteiten zoals eten, radio luisteren, tv kijken	niet tijdens de voorbije maand (0)	minder dan 1x per week (1)	1 of 2 maal per week (2)	3 of meer maals per week (3)
Vraag 9 In welke mate was het de voorbije maand een probleem voor je om uitgerust aan de dag te beginnen? Je voelde je 's ochtends bij het ontwaken nog te moe om je uitgeslapen te voelen?	geen enkel probleem (0)	slechts een klein probleem (1)	toch wel een probleem (2)	heel groot probleem (3)

4. GERIATRIC DEPRESSION SCALE (GDS-8)

reference: Jongenelis et al 2007, Smallbrugge et al 2008

GDS 8 punten schaal

Zet een cirkeltje om het antwoord dat op u van toepassing is.

	JA	NEEN
1. Bent u innerlijk tevreden met uw leven?		
2. Hebt u het gevoel dat u leven leeg is?		
3. Verveelt u zich vaak?		
4. Hebt u meestal een goed humeur?		
5. Voelt u zich meestal wel gelukkig?		
6. Voelt u zich vaak hopeloos?		
7. Vindt u het fijn om te leven?		
8. Hebt u het gevoel dat uw situatie hopeloos is?		

SOCIALE CONTACTEN

Doet u volgende zaken regelmatig? (minstens 1x / week)

Meedoen aan sociale activiteiten $_0$ NEEN $_1$ JA

Bezoek van buitenaf $_0$ NEEN $_1$ JA

Bezoek van mede-bewoners $_0$ NEEN $_1$ JA

Lezen $_0$ NEEN $_1$ JA

Geheugenspelletjes (kruiswoord/sudoku/…) $_0$ NEEN $_1$ JA

TV kijken $_0$ NEEN $_1$ JA

Gemeenschappelijk eten met rusthuisbewoners $_0$ NEEN $_1$ JA

Ergotherapie? $_0$ NEEN $_1$ JA

PIJN BEVRAGING

Hebt u regelmatig pijn? $_0$ NEEN $_1$ JA

Zo ja: Hoeveel? $_1$ Dagelijks $_2$ Wekelijks $_3$ Maandelijks $_3$ Minder

Overdag? $_0$ NEEN $_1$ JA

'S nachts? $_0$ NEEN $_1$ JA

Hoe sterk kan die pijn zijn? …….. (gezichtjes 'mosby schaal')

6. QUESTIONNAIRES CHAPTER 6

developed specifically for our research

Universiteit Antwerpen
Masteropleiding Verpleeg- en Vroedkunde

Studienummer wzc ☐☐☐

Studienummer resident ☐☐☐

Onderzoek naar het chronisch gebruik van benzodiazepine bij rusthuisresidenten

VRAGENLIJST RESIDENT

Gelieve hieronder de gegevens van de resident aan te kruisen of in te vullen.
Alvast bedankt voor uw medewerking aan dit onderzoek.

1. PERSOONSKENMERKEN VAN DE RESIDENT	
1.1.	**Wat is het geslacht van de resident?**
	1 ☐ man 2 ☐ vrouw
1.2.	**Wat is de leeftijd van de resident?**
	…… jaar
2. VERBLIJFSGEGEVENS VAN DE RESIDENT	
2.1.	**Hoelang verblijft de resident al in dit woon- zorgcentrum?**
	……. jaar …… maanden
2.2.	**Verblijft de resident op een open of gesloten afdeling?**
	1 ☐ open 2 ☐ gesloten
3. BIJKOMENDE GEGEVENS VAN DE RESIDENT	
3.1.	**Gelieve de Katz- schaal van deze resident in te vullen** *(zie ommezijde)*
3.2.	**Wat is het resultaat van de meest recente MMSE- score?**
	Totaalscore: ……/30
3.3.	**Gelieve de merknaam of stofnaam van benzodiazepine of z-drug te noteren, totale voorgeschreven dagelijkse dosis en moment van inname (medicatiefiche)**
	Merknaam of stofnaam / Totale voorgeschreven dagelijkse dosis / Toedieningsmoment: 8-12-17-20u

UNIVERSITEIT GENT

Universiteit Antwerpen

Masteropleiding Verpleeg- en Vroedkunde

Studienummer wzc ☐☐☐

Studienummer huisarts A☐☐

Onderzoek naar het chronisch gebruik van benzodiazepine bij rusthuisresidenten

VRAGENLIJST HUISARTS (deel 1)

Gelieve hieronder uw gegevens aan te kruisen of in te vullen. Indien u als huisarts meerdere residenten hebt die aan deze studie deelnemen, dient u dit formulier slechts één keer in te vullen. Alvast bedankt voor uw medewerking aan dit onderzoek.

1. ALGEMENE KENMERKEN

1.1. Wat is uw geslacht?

1 ☐ man 2 ☐ vrouw

1.2. Wat is uw leeftijd?

…… jaar

1.3. Hoelang werkt u al als huisarts?

…… jaar

1.4. Hoelang komt u al in dit woon- zorgcentrum langs?

…… jaar

1.5. Bent u CRA van het woon- zorgcentrum waar het onderzoek door gaat?

0 ☐ neen 1 ☐ ja

1.6. Indien u geen CRA bent: Hoeveel keer hebt u in 2011 met CRA overleg gehad?
(overleg= overleg dat wordt gehouden tussen de CRA en de huisarts en waarvan een verslag terug te vinden is)

…… keer

2. ALGEMENE HOUDING OVER MOGELIJKE BARRIÈRES VOOR HET AFBOUWEN OF STOPZETTEN VAN BENZODIAZEPINE (BENZO) OF Z-DRUG

In dit deel kan u een antwoord geven op de mate waarin u volgende stellingen als een barrière (belemmering) ervaart. Duid met een kruisje aan in welke mate dat overeenkomt met uw ervaring; van geen barrière (in geen mate) tot een sterke barrière (in sterke mate).

Barrière	*Score*
1.Ik heb onvoldoende noodzakelijke wetenschappelijke informatie om benzo of z-drug af te bouwen of stop te zetten.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate

2. Ik heb onvoldoende kennis over mogelijke alternatieven om problemen bij afbouwen of stopzetten van benzo of z-drug op te vangen.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate

Barrière	*Score*
3. Het uitproberen van alternatieven voor benzo of z-drug kost teveel tijd en moeite.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate
4. De afwezigheid van een psycholoog in het wzc vormt een barrière om de afbouw of het stopzetten van benzo of z-drug te ondersteunen.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate
5. Het ritme in het wzc (het vroege slapen gaan) vormt een barrière om te kunnen afbouwen of stoppen met benzo of z-drug.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate
6. Hoe langer de resident de benzo of z-drug neemt, hoe moeilijker het is om af te bouwen of te stoppen.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate
7. Het overlegmoment tussen huisarts en verpleegkundige is te kort om over afbouwen of stopzetten van benzo of z-drug te praten.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate
8. Het gebruik van een elektronisch herhalingsmedicatie-voorschrift zorgt ervoor dat er niet kan overlegd worden over eventueel afbouwen of stopzetten van benzo of z-drug.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate
9. Het ontbreken van een apotheker verbonden aan het wzc vormt een barrière om het afbouwen of stopzetten van benzo of z-drug te ondersteunen.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate
10. De leeftijd van residenten en het langdurig gebruik van benzo of z-drug maken het zinloos om af te bouwen of te stoppen.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate

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Onderzoek naar het chronisch gebruik van benzodiazepine bij rusthuisresidenten

VRAGENLIJST HUISARTS (deel 2)

*Gelieve hieronder de gegevens voor **elke geselecteerde patiënt** aan te kruisen of in te vullen.*
Alvast bedankt voor uw medewerking aan dit onderzoek.

1. INDICATIE EN GEBRUIK VAN BENZODIAZEPINE (BENZO) OF Z-DRUG BIJ ***DEZE RESIDENT***

1.1. Voor welke indicatie werd de benzo of z-drug bij deze resident voorgeschreven?
(meerdere antwoorden zijn mogelijk)

1 ☐ slapeloosheid
2 ☐ angst
3 ☐ depressie
4 ☐ kalmering (acute agitatie)
5 ☐ ik weet het niet
6 ☐ andere:…….

1.2. A. Waar is deze resident met de benzo of z-drug gestart?

0 ☐ onbekend *(ga naar vraag 1.3)*
1 ☐ gestart alvorens het verblijf in het wzc *(ga naar vraag B)*
2 ☐ gestart tijdens het verblijf in het wzc *(ga naar vraag B)*
3 ☐ gestart tijdens ziekenhuisopname gedurende het verblijf in het wzc *(ga naar vraag B)*

B. Hoelang gebruikt de resident de benzo of z-drug?

…… jaren …… maanden

1.3. Werd er het afgelopen jaar…?

1	overwogen om de dosis te **verminderen**?	0 ☐ neen	1 ☐ ja
2	een poging ondernomen om de dosis te **verminderen**?	0 ☐ neen	1 ☐ ja
3	overwogen om te **stoppen**?	0 ☐ neen	1 ☐ ja
4	een poging ondernomen om te **stoppen**?	0 ☐ neen	1 ☐ ja

1.4. Zou volgens u de benzo of z-drug bij deze rusthuisresident kunnen gestopt worden?

0 ☐ neen 1 ☐ ja
reden: ……..

1.5. Hebt u de indruk dat het gebruik van benzo of z-drug bij deze resident het gewenste effect geeft? *(het gewenste effect is goede slaapkwaliteit, minder angstig of minder depressief)*

0 ☐ neen 1 ☐ ja

1.6. Zijn er volgens u bijwerkingen van benzo of z-drug merkbaar bij deze resident?
(meerdere antwoorden zijn mogelijk)

1 ☐ slaperigheid overdag
2 ☐ verwardheid
3 ☐ spierzwakte
4 ☐ concentratiestoornis
5 ☐ apathie
6 ☐ geheugenstoornis
7 ☐ duizeligheid
8 ☐ afhankelijkheid (fysisch)
9 ☐ afhankelijkheid (psychisch)
10 ☐ ik weet het niet
11 ☐ geen
12 ☐ andere: ……

2. MOGELIJKE BARRIÈRES OM EEN AFBOUWPOGING VAN BENZODIAZEPINE (BENZO) OF Z-DRUG BIJ **DEZE RESIDENT** TE ONDERNEMEN

In dit deel kan u een antwoord geven op de mate waarin u volgende stellingen als een barrière (belemmering) ervaart. Duid met een kruisje aan in welke mate dat overeenkomt met uw ervaring bij deze resident; van geen barrière (in geen mate) tot een sterke barrière (in sterke mate).

Barrière	*Score*
1. Bij afbouw of stopzetten van benzo of z-drug vrees ik dat de initiële problemen bij deze resident zullen terugkomen.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate
2. Bij afbouw of stopzetten van benzo of z-drug vrees ik dat de zorglast voor het personeel zal toenemen.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate
3. Bij afbouw of stopzetten van benzo of z-drug vrees ik dat bij deze resident mogelijke ongewenste symptomen zullen optreden.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate
4. Het afbouwen of stopzetten van benzo of z-drug is niet nodig zolang deze resident goed functioneert.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate
5. Bij afbouw of stopzetten van benzo of z-drug vrees ik dat de resident zelf niet gemotiveerd is.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate
6. Bij afbouw of stopzetten van benzo of z-drug vrees ik dat de familie zich hier tegen zal verzetten.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate
7. Bij afbouw of stopzetten van benzo of z-drug bij deze resident vrees ik dat het personeel niet gemotiveerd is.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate
8. Bij deze resident gaat mijn voorkeur naar medicatie in plaats van een niet-medicamenteuze behandeling.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate

UNIVERSITEIT GENT Universiteit Antwerpen
Masteropleiding Verpleeg- en Vroedkunde

Studienummer wzc ☐☐☐

Studienummer verpleegkundige V☐☐

Onderzoek naar het chronisch gebruik van benzodiazepine bij rusthuisresidenten

VRAGENLIJST VERPLEEGKUNDIGE (deel 1)

Gelieve hieronder uw gegevens aan te kruisen of in te vullen. Indien meerdere residenten van uw afdeling deelnemen aan dit onderzoek, dient u dit formulier slechts één keer in te vullen.
Alvast bedankt voor uw medewerking aan dit onderzoek.

1. ALGEMENE KENMERKEN

1.1. Wat is uw geslacht?
1 ☐ man 2 ☐ vrouw

1.2. Wat is uw leeftijd?
…… jaar

1.3. Wat is uw hoogst behaalde diploma?
1 ☐ master in de verpleeg- en vroedkunde
2 ☐ bachelor/ gegradueerde verpleegkundige (A1)
3 ☐ gediplomeerde/ gebrevetteerde verpleegkundige (A2)
4 ☐ verpleegassistente

1.4. Heeft u een bijkomende opleiding in de gezondheidszorg gevolgd?
(vb: beroepstitel/ beroepsbekwaamheid in geriatrie, palliatieve zorg, dementie)
0 ☐ neen 1 ☐ ja

1.5. Hoeveel uren vorming heeft u in 2011 gevolgd? *(banaba of vormingsuren waarvoor u educatief verlof kreeg niet meegeteld)*
…… uren

1.6. Hoeveel jaren werkt u al in de gezondheidszorg?
…… jaren

1.7. Hoeveel jaren werkt u in dit woon- zorgcentrum?
…… jaren

1.8. Wat is uw huidige functie?
1 ☐ hoofdverpleegkundige 2 ☐ verpleegkundige

1.9. Wat is uw huidig arbeidsregime?
…… %

1.10. Hoeveel keer per week zet u medicatie klaar? *(aantal)*
…… keer

1.11. Hoeveel keer per week deelt u medicatie uit? *(aantal)*

2. ALGEMENE HOUDING OVER MOGELIJKE BARRIÈRES VOOR HET AFBOUWEN OF STOPZETTEN VAN BENZODIAZEPINE (BENZO) OF Z-DRUG	
In dit deel kan u een antwoord geven op de mate waarin u volgende stellingen als een barrière (belemmering) ervaart. Duid met een kruisje aan in welke mate dat overeenkomt met uw ervaring; van geen barrière (in geen mate) tot een sterke barrière (in sterke mate).	
Barrière	***Score***
1. Ik heb onvoldoende noodzakelijke wetenschappelijke informatie om benzo of z-drug af te bouwen of stop te zetten.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate
2. Ik heb onvoldoende kennis over mogelijke alternatieven om problemen bij afbouwen of stopzetten van benzo of z-drug op te vangen.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate
3. Het uitproberen van alternatieven voor benzo of z-drug kost teveel tijd en moeite.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate
4. De afwezigheid van een psycholoog in het wzc vormt een barrière om de afbouw of het stopzetten van benzo of z-drug te ondersteunen.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate
5. Het ritme in het wzc (het vroege slapen gaan) vormt een barrière om te kunnen afbouwen of stoppen met benzo of z-drug.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate
6. Hoe langer de resident de benzo of z-drug neemt, hoe moeilijker het is om af te bouwen of te stoppen.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate
7. Het overlegmoment tussen huisarts en verpleegkundige is te kort om over afbouwen of stopzetten van benzo of z-drug te praten.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate
8. Het gebruik van een elektronisch herhalingsmedicatie-voorschrift zorgt ervoor dat er niet kan overlegd worden over eventueel afbouwen of stopzetten van benzo of z-drug.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate
9. Het ontbreken van een apotheker verbonden aan het wzc vormt een barrière om het afbouwen of stopzetten van benzo of z-drug te ondersteunen.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate
10. De leeftijd van de resident en het langdurig gebruik van benzo of z-drug maken het zinloos om af te bouwen of te stoppen.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate

UNIVERSITEIT GENT
Universiteit Antwerpen
Masteropleiding Verpleeg- en Vroedkunde

Studienummer wzc ☐☐☐
Studienummer verpleegkundige V☐☐
Studienummer resident ☐☐☐

Onderzoek naar het chronisch gebruik van benzodiazepine bij rusthuisresidenten

VRAGENLIJST VERPLEEGKUNDIGE (deel 2)

*Gelieve hieronder de gegevens voor **elke geselecteerde resident** aan te kruisen of in te vullen.*
Alvast bedankt voor uw medewerking aan dit onderzoek.

1. INDICATIE EN GEBRUIK VAN BENZODIAZEPINE (BENZO) OF Z-DRUG BIJ ***DEZE RESIDENT***

1.1. Voor welke indicatie werd de benzo of z-drug bij deze resident voorgeschreven?
(meerdere antwoorden zijn mogelijk)

1 ☐ slapeloosheid
2 ☐ angst
3 ☐ depressie
4 ☐ kalmering (acute agitatie)
5 ☐ ik weet het niet
6 ☐ andere:……

1.2. A. Waar is deze resident met de benzo of z-drug gestart?

0 ☐ onbekend *(ga naar vraag 1.3)*
1 ☐ gestart alvorens het verblijf in het wzc *(ga naar vraag B)*
2 ☐ gestart tijdens het verblijf in het wzc *(ga naar vraag B)*
3 ☐ gestart tijdens ziekenhuisopname gedurende het verblijf in het wzc *(ga naar vraag B)*

B. Hoelang gebruikt de resident de benzo of z-drug?

…… jaren …… maanden

1.3. Werd er het afgelopen jaar…?

1 overwogen om de dosis te **verminderen**? 0 ☐ neen 1 ☐ ja
2 een poging ondernomen om de dosis te **verminderen**? 0 ☐ neen 1 ☐ ja
3 overwogen om te **stoppen**? 0 ☐ neen 1 ☐ ja
4 een poging ondernomen om te **stoppen**? 0 ☐ neen 1 ☐ ja

1.4. Zou volgens u de benzo of z-drug bij deze rusthuisresident kunnen gestopt worden?

0 ☐ neen 1 ☐ ja
reden: ……..

1.5. Hebt u de indruk dat het gebruik van benzo of z-drug bij deze resident het gewenste effect geeft?
(het gewenste effect is goede slaapkwaliteit, minder angstig of minder depressief)

0 ☐ neen 1 ☐ ja

1.6. Zijn er volgens u bijwerkingen van benzo of z-drug merkbaar bij deze resident?
(meerdere antwoorden zijn mogelijk)

1 ☐ slaperigheid overdag
5 ☐ apathie
9 ☐ afhankelijkheid (psychisch)

2 ☐ verwardheid	6 ☐ geheugenstoornis	10 ☐ ik weet het niet
3 ☐ spierzwakte	7 ☐ duizeligheid	11 ☐ geen
4 ☐ concentratiestoornis	8 ☐ afhankelijkheid (fysisch)	12 ☐ andere: ……

2. MOGELIJKE BARRIÈRES OM EEN AFBOUWPOGING VAN BENZODIAZEPINE (BENZO) OF Z-DRUG BIJ **DEZE RESIDENT** TE ONDERNEMEN

In dit deel kan u een antwoord geven op de mate waarin u volgende stellingen als een barrière (belemmering) ervaart. Duid met een kruisje aan in welke mate dat overeenkomt met uw ervaring bij deze resident; van geen barrière (in geen mate) tot een sterke barrière (in sterke mate).

Barrière	*Score*
1. Bij afbouw of stopzetten van benzo of z-drug vrees ik dat de initiële problemen bij deze resident zullen terugkomen.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate
2. Bij afbouw of stopzetten van benzo of z-drug vrees ik dat de zorglast voor het personeel zal toenemen.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate
3. Bij afbouw of stopzetten van benzo of z-drug vrees ik dat bij deze resident mogelijke ongewenste symptomen zullen optreden.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate
4. Het afbouwen of stopzetten van benzo of z-drug is niet nodig zolang deze resident goed functioneert.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate
5. Bij afbouw of stopzetten van benzo of z-drug vrees ik dat de resident zelf niet gemotiveerd is.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate
6. Bij afbouw of stopzetten van benzo of z-drug vrees ik dat de familie zich hier tegen zal verzetten.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate
7. Bij afbouw of stopzetten van benzo of z-drug bij deze resident vrees ik dat het personeel niet gemotiveerd is.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate
8. Bij deze resident gaat mijn voorkeur naar medicatie in plaats van een niet-medicamenteuze behandeling.	in geen mate ☐☐☐☐☐☐☐☐☐☐ in sterke mate

Indien u in de praktijk nog andere indicaties of barrières ondervindt en die voor u in dit onderzoek ontbreken, mag u dit hier geheel vrijblijvend noteren en beoordelen:

……

……

……

……

7. BENZODIAZEPINE WITHDRAWAL SYMPTOM QUESTIONNAIRE- BWSQ

reference: Tyrer et al 1990

Wilt u trachten zich te herinneren welke van deze gewaarwordingen u de laatste weken hebt gehad en een vinkje zetten in het overeenkomstige vakje?

	Nee	Ja, matig	Ja, hevig/ ernstig
1. Onwezenlijk gevoel			
2. Erg gevoelig voor geluid			
3. Erg gevoelig voor licht			
4. Erg gevoelig voor geur			
5. Erg gevoelig voor aanraking			
6. Vreemde smaak in de mond			
7. Spierpijnen			
8. Spiertrekkingen			
9. Schudden en beven			
10. 'Slapen' van handen, armen of benen			
11. Duizeligheid			
12. Flauw gevoel			
13. Misselijk gevoel			
14. Neerslachtig gevoel			
15. Irritatie van de ogen			
16. Gewaarworden dat de dingen bewegen terwijl ze stilstaan			
17. Zien of horen van dingen die er in werkelijkheid niet zijn (hallucinaties)			
18. Niet bij machte uw bewegingen te beheersen			
19. Geheugenverlies			
20. Verlies van eetlust			
Heeft u nog andere nieuwe verschijnselen? (beschrijf elk verschijnsel hieronder)			
21.			
22.			
23.			
24.			

8. EQ-5D-3L

reference: Euroquol 1990

Zet bij iedere hieronder vermelde groep een kruisje in één hokje achter de zin die het best uw gezondheidstoestand van vandaag weergeeft.

Mobiliteit

Ik heb geen problemen met rondwandelen ❑

Ik heb enige problemen met rondwandelen ❑

Ik ben bedlegerig ❑

Zelfzorg

Ik heb geen problemen om voor mezelf te zorgen ❑

Ik heb enige problemen om mezelf te wassen of aan te kleden ❑

Ik ben niet in staat mezelf te wassen of aan te kleden ❑

Dagelijkse activiteiten *(bijv. werk, studie, huishouden, gezins- of vrijetijdsactiviteiten)*

Ik heb geen problemen met mijn dagelijkse activiteiten ❑

Ik heb enige problemen met mijn dagelijkse activiteiten ❑

Ik ben niet in staat mijn dagelijkse activiteiten uit te voeren ❑

Pijn/klachten

Ik heb geen pijn of andere klachten ❑

Ik heb matige pijn of andere klachten ❑

Ik heb zeer ernstige pijn of andere klachten ❑

Angst/depressie

Ik ben niet angstig of depressief ❑

Ik ben matig angstig of depressief ❑

Ik ben erg angstig of depressief ❑

7 CHAPTER
ABBREVIATIONS

ABBREVIATIONS

AD:	Antidepressant
ADL:	Activities of Daily Living
ATC:	Anatomic Therapeutic Chemical
BZD:	benzodiazepines
BZD/Z:	benzodiazepine and Z-drugs
CBT:	Cognitive Behavioural Therapy
CNS:	Central Nervous System
COPD:	Chronic Obstructive Pulmonary Disease
DDD:	Defined Daily Dose
DSM-IV-TR:	Diagnostic and Statistical Manual of Mental Disorders, 4th edition 2000 revision
DSM-V:	Diagnostic and Statistical Manual of Mental Disorders, 5th edition 2013
EMA:	European Medicine Agency
FDA:	Federal Drug Agency (United States)
GABA:	gamma-butyric acid
GDS:	geriatric depression scale
GP:	General Practitioner
GAD:	Generalised Anxiety Disorder
ICSD-2:	International Classification of Sleep Disorders, 2nd edition 2005
ICD-10:	International Classification of Diseases, WHO 1991
MMSE:	Mini Mental State Examination
MED:	Minimal Effective Dose
NREM sleep:	nonrapid eye movement sleep
NICE:	National Institute for Health and Care Excellence
OBRA-87:	Omnibus Budget Reconciliation Act of 1987 (Federal Nursing Home Reform Act in the US)
OCD:	Obsessive Compulsive Disorder
OR:	Odds Ratio
PHEBE:	Prescribing in Homes for the Elderly in Belgium
PDD:	Prescribed Daily Dose
PSG:	polysomnography
PSQI:	Pittsburgh Sleep Quality Index (questionnaire)
RCT:	Randomised controlled trial
REM sleep:	rapid eye movement sleep
SAD:	Social Anxiety Disorder
SNRI:	Selective Norepinephrine Reuptake Inhibitor
SPSS:	Statistical Package for the Social Sciences
SSRI:	Selective Serotonin Reuptake Inhibitor
SWS :	slow wave sleep
TCA:	Tricyclic Antidepressant
US:	United States
UK:	United Kingdom
WHO:	World Health Organisation

8

CHAPTER

ABOUT THE AUTHOR

ABOUT THE AUTHOR

Jolyce Bourgeois, 03/02/1987, Aalst

Contact

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jolyce.bourgeois@hotmail.com

Education

2011-2013

Clinical Pharmacologist (Dutch Society of Clinical Pharmacology & Biopharmacy - Education centre: Research unit Clinical Pharmacology, Ghent University. Prof Luc Van Bortel)

2005-2010

Master in pharmaceutical sciences (Ghent University)

Work experience

November 2010-

Doctoral researcher, Heymans Institute of Pharmacology, Ugent

Teaching pharmaco-therapeutic education to master students of the Medicine faculty and Pharmaceutical science faculty (Ghent University)
Guiding master students of Nursing sciences (Antwerp University)
Guest lecturer at the KaHo Sint-Lieven
Invited speaker for training in psychotropic drugs in older adults.

July 2010-

Pharmacist in community pharmacy (COOP pharmacies, Ghent)
Fulltime till November 2010, weekends since November 2010

Courses

"ICH GCP Qualification Training Course and Examination" (March 2011). Prof Dr H Pieterse

"Project Management": 3 day course Ugent (2011)

"Teaching the teacher": effective teaching strategies (Utrecht 2011) prof C Kramers, Dutch Society of Clinical Pharmacology & Biopharmacy

"Design and analysis clinical studies" (March 2011, Ghent) prof David Harrington-Professor of Biostatistics, Harvard University

"Neuropsychological aspects of aging" (January 2012) prof J De Keyser, VUB, Brussels

"Sleep Medicine Course" (November 2013), International Sleep Medicine Course, Blankenberge, Belgium

Conference attendance

International:

SLEEP, the 28th Annual Meeting of the Associated Professional Sleep Societies, Minneapolis USA 2014

International Research Conference on Nursing Homes, Global Aging Research Network, St Louis USA 2013

European Association for Clinical Pharmacology and Therapeutics (EACPT), Budapest 2011, Geneva 2013

International Psychogeriatrics (IPA), Den Hague Sept, 2011

International Society for Pharmacoepidemiology (ISPE), Barcelona, 2012

Dutch Society of Clinical Pharmacology & Biopharmacy: Mededelingendag 2011, 2012, 2013, 2014

European Drug Utilisation Group (Euro DURG)

National :

Belgian Society for Gerontology and Geriatrics, Wintermeeting 2011/2012/2013/2014

Update Acute Intoxications, Ghent, 2011 and 2013

Board member of the Belgian Society for Pharmaco-epidemiologie (BESPE)

Member of the Federal initiative 'work task for improving Quality of Medication in the nursing homes' (since 2013).

Publications

A1

Bourgeois J et al, Eur J Clin Pharmacol. 2012 May;68(5):833-44
"Benzodiazepine use in Belgian nursing homes: a closer look into indications and dosages"

Bourgeois J et al, Drugs and Aging. 2012 Sep;29(9):759-69.
"The use of antidepressants in Belgian nursing homes: focus on indications and dosages in the PHEBE study."

Bourgeois J et al, Sleep Medicine. 2013 July;14(7): 614-621
"Sleep quality of benzodiazepine users in nursing homes: a comparative study with non-users"

Bourgeois J et al, European Geriatric Medicine. 2014 Jun; 5 (3): 181-187
"Barriers to discontinuation of chronic benzodiazepine use in nursing home residents: Perceptions of general practitioners and nurses."

Bourgeois J et al, Eur J Clin Pharmacol 2014 Sept; 70(10):1251-1260
« Feasibility of discontinuing chronic benzodiazepine use in nursing home residents: a pilot study."

Bourgeois J et al, Drugs and Aging 2014, Sept 31(9):677-682
"One-year evolution of sleep quality in older benzodiazepine users: A longitudinal cohort study in Belgian nursing home residents."

Azermai, M., Petrovic, M., Elseviers, M. M., Bourgeois, J., Van Bortel, L. M. and Vander Stichele, R. H. (2012). Ageing research reviews, 11, 78-86
"Systematic appraisal of dementia guidelines for the management of behavioural and psychological symptoms."

Rolland Y, Resnick B, Katz PR, Little MO, Ouslander JG, Bonner A, Geary CR, Schumacher KL, Thompson S, Martin FC, Wilbers J, Zúñiga F, Ausserhofer D, Schwendimann R, Schüssler S, Dassen T, Lohrmann C, Levy C, Whitfield E, de Souto Barreto P, Etherton-Beer C, Dilles T, Azermai M, Bourgeois J, Orrell M, Grossberg GT, Kergoat H, Thomas DR, Visschedijk J, Taylor SJ; OPERA Study Team, Handajani YS, Widjaja NT, Turana Y, Rantz MJ, Skubic M, Morley JEJ Am Med Dir Assoc. 2014 May;15(5):313-25
"Nursing Home Research: The First International Association of Gerontology and Geriatrics (IAGG) Research Conference."

A2

Jolyce Bourgeois, Monique Elseviers, Lucas Van Bortel, Mirko Petrovic, Robert Vander Stichele 2013 TIJDSCHRIFT VOOR GENEESKUNDE. 69(21). p.1039-1045
"Belgische woonzorgcentra: slaapkwaliteit van chronische benzodiazepinegebruikers"

Jolyce Bourgeois, Robert Vander Stichele 2013 HUISARTS NU. 42(6)
"Helft rusthuisbewoners aan de slaappil" commentaar

Majda Azermai, Jolyce Bourgeois, Annemie Somers, Mirko Petrovic (2013) AGEING HEALTH.
"Inappropriate use of psychotropic drugs in older people: implications for practice.

A3

Azermai M., Bourgeois J., Petrovic M., Minerva 2012; 11(6): 75-76
"Werkzaamheid en doeltreffendheid van atypische antipsychotica bij volwassenen voor niet-geregistreerde indicaties."

Contribution to conferences

2014	SLEEP 2014, May 31-June 4, Minneapolis USA 1 poster "Evolution of sleep quality in chronic benzodiazepine users compared to nonusers"
	PHYSPHAR, April 4th and 5th, Maastricht 1 poster "Does long-term benzodiazepine use has an impact on cognitive deterioration?"
2013	International Research Conference on Nursing Homes, St Louis USA Symposium organisation "Stopping Benzodiazepines: feasibility, barriers and recommendations for practice"
	European Association for Clinical Pharmacology and Therapeutics (EACPT), Geneva 2013 1 oral presentation + 1 poster "Sleep quality of chronic benzodiazepine users in nursing homes: a comparative study with non-users." "Perceptions about benzodiazepine discontinuation in nursing homes."
	Belgian Association for Gerontology & Geriatrics: Wintermeeting 1 oral presentation "Slaapkwaliteit van chronisch benzodiazepine gebruikers in woonzorgcentra: een vergelijkende studie met niet-gebruikers."
	Dutch Society of Clinical Pharmacology & Biopharmacy: Mededelingendag 1 poster "SLEEP QUALITY OF CHRONIC BENZODIAZEPINE USERS IN NURSING HOMES: a comparative study with non-users."
2012	Belgian Association for Gerontology & Geriatrics: Wintermeeting 1 poster "Het gebruik van antidepressiva in Belgische rusthuizen: de focus op indicaties en dosissen."
	Wetenschapsdag, Ghent University 1 poster "Antidepressants in Belgian nursing homes in Belgian nursing homes: indications and dosages."

2011

European Association for Clinical Pharmacology and Therapeutics (EACPT), Budapest 2011
2 posters
"USE of ANTIDEPRESSANTS IN BELGIAN NURSING HOMES"
"CHRONIC BENZODIAZEPINE USE IN NURSING HOME RESIDENTS: A CLOSER LOOK INTO INDICATIONS AND DOSAGES"

International Psychogeriatrics (IPA),
Den Hague Sept, 2011
1 poster
"Barriers to discontinuation of chronic use of benzodiazepines in Belgian nursing home residents: A focus group study."

THANKS

To everyone who made this possible…

People may think it is rude not to give special thanks and acknowledge the persons who contributed to this work, and indeed they are right. Therefore, turn the page.

After my graduation in 2010, I got interested in clinical pharmacology. As this was/is not readily available as a master in Belgium, I started to search for possible education opportunities. The clinical pharmacology department led by professor Luc Van Bortel at the university of Ghent had such a program. Luckily a PhD position at the same department opened and made it possible to combine this education with research. I am very grateful that the two people in front of me during my solicitation saw 'my potential' and had confidence in me. Therefore I thank my promotor Robert 'Bob' VanderStichele and copromotor Monique Elseviers for guiding me and being my backbone. In the beginning it was sometimes difficult during the endless discussion rounds and paper preparations. But as Bob always says: 'a diamond in the rough needs several polishing turns'. A special thanks to professor Mirko Petrovic, who was officially in my steering committee, but appeared to be very close involved in my PhD project. He was a great mentor on the benzo level and a great support. I thank professor Luc Van Bortel for always seeing the big picture and giving me the opportunity to become a clinical pharmacologist during my PhD research.
As every PhD student knows it is a lot of individual work and discipline, so a good work atmosphere is essential. And I must say I really liked going to the Heymans Institute, so thank you colleagues. As our research department is young and dynamic, the faces in the kitchen often change. In order of appearances: Thank you Karen, Ilse, Majda, Jan, Seba, Tine, Sofie, Carlos, Elien, Sandrien, Jelle, Isabelle, Katrina, Maarten and Wendy. In addition to our many laughs, I appreciated all the help. During my four PhD years I shared an office space with equally chaotic persons as myself: Majda, who was there from the beginning and was a great congress buddy, and since two years Katrina who gives the best advice and was actually my lifelike 'google translate'. I also got acquainted with a lot of inspiring and helpfull people along the way, in the UZ and especially in the nursing homes. This research was not possible without the helping hands of the 5 master thesis students from Antwerp University, who were responsible for parts of the data collection in the nursing homes.

A good group of supporters is necessary to get to the finish.
Thank you dear mam and dad for supporting me on every possible level. Thank you dear friends for the good advice.

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