Survey on the use of benzodiazepines and Z-drugs to treat insomnia in Belgium

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Abstract

Background and objectives

Sleep disorders, and in particular insomnia, are highly prevalent in the general population. Non-pharmacological alternatives are recommended as first-line treatment for chronic insomnia in adults. However, hypnotic drugs are the preferred treatment for many patients. Benzodiazepine receptor agonists (BZRA: benzodiazepines and Z-drugs) are the most commonly used hypnotic drugs in primary care. Despite guidelines and awareness campaigns, both in Belgium as in other countries, they are still widely prescribed and probably overused. In particular, long-term (chronic; one month or more) use may be of concern because of the high risk of adverse effects, tolerance, dependence and abuse. The main objective of this study was to evaluate the level of BZRA misuse in non-institutionalised adult patients treated for insomnia in Belgium. Additionally, their perceived level of dependence on BZRA was also assessed.

Methods

A cross-sectional study was conducted in 2020 in Belgium. Patients aged 18 years or older were invited by pharmacists to complete an online survey. Participation was voluntary and anonymous. Respondents were asked about their use of BZRA as sleeping pills in terms of dosage, frequency and duration of use, their subjective dependence on BZRA, and the use of alternative approaches to treat their insomnia. Data were analysed using descriptive statistics; no hypotheses were formally tested. Confidence intervals of the proportions were presented for the main variables of interest.

Results

A total of 808 patients responded to the survey, of which 550 were included in the analysis. Zolpidem was the most frequently used as sleeping pill, followed by lormetazepam. High levels of misuse were reported, particularly in terms of duration of use. More than one-third of the respondents showed psychological signs of dependence on BZRA. The majority of respondents had already tried to stop their treatment in the past. Furthermore, the majority of the respondents wished they could stop their BZRA treatment and almost half of the respondents would find it very hard or impossible to stop. The majority of respondents had tried other approaches than BZRA to treat insomnia. The most reported alternative treatments were dietary supplements, homeopathic and/or herbal remedies.

Conclusions

Although this survey coincided with the onset of the COVID-19 pandemic, which most likely contributed to the limited sample size, it provides some valuable insights. The results suggest that recommendations, particularly in terms of duration, are not being followed by patients or healthcare professionals (HCPs) who may continue to prescribe these medications on a long-term basis. A majority of the respondents have tried alternative methods, mostly remedies often perceived as "natural" and safer than classic medicinal products, even if there is a lack of scientific evidence for most of them and risk concerns have been raised. It is essential to target both patients and HCPs when considering methods to minimise misuse/abuse of BZRA. They should be reminded that medication should not be considered as a first-line treatment for insomnia. To this end, non-pharmaceutical alternatives should be effective, financially accessible and available. HCPs should be encouraged to discuss the risks of BZRA with the patient and to prescribe smaller boxes of BZRA (less than 30 tablets). The current supply of small pack sizes should thus be expanded. In the meantime, deprescribing of BZRA should be considered in chronic BZRA users, especially those aged 65 and older. Overall, it is important to continue and improve communication and access to educational resources for both patients and HCPs when aiming to a rationale use of BZRA in insomnia.

Samenvatting

Achtergrond en doelstellingen
Slaapstoornissen, en in het bijzonder slapeloosheid, komen vaak voor in de algemene bevolking. Niet-farmacologische alternatieven worden aanbevolen als eerstelijnsbehandeling voor chronische slapeloosheid bij volwassenen, maar veel patiënten geven echter de voorkeur aan hypnotica. Benzodiazepine receptor agonisten (BZRA's: benzodiazepines en Z-drugs) zijn de meest gebruikte hypnotica in de eerstelijnszorg. Ondanks richtlijnen en bewustmakingscampagnes in België en andere landen, worden ze nog steeds op grote schaal voorgeschreven en waarschijnlijk overmatig gebruikt. Vooral langdurig gebruik (chronisch; één maand of langer) kan zorgen baren vanwege het hoge risico op bijwerkingen, tolerantie, afhankelijkheid en misbruik. Het hoofddoel van deze studie was het evalueren van de mate van verkeerd gebruik van BZRA's bij niet-geïnstitutionaliseerde volwassen patiënten die in België worden behandeld voor slapeloosheid. Daarnaast werd ook hun waargenomen mate van afhankelijkheid van BZRA's geëvalueerd.

Methode
Een cross-sectionele studie werd in 2020 uitgevoerd in België. Patiënten van 18 jaar of ouder werden door apothekers uitgenodigd om een online bevraging in te vullen. Deelname was vrijwillig en anoniem.
De respondenten werden bevraagd over hun gebruik van BZRA als slaapmiddel, meer specifiek over de dosering, frequentie en gebruiksduur, hun subjectieve afhankelijkheid van deze behandeling en het gebruik van alternatieven die ze hebben geprobeerd om hun slapeloosheid te behandelen. De gegevens werden geanalyseerd met behulp van beschrijvende statistieken, er werden geen hypothesen getest. Betrouwbaarheidsintervallen van de proporties werden gepresenteerd voor de belangrijkste variabelen.

Resultaten
In totaal hebben 808 patiënten deelgenomen aan de bevraging, waarvan er 550 in de analyse werden opgenomen. Zolpidem was het meest gemelde slaapmiddel dat door de respondenten werd gebruikt, gevolgd door lormetazepam. Er werd een hoge mate van verkeerd gebruik gemeld, met name wat de gebruiksduur betreft. Meer dan een derde van de respondenten vertoonde psychologische tekenen van afhankelijkheid van BZRA's. De meeste respondenten hebben in het verleden geprobeerd om hun behandeling te stoppen. Bovendien wenste de meerderheid van de respondenten hun behandeling te kunnen stoppen en zou bijna de helft het zeer moeilijk of onmogelijk vinden om te stoppen. De meerderheid van de respondenten had naast BZRA's andere methoden geprobeerd om slapeloosheid te behandelen. De meest gemelde alternatieve behandelingen waren voedingssupplementen, homeopathische en/of kruidengeneesmiddelen.

Besluit
Ondanks het feit dat deze bevraging samenviel met het begin van de COVID-19-pandemie, wat hoogstwaarschijnlijk heeft bijgedragen tot de beperkte omvang van de studie, levert de studie een aantal waardevolle inzichten. De resultaten wijzen er op dat de aanbevelingen, vooral wat de duur van de behandeling betreft, niet worden opgevolgd door patiënten, noch door gezondheidszorgbeoefenaars (HCP's) die deze geneesmiddelen op lange termijn wellicht blijven voorschrijven. Een meerderheid van de respondenten heeft alternatieve methoden geprobeerd, meestal remedies die vaak als "natuurlijk" en veiliger dan conventionele geneesmiddelen worden beschouwd, ook al ontbreekt het voor de meeste ervan aan wetenschappelijk bewijs en is er bezorgdheid over de risico's. Het is van essentieel belang dat zowel patiënten als HCP's worden aangesproken wanneer wordt nagedacht over methoden om verkeerd gebruik/misbruik van BZRA's tot een minimum te beperken. Zij moeten eraan worden herinnerd dat medicatie niet moet worden beschouwd als een eerstelijnsbehandeling voor slapeloosheid. Daarom moeten niet-medicamenteuze alternatieven doeltreffend, betaalbaar en beschikbaar zijn. HCP's moeten worden aangemoedigd om de risico's van BZRA's met de patiënt te bespreken en kleinere verpakkingen van BZRA's (minder dan 30 tabletten) voor te schrijven. Het huidige aanbod van kleine verpakkingen moet daarom worden uitgebreid. Intussen moet worden overwogen om minder BZRA's voor te schrijven ("deprescribing") bij alle chronische BZRA-gebruikers, met name bij 65-plussers. In het

algemeen is het belangrijk om de communicatie en de toegang tot educatieve middelen voor zowel patiënten als HCP's voort te zetten en te verbeteren bij het streven naar een rationeel gebruik van BZRA’s bij slapeloosheid.

Résumé

Contexte et objectifs

Les troubles du sommeil, en particulier l'insomnie, sont très répandus dans la population générale. Les alternatives non-médicamenteuses sont recommandées comme traitement de première intention de l'insomnie chronique chez l'adulte. Cependant, les médicaments hypnotiques sont le traitement préféré de nombreux patients. Les agonistes des récepteurs des benzodiazépines (BZRA: benzodiazépines et « Z-Drugs ») sont les hypnotiques les plus couramment utilisés en soins primaires. Malgré les recommandations et les campagnes de sensibilisation, tant en Belgique que dans d'autres pays, ils sont encore largement prescrits et probablement surutilisés. En particulier, l'utilisation à long terme (chronique, un mois ou plus) peut être préoccupante en raison du risque élevé d'effets indésirables, de tolérance, de dépendance et d'abus. L'objectif principal de cette étude était d'évaluer le niveau de mésusage des BZRA chez les patients adultes non institutionnalisés traités pour insomnie en Belgique. En outre, leur niveau perçu de dépendance aux BZRA a également été évalué.

Méthodes

Une étude transversale a été menée en 2020 en Belgique. Des patients âgés de 18 ans ou plus ont été invités par des pharmaciens à répondre à une enquête en ligne. La participation était volontaire et anonyme. Les répondants ont été interrogés sur leur utilisation des BZRA comme somnifères en termes de dosage, de fréquence et de durée d'utilisation, sur leur dépendance subjective aux BZRA et sur l'utilisation d'approches alternatives pour traiter leur insomnie. L' analyse des données a été effectuée à l'aide de statistiques descriptives ; aucune hypothèse n'a été formellement testée. Les intervalles de confiance des proportions ont été présentées pour les principales variables d'intérêt.

Résultats

Au total, 808 patients ont répondu à l'enquête, dont 550 ont été inclus dans l'analyse. Le zolpidem était le somnifère le plus fréquemment utilisé, suivi du lormétazépam. Des niveaux élevés de mésusage ont été signalés, notamment en termes de durée d'utilisation. Plus d'un tiers des répondants présentaient des signes psychologiques de dépendance aux BZRA. La majorité des répondants avaient déjà essayé d'arrêter leur traitement dans le passé. De plus, la majorité des répondants souhaitaient pouvoir arrêter leur traitement aux BZRA et près de la moitié des répondants trouveraient très difficile ou impossible de arrêter. La majorité des répondants avaient essayé d'autres approches que les BZRA pour traiter l'insomnie. Les traitements alternatifs les plus rapportés étaient les compléments alimentaires et/ou les remèdes homéopathiques et à base de plantes.

Conclusions

Bien que cette enquête ait coïncidé avec le début de la pandémie de COVID-19, ce qui a très probablement contribué à la taille limitée de l'échantillon, elle fournit des données précieuses. Les résultats suggèrent que les recommandations, notamment en termes de durée de traitement, ne sont pas suivies par les patients ou par les professionnels de santé qui peuvent continuer à prescrire ces médicaments à long terme. Une majorité de personnes interrogés ont essayé des méthodes alternatives, en essayant surtout des remèdes souvent perçus comme « naturels » et plus sûrs que les médicaments classiques, même si les preuves scientifiques manquent pour la plupart d'entre eux et que des inquiétudes quant aux risques ont été soulevées. Il est essentiel de cibler à la fois les patients et les professionnels de la santé lors de l'examen des méthodes visant à minimiser le mésusage/abus des BZRA. Il convient de rappeler aux patients que les médicaments ne doivent pas être considérés comme un traitement de première intention de l'insomnie. À cette fin, les alternatives non-médicamenteuses doivent être efficaces, financièrement accessibles et disponibles. Les professionnels de santé devraient être encouragés à discuter des risques des BZRA avec le patient et à prescrire des boîtes de BZRA plus petites (moins de 30 comprimés). L'offre actuelle de petites boîtes devrait donc être élargie. Dans l'intervalle, la déprescription des BZRA devrait être envisagée chez tous les utilisateurs chroniques de BZRA, en particulier chez les personnes âgées de 65 ans et plus. Dans l'ensemble, il est important de poursuivre et

d'améliorer la communication et l'accès aux ressources éducatives, tant pour les patients que pour les professionnels de santé, afin de parvenir à une utilisation rationnelle des BZRA en cas d'insomnie.

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Abbreviations

ANSM	National Agency for the Safety of Medicines and Health Products (France)
APB	General Pharmaceutical Association
BE	Belgium
BelPEP	Belgian Psychotropics Experts Platform
BZD	Benzodiazepine
BZRA	Benzodiazepine Receptor Agonist (Benzodiazepine or Z-drug)
CBIP/BCFI	Belgian Centre for Pharmacotherapeutic Information
CBT-I	Cognitive Behavioural Therapy for Insomnia
CI	Confidence Interval
CHM	Commission for Human Medicines
DDD	Defined Daily Dose
DG POST	Directorate-General Post authorisation
DME	Diazepam Milligram Equivalence
FAMHP	Federal Agency for Medicines and Health Products
FPS	Federal Public Service
GDPR	General Data Protection Regulation
GP	General practitioner
HCPs	Healthcare professionals
INCB	International Narcotics Control Board
IQR	Interquartile range
LMZ	Lormetazepam
LRZ	Lorazepam
LOP	Loprazolam
NA	Not applicable
NR	No response
OPHACO	Association of Cooperative Pharmacies of Belgium
PhEpi	Pharmacoepidemiology
PhV	Pharmacovigilance
RDD	Recommended Daily Dose
SDS	Severity of Dependence Scales
SmPC	Summary of product characteristics
ZLP	Zolpidem
ZOP	Zopiclone

Introduction

Background

Sleep disorders, and in particular insomnia, are highly prevalent in the general population (prevalence of at least 10%) and may be linked to a broad spectrum of underlying conditions and medications (1, 2, 3). Non-pharmacological alternatives such as cognitive behavioural therapy for insomnia (CBT-I) are recommended as the first-line treatment for chronic insomnia in adults (1, 3, 6). In reality, however, hypnotic medication is the preferred treatment of many patients because it works quickly (1). Benzodiazepines and Z-drugs (BZRA) are the most commonly used hypnotic medication in primary care since their introduction 50 years ago (2, 4, 6).

BZRA are considered effective if used appropriately (1, 2, 3, 7). The use of BZRA for insomnia is recommended to be restricted in time for a period not exceeding four weeks (3, 5, 6). In general, longer use or use of higher doses than recommended are not advisable because of the risk of tolerance (BZRA tend to lose effectiveness), dependency and misuse/abuse (3, 4, 5, 6). Abuse of BZRA is often reported in combination with other drugs used for recreational purposes (5). Moreover, a link between long-term use of BZRA and serious adverse effects (e.g. dementia and respiratory disease exacerbation) has been suggested (5, 7, 8).

Even when used appropriately, the use of BZRA can cause cognitive and psychomotor adverse effects like memory loss, fatigue, accidents and falls (1, 3, 4, 7) and discontinuation can lead to withdrawal symptoms and rebound effects (2, 3, 5).
Despite guidelines and campaigns to change prescribing behaviour, BZRA are still widely prescribed and probably overused worldwide (2, 4, 6). In particular, long-term (chronic, one month or more) use of BZRA is probably highly prevalent despite being discouraged because of the high risk of adverse effects, tolerance, dependence and abuse (6, 9, 10).

Rationale and aim of the study

In Belgium, the prevalence of the use of BZRA (hypnotics and anxiolytics) seems to be particularly high. In 2018, according to the data published by the International Narcotics Control Board (INCB), Belgium was the second European country with the highest rate of consumption of BZRA (11). National health surveys conducted in 2013 and in 2018 have estimated that around 16% of the Belgian population aged 15 and older had consumed one or more psychotropic drugs under prescription within the two weeks preceding the survey. Among these drugs, BZRA were the most commonly used (12, 20). In 2016, a total of 1,260,034 Defined Daily Doses (DDDs) of sleeping pills and tranquilizers were delivered by Belgian pharmacies (21). The use of these medications has however slightly decreased over the last ten years from 14% in 2008 to 12% in 2018 (20).

Alarmed by these data, the Minister of Public Health launched a new campaign in early 2018 in collaboration with the Federal Public Service of Health. The aim was to raise awareness among healthcare providers and their patients of the risks associated with sedatives and sleeping pills and to promote non-pharmacological alternatives (21).

At the end of 2018, the Vigilance Division of the FAMHP presented a report on the use and misuse of zolpidem (ZLP) in Belgium to the Commission on Human Medicine (CHM) (22). This report followed the implementation of new regulation measures for this substance in France (13) as well as the observation, by the pharmacovigilance inspectors of the FAMHP, of growing number of cases of ZLP abuse and falsification of prescriptions in Belgium. After reviewing the available national data on this issue, the Vigilance Division and the CHM considered it necessary to set up a national survey to collect data on the use of BZRA in Belgium. This study provides a snapshot view of the issues of BZRA abuse/misuse in the general population in Belgium.

Research questions and objectives

Research questions

- What is the level of BZRA misuse/abuse[1] among non-institutionalized adults who use BZRA for insomnia in Belgium?
- What is the perceived level of BZRA dependence among non-institutionalized adults who use BZRA(s) for insomnia?
- What are the alternative methods used by non-institutionalized patients for insomnia?

Primary objectives

- To describe the pattern of BZRA consumption as reported by non-institutionalized patients who use BZRA for insomnia:
    - in terms of dosage,
    - in terms of duration of use,
    - in terms of frequency of use.
- To assess the prevalence of compliance with the recommended use as reported by non-institutionalized patients who use BZRA for insomnia:
    - in terms of dosage,
    - in terms of duration and frequency of use.

Secondary objectives

- To assess the dependence on BZRA, as perceived by non-institutionalized patients who use BZRA(s) for insomnia.
- To assess the willingness to stop taking BZRA(s), as reported by non-institutionalized patients who use BZRA(s) for insomnia.
- To describe the alternatives to BZRA used by non-institutionalized patients for insomnia.

Methods

Study design and setting

This cross-sectional study used a web-based, self-administered questionnaire as a collection tool. This design was considered as appropriate to evaluate the objectives of the study. Online surveys in particular are relatively simple and quick to complete. Financial costs are also kept to a minimum, making them a feasible alternative for exploring some questions that cannot be easily addressed with other data sources (e.g. administrative databases) due to the lack of reimbursement. Strengths and limitations of this design are discussed in the section Discussion.

The study protocol was developed by the FAMHP in collaboration with a group of external experts. This group was composed by HCPs, members of universities, the Belgian Psychotropics Experts Platform (BelPEP), the Belgian Centre for Pharmacotherapeutic Information (CBIP/BCFI), and the representative and professional body for community pharmacists in Belgium (General Pharmaceutical Association - APB, and Association of Cooperative Pharmacies of Belgium - OPHACO).

Members of APB and OPHACO also participated in the design of the communication plan and in the distribution of the survey by involving community pharmacists affiliated to APB/OPHACO in the recruitment process.

The target population consisted of patients aged eighteen years or older treated with one or more BZRA(s) in the outpatient setting in Belgium. The list of BZRA of interest was limited to drugs indicated for insomnia (as per SmPC) that were commercialized in Belgium at the time of the survey (see **Table 1**).

The study was sponsored and financed by the FAMHP, and received approval from the Ethics Committee of the Hospital Erasme-ULB (Ref. P2019/404 / B406201941045.

[1] As defined in EMA's Guideline on good pharmacovigilance practices (GVP): Module VI (EMA/876333/2011 Rev 4).

Table 1. List of BZRA licensed for insomnia.

	Name	Trade name	Recommended dose
Benzodiazepines	Brotizolam	Lendormin	0.25 mg
	Clotiazepam	Clozan	10 mg
	Ethyl loflazepate	Victan	4 mg
	Flunitrazepam	Flunitrazepam EG	1 mg
	Flurazepam	Staurodorm	27 mg
	Lorazepam	Lorazepam EG, Lorazetop, Serenase, Temesta	2.5 mg
	Lormetazepam	Loramet, Lormetazepam EG, Lormetazepam Sandoz, Metapop, Noctamid, Stilaze	2 mg
	Loprazolam	Dormonoct	1 mg
	Nitrazepam	Mogadon	5 mg
	Triazolam	Halcion	0.25 mg
Z-drugs	Zolpidem	Stilnoct, Zolpeduar, Zolpidem EG, Zolpidem Mylan, Zolpidem Sandoz, Zolpidem Teva, Zolpitop	10 mg
	Zopiclone	Imovane, Zopiclone EG, Zopiclone Mylan, Zopiclone Teva	7.5 mg

Research tool

The PharmacoEpidemiology (PhEpi) team of the FAMHP developed a questionnaire in French, which is included in Annex 1. The questionnaire was then translated into Dutch (Annex 1) by two native speakers of the PhEpi team and reviewed by external experts and FAMHP's Communications Division.

The SurveyMonkey® software was used to host the questionnaire and to collect the responses.

Once online, the questionnaire was pre-tested by FAMHP staff (DG POST authorisation, DG Inspection and Communications Division). A pilot phase was carried out with seven French-speaking people and four Dutch-speaking people (BZRA users) via personal contacts of the Pharmacovigilance (PhV) evaluators.

On the first page of the questionnaire (cover page) patients were invited to participate in the study. The cover page briefly described the main purpose of the survey, the target population, sponsor, scope and voluntary nature of the survey. The cover page also provided information about the guarantee of data confidentiality, the estimated response time (between five and ten minutes), the time period of the survey (four weeks, then extended to three months) including start and end dates, the list of drugs of interest, and the possibility of asking for help from a third party in completing the questionnaire (e.g. in case of difficulties with

comprehension/reading, internet use, etc.).

The last page of the questionnaire consisted of an acknowledgment including a link to the campaign of the SPF Public Health on sedatives and sleeping pills (21) and some useful information on the rational use of these medications.

The questionnaire consisted of fourteen pages, including the cover and acknowledgement page. A total of fifteen questions were displayed in twelve pages. Three questions on dosage were mutually exclusive so that a maximum of thirteen questions could be asked.

The main questions focused on the use of one BZRA, including the specific product name (listed in Table 1), pill dose/strength, number of pills taken per day, frequency and duration of use. Other questions collected sociodemographic data (sex and age), alternative therapies for insomnia and questions to assess psychological dependence on sleeping pills. All the questions were closed-ended, improving the level of standardization of the instrument. The majority of the questions were single-punch; only two multi-punch questions (check boxes) were part of the questionnaire (other BZRA used and possible alternatives to BZRA). Skip logic and conditional branching were used where appropriate.

To measure the perception of the severity of dependence, a slightly modified version of the Severity of Dependence Scales (SDS) questionnaire was used (translated into French and Dutch). The SDS is a five-item questionnaire designed to measure the degree of subjective dependence on a variety of drugs (16). Its usefulness as screening test for evaluating benzodiazepine (BZD) dependence has already been examined yielding positive results (17). The SDS questions are: 1) Did you think your use of tranquillizers was out of control?, 2) Did the prospect of missing a dose make you anxious or worried?, 3) Did you worry about your use of tranquillizers?, 4) Did you wish you could stop?, 5) How difficult would you find it to stop or go without your tranquillizers? The responses refer to behaviour and experiences during a specific period of time, namely "during the last month" (17).

The questionnaire was made available from 19 February until 19 May 2020.

Sample Selection

The aim was to invite all potential eligible patients to participate in the study. No specific sampling techniques were used (e.g. convenience sampling).

Recruitment was mostly done through the pharmacies affiliated to ABP/OPHACO. Approximately 4,800 pharmacies in Belgium are affiliated to APB/OPHACO. The number of pharmacies in Belgium in 2019 was 4,943 [2]. The source population was defined as the population of patients aged 18 and over, identified by the pharmacist as taking BZRA(s) when buying drugs during the time period of the survey in Belgium. BZRA(s) users could be identified by presenting at least one prescription or by information in the shared pharmaceutical dossier. When buying medication, patients identified as potential users of BZRA(s) were informed about the survey by community pharmacists. A sticker, supplied by the FAMHP through APB/OPHACO and providing the internet address of the FAMHP, was stuck on a medicine's box. Community pharmacists were also given links to download a short animated presentation to upload on pharmacy screens. The short animated presentation informed patients about the ongoing survey together with the internet address of the FAHMP and a QR code to enter the survey. On the welcome page of the FAMHP website an insert was added with a link to an information page on the study and a link to the questionnaire.

The survey website was also distributed via other communication channels (i.e. FAMHP Facebook and Twitter accounts, patient associations, health insurance) to increase the possibility of reaching and recruiting relevant patients (i.e. to improve coverage). The source population would therefore be theoretically representative of the target population.

The study population consisted of those patients in the source population who received the

[2] Source: https://siriusinsight.be/

information requesting their participation in the survey (or who had access to the relevant information via other communication channels), who responded to the questionnaire, and who were evaluated as eligible for participation (i.e. older than 17 years, taking BZRA as a sleeping pill). Because participation was voluntary, the representativeness of the study population with regards to the target population cannot be guaranteed and the possibility of response bias is discussed below as an important limitation.

Survey administration

Four days before the survey was launched, a letter to pharmacists was sent to APB/OPHACO affiliates. It consisted of a document introducing the survey and explaining the role of the pharmacist, joined by two A4 sheets of stickers and a link to a short animated presentation on the survey. All the BZRA involved in the investigation were clearly specified. The letter to pharmacists is included in Annex 22.

In the document, community pharmacists were encouraged to systematically put the sticker on the box of the BZRA, or of any other medication delivered to patients identified as BZRA(s) user via the shared pharmaceutical dossier at the time of drug delivery. They were also instructed not to select patients on criteria other than BZRA(s) use. The patient's attention was to be drawn to the sticker and the pharmacist was requested to provide a brief explanation. Pharmacists were encouraged to refer patients to the survey throughout the duration of the study.

In an attempt to increase the potential response rate, a reminder letter and new stickers were sent to the pharmacists by APB/OPHACO during the second week of the survey. At the same time, several reminders have been published on the website and the social media of APB/OPHACO.

All FAMHP communication on the survey was published on the FAMHP website and on the FAMHP social networks. The posts on social networks were accompanied by an illustration.

A pre-launch communication was published on 20 January 2020 to inform HCPs, patients and media about the background and scope of the survey. A reminder was published on the FAMHP website two weeks after the launch of the survey and its communication. Given the low participation in the first month and the context of the COVID-19 pandemic, it was decided to extend the survey by two months (closing on 19 May 2020).This decision was published on the FAMHP and APB/OPHACO websites.

All FAMHP communications were sent via e-mail to people who are subscribed to VIG-news/Flash VIG-news (FAMHP vigilance newsletters), the so-called "VIG-news mailing list". This mailing list contains email addresses of everyone who has asked to be added to the mailing list. Most of the email addresses belong to HCPs.

Information on the survey has also been distributed via CBIP/BCFI and patients platforms (e.g. mutual health magazines, Test-Achats/Test-Aankoop ...). These communications were published after the letter to pharmacists was sent.

No financial incentives were given to pharmacists or patients.

As mentioned above, participation was entirely voluntary and anonymous. Respondents' IP addresses were not collected. Data confidentiality was also ensured by restricting access to individual data (reserved for qualified personnel) and by presenting only aggregated data in the study report. The following SurveyMonkey options were also used: "response editing ON" (to allow participants to edit their responses either while completing the survey or after they have submitted it) and "multiple responses OFF" (to prevent multiple surveys from being submitted by the same participant).

Variables

The questionnaire was composed of questions on demographic variables, drug use (which BZRA taken, dose, frequency of use, duration of use, attempt to stop), the perception of

severity of dependence, and the use of possible alternatives to treat insomnia. All primary variables, as well as the degree of dependence and attempt to stop, only relate to one BZRA. If patients use more than one BZRA, they were invited to select the one they use the most regularly.

Primary variables

Frequency counts of patients taking BZRA for insomnia, per drug (by active substance and medicinal product name).
Frequency counts of patients taking BZRA for insomnia, per drug and daily dose.
Frequency counts of patients taking BZRA for insomnia, per drug and duration of use.
Frequency counts of patients taking BZRA for insomnia, per drug and frequency of use.

Secondary variables

Degree of dependence on BZRA, measured by the Severity of Dependence Scale (SDS), per drug.
Frequency counts of patients taking BZRA for insomnia who tried to stop taking BZRA, overall and per drug.
Frequency counts of patients taking BZRA for insomnia who reported to have tried alternatives to BZRA.
Frequency counts of alternatives to BZRA used by patients taking BZRA for insomnia.
Frequency counts of patients taking one or more BZRA for insomnia in the last year.

Demographic variables

Sex.
Age (in years).
Language (based on the version of the questionnaire the patient has started to fill in).

Data management

The data collection tool (online questionnaire) was distributed using SurveyMonkey. The responses collected by SurveyMonkey were exported in Excel (xlsx files). The quality of the collected data was examined, using Microsoft Excel and the statistical software SAS (9.4), in order to check for potential inconsistencies. All identified inconsistencies as well as possible corrective measures were documented in audit log files.

The responses to the questionnaire were collected at the FAMHP. After the deadline for the receipt of completed questionnaires, the original raw database (XLSX format) was locked and stored on a server at the FAMHP with reading and writing rights managed by its ICT department. A working copy of the database was imported in SAS and used for data cleaning and analysis. The SAS programmes, SAS analysis datasets, SAS outputs, and log files were stored on the server. Only researchers responsible for the project at the FAMHP had access to the database.

Data analysis

In this cross-sectional survey study only descriptive analyses were performed.

Only patients who reported using at least one of the BZRA listed in Question 3 were included in the analysis.

A response rate cannot be estimated because of the lack of sampling frame (i.e. convenience sample). Not even a rough estimate of the participation rate could be calculated because an approximate number of distributed labels was not available. The potential differences between respondents and non-respondents could not be explored because of the lack of information on non-respondents.

The completion rate was calculated by dividing the number of respondents who answered all relevant questions (full respondents or completers) by the total number of respondents (completers and partial respondents).

The primary analysis was based on the completers dataset. A secondary analysis was also

carried out on the full study dataset (i.e. full and partial respondents). Data were analysed using SAS statistical software (version 9.4) and Microsoft Excel.

Descriptive data for categorical variables were presented using frequencies (counts) and proportions (presented as percentages). For the calculation of proportions, the numerator was the number of respondents that had answered each specific question and the denominator the total number of respondents in the study population. Observations with missing values were not included in the denominator for the calculations of the proportions.

The study population was statistically described by sex, language and age. Age was summarized with descriptive statistics (mean, median, standard deviation, minimum, maximum, first and third quartile) and also in age groups according to two categorizations:

- 18-24, 25-35, 36-50, 51-64, 65+ years
- 18-65, 65+ years

Frequencies and percentages were presented for categorical variables.

The mid-P 95% confidence intervals (95% CI) were calculated for the main variables of interest (use of specific BZRA, patients taking doses higher than recommended, long-term use, daily use for at least one month, daily use for at least six months, patients who tried to stop taking BZRA, patients with SDS score greater than seven).

Missing values were not imputed and were recoded as not applicable (NA) or no response (NR). The code "NA" was applied for legitimate missing values (the question was not relevant because of the skip logic, i.e. the question was not applicable). The code "NR" was applied for illegitimate missing values. For the multi-punch questions (Question 11 and 22), if a person selected one or more of the available options as well as "None of the options", all specific options except "None" were retained in the analysis.

New users (starters) were identified as those who answered "I'm starting today" to Question 6, and were excluded from the main analyses.

"Long-term use" was defined as the use of at least one BZRA of interest over a period of at least one month. "Very long-term use" was defined as taking at least one BZRA of interest for at least six months.

For each drug, the recommended daily doses (RDDs), as indicated in the SmPCs and product leaflets, were used. For elderly (> 65 years), the RDDs are generally lower than those recommended for non-elderly adults. Depending on the specific drug, the RDDs for older adults range between 50% and 100% of the RDD (8). For simplicity, we defined the RDDs for elderly at 0.5×RDD. The list of RDDs for the drugs of interest is shown in Table 1.

"Daily use" was defined as taking BZRA one or more times a day. "Regular use" was defined as use of sleeping pills at least once a week but not every day. "Occasional use" was defined as less than once a week.

As described above, the perceived level of dependence on BZRA was based on a slightly modified SDS questionnaire, translated into French and Dutch. Numerical responses were assigned to the responses of all the items of Question 9:

- never or almost never = 0
- sometimes = 1
- often = 2
- always or almost always = 3

Numerical responses were assigned to the responses of Question 10:

- not difficult at all = 0
- quite difficult = 1
- very difficult = 2
- impossible = 3

The numerical responses are summed up and a global score is calculated. A score of seven is considered as a cut-off for measuring psychological dependence to BZD (17). By using skip logic and conditional branching, no SDS scores were calculated for new users (starters).

The following indicators were calculated:

- Percentage of patients who reported taking a BZRA for insomnia, by drug. Answers to Question three were used to calculate this indicator. The numerator was defined by the number of patients taking a specific BZRA. Different trade names for the same drug were considered separately and grouped by generic name. The denominator was defined as the total number of patients taking at least one of the BZRA of interest. If the patients are taking more than one BZRA, they were asked to choose the one they are taking most regularly.
- Percentage of patients who reported taking BZRA, by drug and actual daily dose. Actual daily dose was calculated using the reported dose (answers to Question 4, [note that some drugs have only one dose available; in these cases, Question 4 is not needed] and the reported number of tablets taken by day (answers to Question 5). Different trade names were presented separately and also grouped by generic name.
- Percentage of patients who reported taking BZRA, by drug and treatment duration (onset of treatment). This indicator was calculated using the answers to Question 6. Different trade names for the same active substance were grouped. Starters were excluded from this analysis.
- Percentage of patients who reported taking BZRA, by drug and frequency of use. This indicator was calculated using the answers to Question 7. Different trade names were presented separately and also grouped by active substance. Starters were excluded from this analysis.
- Percentage of patients who reported taking a BZRA dose higher than the RDD, by drug and age category (elderly vs. non-elderly adults). Different trade names were presented separately and also grouped by active substance. Starters were excluded from this analysis.
- Percentage of patients who reported taking a BZRA dose higher than the 2×RDD, by drug and age category (elderly vs. non-elderly adults). Different trade names were presented separately and also grouped by active substance. Starters were excluded from this analysis.
- Percentage of patients who reported taking BZRA daily for a time period of one month or longer, by drug. For the numerator, all the options that include at least one month of utilization were grouped. Individuals answering "do not know/do not remember" and starters were excluded from the denominator.
- Percentage of patients who reported taking BZRA every day for a time period of six months or longer, by drug. Individuals answering "do not know/do not remember" and starters were excluded from the denominator.
- Percentage of patients who reported taking a BZRA dose higher than the respective RDD or who reported taking BZRA every day for a time period of one month or longer, by drug. Starters were excluded from this analysis.
- Percentage of patients who reported taking a BZRA dose higher than the respective RDD or who reported taking BZRA at least once a week for a time period of one month or longer, by drug. Starters were excluded from this analysis.
- Percentage of patients who reported trying to stop taking BZRA. This indicator was calculated using the answers to Question 8. Starters were excluded from this analysis.
- Percentage of patients who reported taking BZRA, by drug and SDS score (calculated using the answers to Question 9 and 10). Only patients with calculated SDS scores were considered in the denominator. Starters were excluded from this analysis.
- Percentage of patients who reported taking BZRA with a SDS score ≥ 7, by drug. Only patients with calculated SDS scores were considered in the denominator. Starters were excluded from this analysis.
- Percentage of patients who reported taking other BZRA of interest for at least one month during 2019, by drug (grouped by active substance). This indicator was calculated using the answers to Question 11.
- Percentage of patients who reported taking BZRA and who tried alternative approaches to

manage insomnia. This indicator was calculated using the answers to Question 12.

- Percentage of patients who tried alternative approaches to manage insomnia, by specific alternative approach. This indicator was calculated using the answers to Question 13.

Results

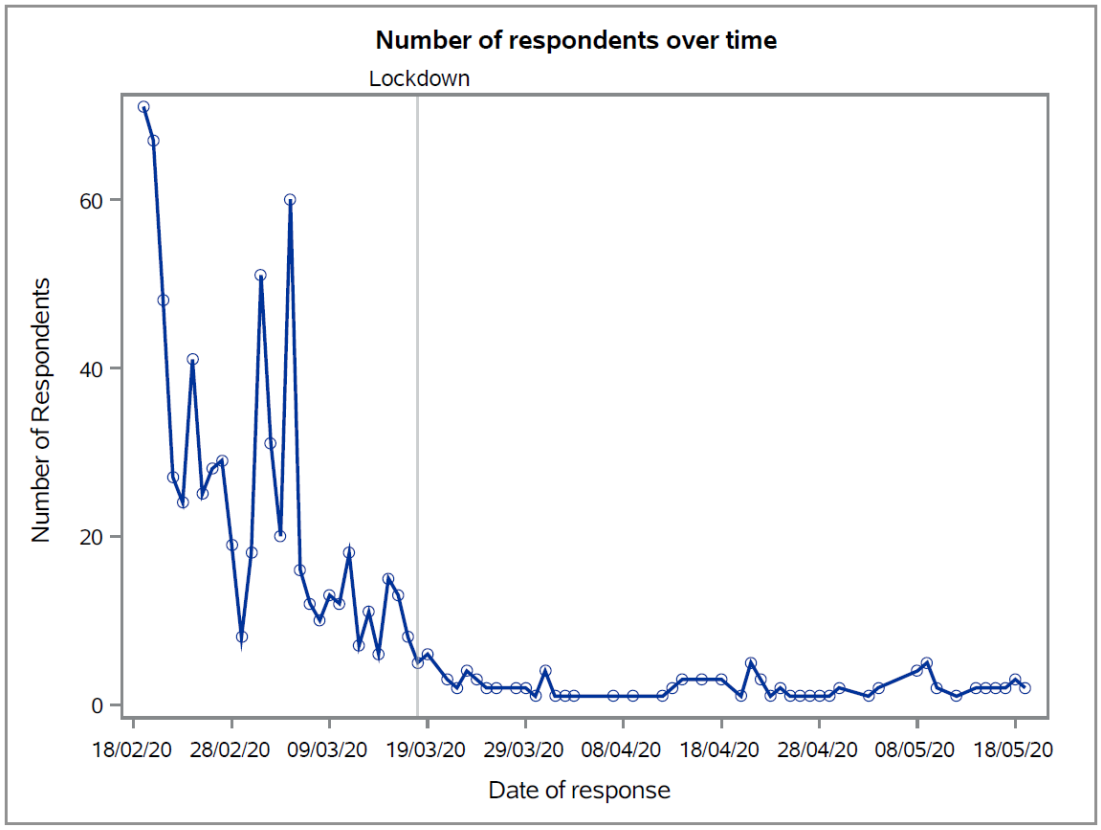
The results based on the analysis of the full dataset are similar to those obtained from the primary analysis of the completers dataset. Only the latter results are presented in the report. All the results for the primary analysis and the secondary analysis are presented in **Annex 3** and **Annex 4** respectively.

Number of respondents

A total of 808 patients responded (e.g., they started the survey by filling in the questionnaire): 509 respondents for the Dutch version and 299 for the French version of the questionnaire. The average time spent on responding the questionnaire was around three minutes.

The evolution of the number of respondents over time is shown in **Figure 1**.

Figure 1. Evolution of the number of respondents over time.

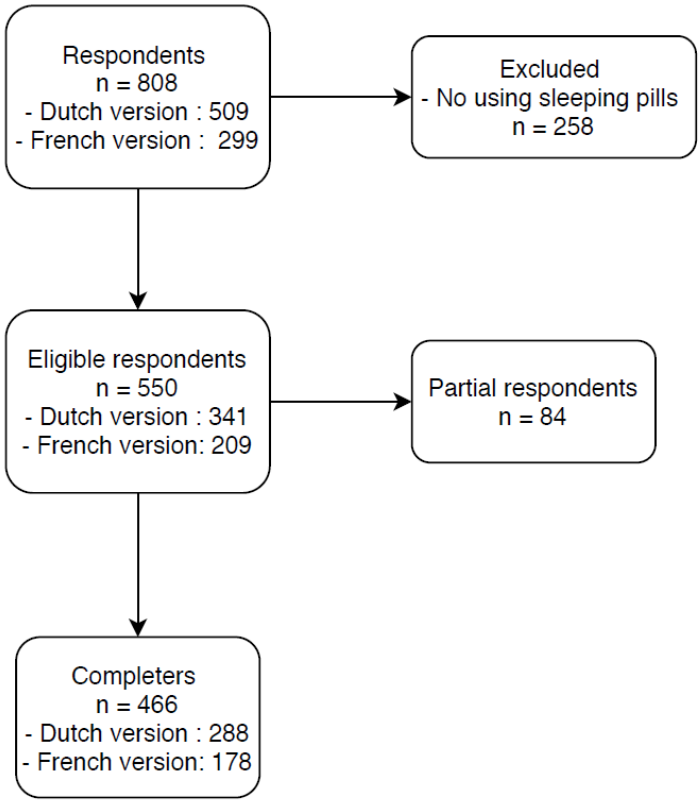


Participant disposition

After inspection of the responses, 258 patients (32%) were not eligible because they had not used any of the BZRA listed in the questionnaire. These patients were excluded from the analysis.

Of the 550 eligible respondents, 466 patients provided complete answers (completers) and 84 patients provided a partial response; the completion rate was estimated at 85%. The full analysis dataset included a total of 550 patients, while the primary analysis dataset included 466 patients.
A flow diagram depicting the progress through the phases of the study is shown in **Figure 2**.

Figure 2. Representation of the phases of the study.



Description of respondents

The mean age of the respondents was 55 years and 63 % of the respondents were women (**Table 2**). A very small number of patients in the youngest age group (18-24 years) participated in the survey (n = 8).

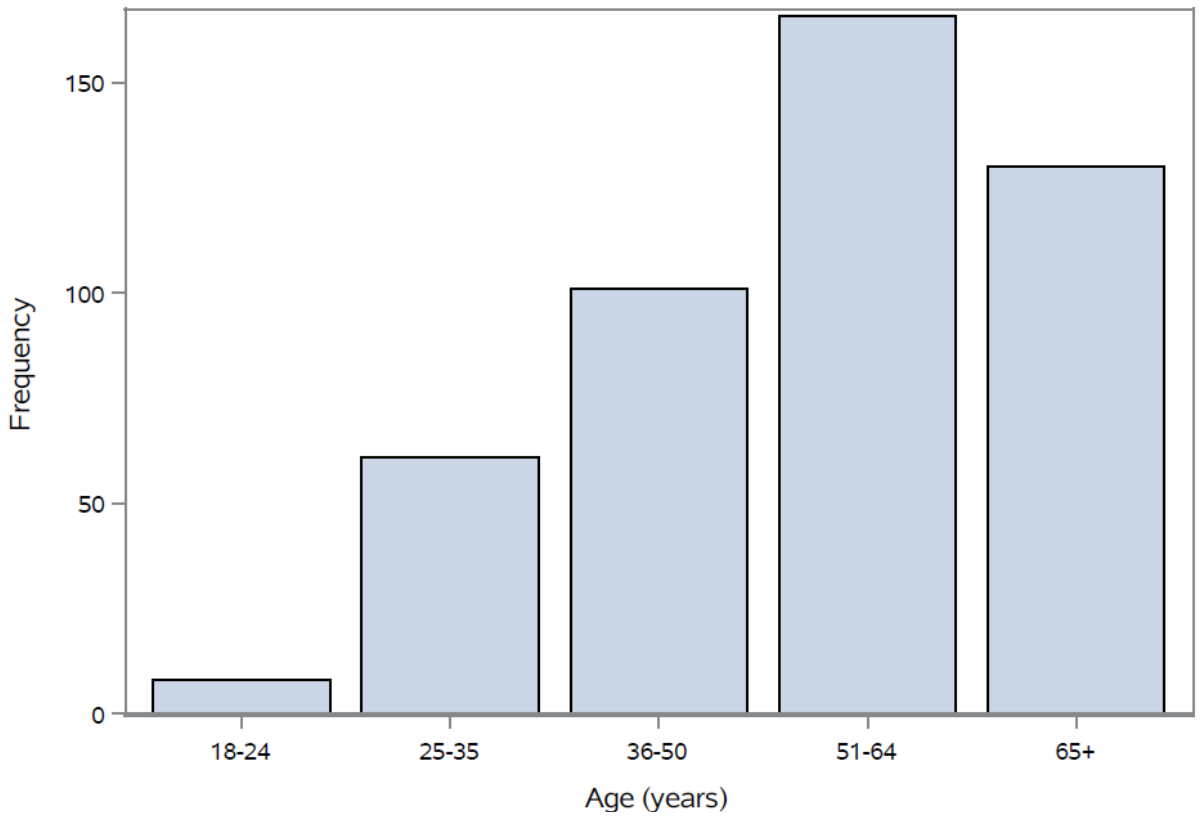
Table 2. Statistical overview of the characteristics of the study population.

Sample characteristic	**Completers, Dutch version** (n=288)	**Completers, French version** (n=178)	**All completers** (n=466)	**All respondents** (n=550)
Age (years), mean (SD)	58 (15)	51 (16)	55 (16)	54 (16)
Age (years), median (Q1-Q3)	58 (49-68)	51 (39-62)	56 (43-66)	56 (42-65)
Age (years), min-max	21-101	20-88	20-101	19-101
Age (categorized), n (%)				
18-24	3 (1)	5 (3)	8 (2)	13 (2)
25-35	31 (11)	30 (17)	61 (13)	77 (14)
36-50	49 (17)	52 (29)	101 (22)	124 (23)
51-64	115 (40)	51 (29)	166 (36)	191 (35)
65+	90 (31)	40 (22)	130 (28)	145 (26)
Sex, n (%)				
Female	180 (62)	113 (64)	293 (63)	342 (63)
Male	108 (38)	65 (36)	173 (37)	204 (37)

SD: standard deviation; Q1: lower quartile; Q3: upper quartile

The majority of the respondents were over 35 years of age (**Figure**).

Figure 3. Distribution of completers by age group.



Analysis of primary variables

Use of BZRA for insomnia by non-institutionalized patients

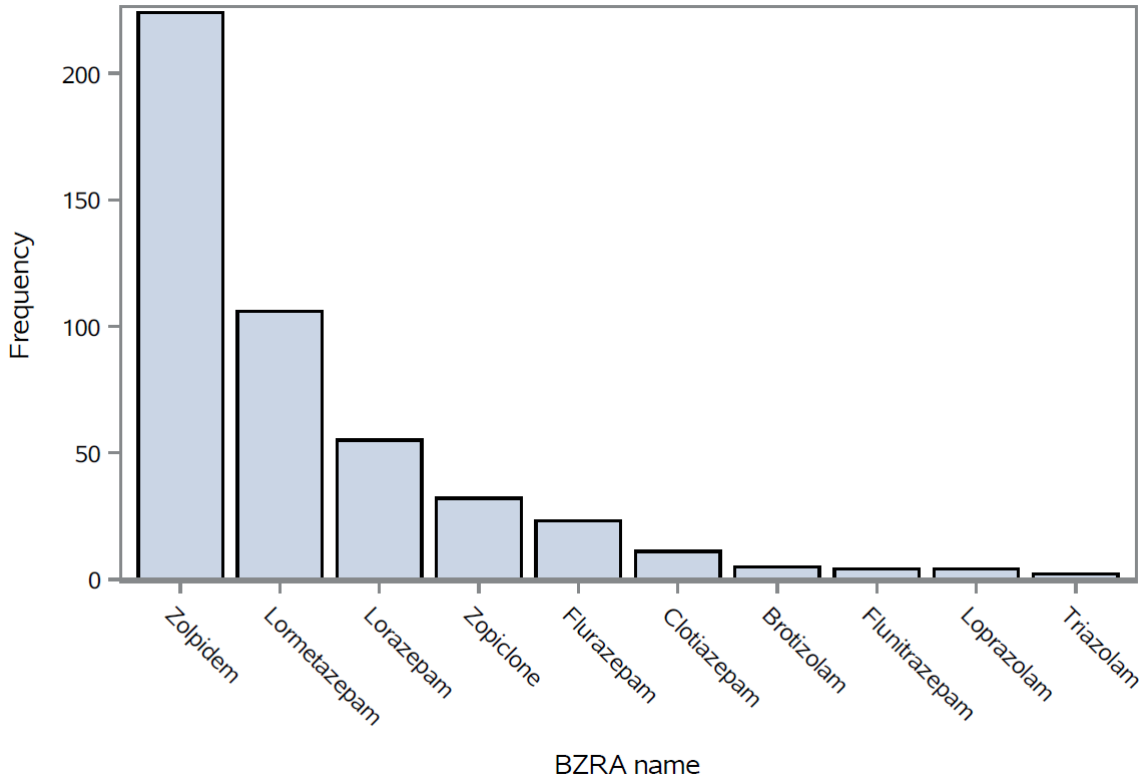
Zolpidem (ZLP) (48%, 95% CI 44-53%) and lormetazepam (LMZ) (23%, 19-27%) were the most frequently reported BZRA used to treat insomnia, followed by lorazepam (LRZ) (12%, 9-15%) and zopiclone (ZOP) (7%, 5-9%).
Table 3 and **Figure 4** show the distribution of use for the most frequently reported BZRA, by trade and generic name, respectively.

Table 3. Number of patients taking BZRA for insomnia categorized by drug (only BZRA reported to be used by ≥ 1% of the study population are presented).

BZRA Generic name	**BZRA Trade name**	**n (%)**
Zolpidem (ZLP)	Any	224 (48)
	Zolpidem EG	123 (26)
	Zolpidem Sandoz	48 (10)
	Stilnoct	25 (5)
	Zolpidem Teva	10 (2)
	Zolpitop	7 (2)
	Zolpeduar	6 (1)
	Zolpidem Mylan	5 (1)
Lormetazepam (LMZ)	Any	106 (23)
	Lormetazepam EG	73 (16)
	Loramet	15 (3)
	Lormetazepam Sandoz	9 (2)
	Metapop	7 (2)
Lorazepam (LRZ)	Any	55 (12)
	Lorazepam EG	30 (6)

	Temesta	21 (4)
Zopiclone (ZOP)	Any Zopiclone EG Imovane Zopiclone Mylan Zopiclone Teva	32 (7 19 (4) 5 (1) 5 (1) 5 (1)
Flurazepam	Staurodorm	23 (5)
Clotiazepam	Clozan	11 (2)
Brotizolam	Lendormin	5 (1)

Figure 4. Use of BZRA by generic name.



Use of BZRA for insomnia by daily dose

The reported daily doses are summarized in **Fout! Verwijzingsbron niet gevonden.**.

Three ZLP users, two LRZ users and one ZOP user reported a daily dose exceeding five times the recommended dose. Of these patients, two ZLP users and one ZOP user reported a daily dose exceeding ten times the recommended dose.

Table 4. Number of patients taking BZRA for insomnia categorized by BZRA (generic name) and reported daily dose (only BZRA reported to be used by ≥ 1% of the study population are presented).

BZRA (active substance)	**Dose (mg)**	**n (%)**
Zolpidem	1.25 2.5 5 10 **15** **20** **30** **60** **110**	1 (<1) 22 (10) 85 (38) 83 (37) **9 (4)** **13 (6)** **8 (4)** **1 (<1)** **2 (1)**

Lormetazepam	0.25 0.5 0.625 1 1.25 1.5 2 **2.5** **3** **4** **5**	3 (3) 18 (17) 1 (1) 30 (28) 3 (3) 2 (2) 39 (37) **2 (2)** **2 (2)** **5 (5)** **1 (1)**
Lorazepam	0.25 0.5 0.625 1 1.25 1.5 2 **2.5** **3** **3.75** **4** **5** **6** **7.5** **15**	3 (6) 7 (13) 3 (6) 10 (18) 6 (11) 2 (4) 2 (4) **7 (13)** **2 (4)** **3 (6)** **1 (2)** **4 (7)** **1 (2)** **2 (4)** **2 (4)**
Zopiclone	1.875 3.75 7.5 **11.25** **15** **22.5** **82.5**	1 (3) 13 (41) 10 (31) **1 (3)** **4 (13)** **2 (6)** **1 (3)**
Flurazepam	6.75 13.5 27 **54**	2 (9) 10 (44) 10 (44) **1 (4)**
Clotiazepam	2.5 5 10	1 (9) 8 (73) 2 (19)
Brotizolam	0.125 0.25	3 (60) 2 (40)

Doses higher than recommended are shown in red and bold

Compliance with the recommended use in terms of dosage

A total of 74 patients (16%, 13-19%) reported taking BZRA doses higher than recommended. The percentage of misuse was lower in LMZ users (9%) and higher in LRZ and ZOP users (27% and 25%, respectively). Zolpidem users showed an intermediate level of misuse (15%). Compared to the elderly, younger age groups (< 65 years of age) showed a higher percentage of taking higher doses than recommended (17% vs. 12%, Chi-Square p = 0.1894). Regarding sex, a higher percentage of males than females reported taking higher BZRA doses than recommended (23% vs. 12%, Chi-Square p=0.0025). A total of 21 patients (5%) reported taking more than twice the recommended dose of BZRA.

Use of BZRA for insomnia by duration of use

No starters were identified among the completers (all the patients could be considered as prevalent users). The majority of patients reported using BZRA for at least one year (

Table ***5***). A total of 47 patients reported that they could not remember for how long they are using BZRA. Among elderly patients (65+ years of age), 18% could not remember the duration of use, compared to 7% among the younger age groups (< 65 years of age).

Table 5. Frequency of patients taking BZRA for insomnia by duration of use.

Duration of use	**n (%)**
<=2 weeks	20 (4)
>2 weeks-<1 month	14 (3)
1 month-<6 months	35 (8)
6 months-<1 year	36 (8)
1 year+	314 (67)
Do not know/remember	47 (10)

Compliance with the recommended duration of use

After excluding 47 patients (10% of the respondents) who did not remember how long they had been using BZRA, a total of 385 patients (92%, 89-94%) were classified as long-term users (≥ 1 month usage) and 350 patients (84%, 80-87%) as very long-term users (≥ 6 months of use). Among elderly patients (65+ years of age), 84% are using BZRA for more than a year, compared to 72% among the younger age groups (< 65 years of age).

Use of BZRA for insomnia by frequency of use

The majority of patients reported daily use of BZRA (

Table 6).

Table 6. Frequency of patients taking BZRA for insomnia by current frequency of use.

Current frequency of use	**n (%)**
Daily (once or several times a day)	299 (64)
>=1/week	101 (22)
<1/week	66 (14)

Misuse of BZRA based on inappropriate use in terms of duration and frequency of use

The majority of patients could be considered misusers, reporting daily and long-term (i.e. daily use for one month or more) use of BZRA (253, 60%, 56-65%). The percentage was higher for ZOP users (77%) compared to LMZ (69%), LRZ (60%) and ZLP users (55%). A very high percentage of misuse was found for loprazolam (LOP) (75%) but this is of limited value given that only four LOP users were identified. The number of patients reporting daily and long-term BZRA use (at least one month) or BZRA daily dose higher than recommended was 264 (63%, 58-68%). The number of patients reporting daily and very long-term use of BZRA (for six months or more) was 238 (57%, 52-61%). The number of patients reporting daily or regular and long-term use was 335 (80%, 76-84%), and the number of patients reporting daily or regular and very long-term use was 307 (73%, 69-77%).

Analysis of secondary variables

Trying to stop using BZRA for insomnia

The number of patients who reported they have already tried to stop taking BZRA was 311 (67%; 62%-71%). The percentage was lower in the youngest age groups (57% in the 25-35 age group) and appeared to stabilize in the 36-50 age group (69%).

Degree of psychological dependence measured by the SDS score

The number of patients with a calculated SDS score of seven or higher (i.e. showing

psychological dependence) was 178 (38%; 34%-43%). The percentage of perceived psychological dependence was relatively similar when comparing the most commonly used BZRA (LRZ: 42%, LMZ: 35%, ZLP: 39%). Male patients showed a slightly larger percentage of SDS-based psychological dependence than female patients (43% vs. 36%). No difference in percentage was found between elderly and younger age groups (both 38%). The results displayed per item are shown in
Table 7.

Table 7. Distribution of responses for the Severity of Dependence Scale by item.

Item	Never n (%)	Sometimes n (%)	Often n (%)	Always n (%)
Did you think your use of BZRA was out of control?	285 (61)	102 (22)	46 (1)	33 (7)
Did the prospect of missing a dose make you anxious or worried?	182 (39)	119 (25)	72 (15)	93 (20)
Did you worry about your use of BZRA?	188 (40)	147 (31)	84 (18)	47 (10)
Did you wish you could stop?	116 (25)	136 (29)	106 (23)	108 (23)

Item	Not hard n (%)	Quite hard n (%)	Very hard n (%)	Impossible n (%)
How difficult would you find it to stop, or go without BZRA?	85 (18)	162 (35)	156 (33)	63 (13)

Alternative approaches used for insomnia

The number of patients who reported trying an alternative approach to BZRA was 326 (70%). The most frequently mentioned approaches were the use of herbal medicines, homeopathy or food supplements, and sleep hygiene, both reported by more than 60% of the patients. The different alternatives that were used are summarized in
Table 8.

Table 8. Distribution of use of alternative approaches for insomnia.

Alternative	n (%)
Herbal medicine/Homeopathy/Food supplements	218 (67)
Sleep hygiene	205 (63)
Melatonin	139 (43)
Physical activity	134 (41)
Relaxation	132 (40)
Support/Therapy	62 (19)

Patients taking multiple BZRA for insomnia

A total of 89 patients (19%) reported taking more than one BZRA for at least one month in the past year:

- 69 used 2 different BZRA;
- 18 used 3 different BZRA;
- 2 used 4 different BZRA.

When analysed by drug, ZOP and LRZ users were more likely to be users of other BZRA than LMZ and ZLP users (34% and 29% vs. 20% and 13%, respectively). The BZRA most

commonly reported as second BZRA treatment of sleep disorders were ZLP and LRZ (7% and 6% of the patients, respectively).

Discussion

Use of BZRA for insomnia

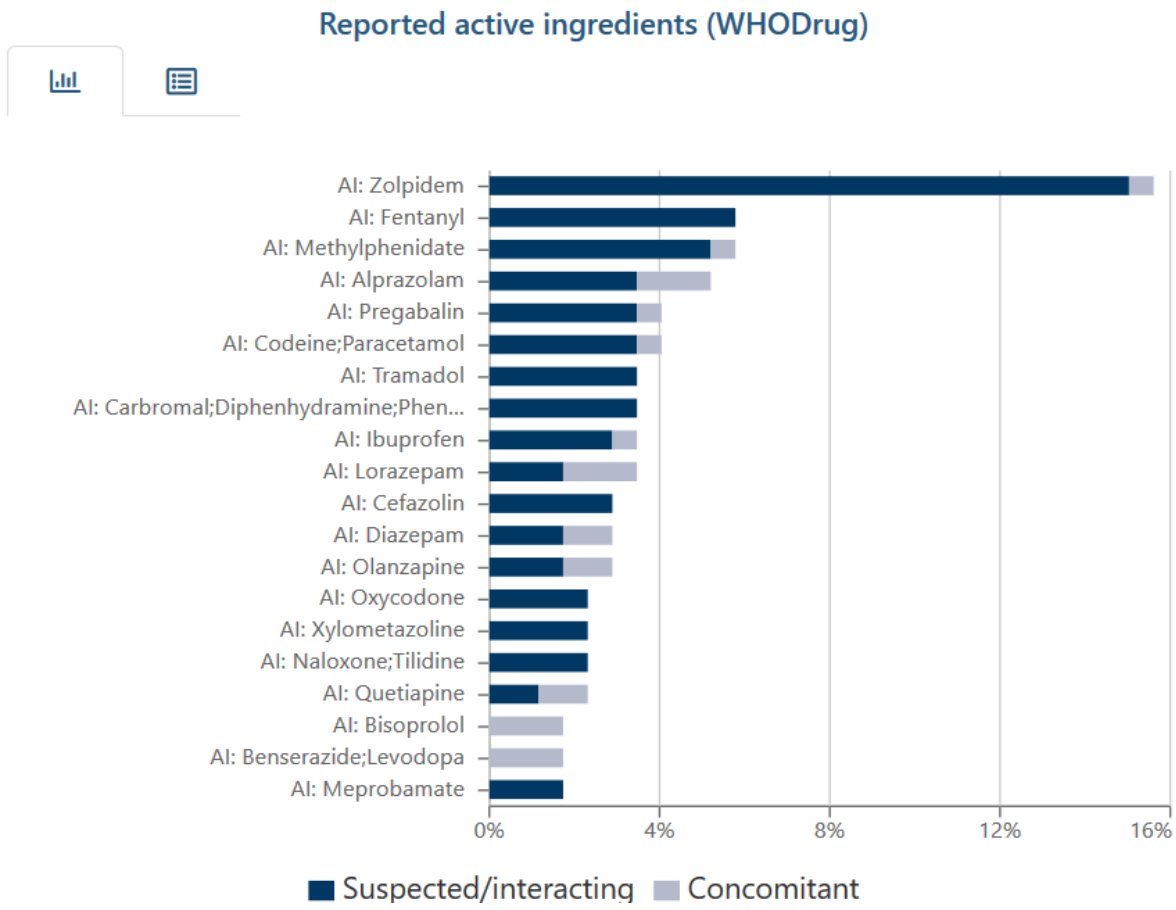
Almost half of the respondents reported the use of ZLP as sleeping pill. The second and third most frequently reported BZRA were LMZ and LRZ. All other BZRA were reported by less than 10% of the respondents. This is in line with the guideline of Domus Medica (40) which favours the use of BZD with medium duration of action (f.i. LMZ, LRZ) or Z-product (f.i. ZLP) as short-term treatment only when medicinal treatment of insomnia is required. According to the INCB 2019 report (11), the global consumption of zolpidem has risen in 2018, compared to 2017, with Belgium reporting the highest rate of consumption. The increased consumption of zolpidem has already been observed at national level: while a very slight decrease was observed for all hypnotics between 2014 and 2016, the number of packages delivered for zolpidem has increased between 2016 and 2018 (22). This prescribing trend (prescribing Z-drugs over BZD drugs) has also been observed in other countries (30 31 32). Although early clinical trials did not reveal any abuse or dependence risk associated with ZLP (24), many cases have been reported in various European countries and the United States (US) following marketing of the product (25).

Considering that the frequency of abuse and dependence with ZLP appeared to be similar to that of BZD hypnotics, WHO decided in 2002 to add ZLP to Schedule IV ("substances with abuse potential of low public health risk but of low to high therapeutic value") of the 1971 Vienna International Convention (24). The SmPC for ZLP-containing drugs includes warnings about the risk of dependence and abuse. These warnings are similar to those in the SmPCs for BZD.

However, several studies have shown that physicians perceived Z-drugs as more effective and safer compared to BZD (30 31 32).

In addition, ZLP is the most reported drug associated with drug abuse in Belgium according to the WHO database for adverse drug reactions, called *VigiBase* (figure 5).

Figure 5. Reported active substances for drug abuse in Belgium (search on https://vigilyze.who-umc.org/ , September 22 2020, MedDRA term reaction PT "Drug Abuse", country "Belgium")



Misuse

Misuse in terms of dosage

The percentage of respondents who reported taking a higher daily dose of BZRA than recommended was relatively low (16%). This percentage was lower among the elderly compared to the younger age groups, and lower among women than among men. The percentage of respondents reporting that they are using more than twice the recommended daily dose was also low. Among users of the most frequently reported BZRA, the percentage of use of daily doses higher than recommended was highest for LRZ and ZOP, lower for ZLP and lowest for LMZ users. Two ZLP users and one ZOP user reported a daily dose more than ten times the recommended dose.

These results should be interpreted with caution due to the possibility of non-response bias. Several studies have suggested that, even with a voluntary sample, estimates from surveys of health compromising behaviours, such as substance abuse, should generally be considered underestimates (18 26).

A search in the WHO *Vigibase* database on 22 September 2020 has shown that 33 cases of drug abuse have been reported in Belgium for the BZRA used in this survey. Among these cases, 79% concerns ZLP. Most of the cases (23) have been reported since 2019. This can be explained by the fact that since 2019, HCPs can report drug abuse directly to the Vigilance Division of the FAMHP. Most of these cases are reported by pharmacists who notice through the shared pharmaceutical file that an excessive number of boxes has been delivered to the patient. Various pharmacists report patients taking an average of one box of ZLP per day.

In the past years, there have been case reports and case series on zolpidem dependence, reporting a maximum dose of 2400 mg/day (36 37), which is significantly higher than the

recommended daily dose of 10 mg. Moreover, since 2002, the French health authorities (National Agency for Medicines and Health Products Safety; ANSM) have conducted national surveys on addiction to evaluate the dependence potential of zolpidem. Several surveys were conducted between 1993 and 2013. The results highlighted the high dependence potential of zolpidem and identified two distinct populations among dependent patients: the first type seeking paradoxical stimulant effects by taking high doses during the day, the second type of patients, treated for insomnia, who have increased their doses given the short half-life and tolerance of this substance (37). These surveys showed a different abuse/dependence profile for ZLP compared to BZD and ZOP in terms of dosage and utilization with a consumption at high dosage of zolpidem by chronic users, but also abuse of the substance in order to obtain an effect other than hypnotic (notably recreational effects). In addition, ZLP was also the drug involved in cases of chemical submission. The French committee for narcotics and psychotropic drugs suggested adding ZLP on the list of drugs subject to special Prescription (13 37 38 39).

Misuse in terms of duration

Almost all respondents could be considered as prevalent users (only two patients were identified as starters). Long-term use (six months or more) and very-long term use (six months or more) was highly prevalent (83% and 75%, respectively) among respondents. In addition, 10% of the respondents overall and 18% of the elderly patients (versus 7% of the younger age groups) replied that they did not know how long they are taking BZRA. It can be assumed that these patients are taking BZRA for relatively long periods of time, suggesting that the proportion of long and very-long use may be underestimated. The majority of respondents reported daily use of BZRA, while approximately 20% were regular users (at least once a week). Furthermore, the majority of the respondents reported both daily and very long-term use of BZRA. All the most frequently used BZRA (ZOP, LMZ, LRZ, ZLP) were reported by the majority of the patients as being used on a daily and very-long term, in particular for ZOP and LMZ compared to ZLP users.

According to the literature, long-term BZD use is a common phenomenon in primary care. A meta-analyses regarding general practitioners' (GP) experiences and perceptions of BZD prescribing showed that GPs were more tolerant of long-term use in older than younger patients (28), despite the increased risk for adverse effects in older people associated with age-related changes in the pharmacokinetics and pharmacodynamics of benzodiazepines (42 43 44).

According to Cook et al. (2007), GPs also felt a lack of alternatives for elderly patients compared to younger patients, due to financial and transportation difficulties (28 41). In this survey, a clear trend of longer durations of use in elderly (65+) is only observed for durations of use of one year or longer.

Tolerance associated with BZRA has long been known (5 6) and guidelines recommend to limit BZD to short-term use. Studies have suggested that when used for more than a short period of time (i.e. two weeks or longer), BZD lose their usefulness in insomnia, even disrupting overall sleep architecture causing a deterioration of sleep quality. Both dependence (physiologic and psychological) and tolerance to the sedative effects occur rapidly within two to four weeks, but the risk of adverse effects remains (10). Memory impairment, daytime sleepiness, falls resulting in fractures, motor vehicle accidents have been linked to the long-term use of BZRA, among other serious adverse effects (5 6 7 8 27). However, many patients ignore this fact and it is known that long-term use still often occurs in patients with chronic insomnia (6). It is interesting to note that in Belgium the most frequently used BZRA are usually commercialized in boxes with thirty or more tablets. Patients may continue to take the drug "to empty the box", despite the GP's recommendations. In 2018 and 2019, the FAMHP conducted two surveys among physicians and pharmacists about small packages (less than thirty tablets) of BZRA. The majority of the respondents found small packages to be useful to reduce the risk of abuse and dependence, particularly among new and occasional users.

Concomitant use of multiple BZRA

About one fifth of the respondents reported using more than one BZRA in the past year. This finding suggests that some people are using at least two different BZRA simultaneously.

Concurrent use of multiple BZRA increases the risk of misuse/abuse and should generally be avoided.

Psychological dependence

The SDS is recognized as a reliable and valid screening tool for assessing the misuse and dependence on BZD (17), with an optimal cut-off score of seven (a score higher than six indicates problematic use of BZD). More than one-third of the respondents showed psychological signs of dependence to BZRA. This number is relatively low compared to the number of patients identified as daily and long-term users (60%). It should be noted that the majority of the respondents had already tried to stop their treatment in the past, which may have failed as the majority of the respondents are long term or very long term users. This might be due to a relapse of insomnia or dependency issues. Furthermore, the majority of the respondents expressed their willingness to stop their BZRA treatment and almost half of the respondents would find it very hard or impossible. We can therefore assume that a significant proportion of misusers did not perceive their signs of psychological dependence.

Studies have estimated that at least 15% and perhaps as many as 44% of chronic users become dependent to their BZRA treatment (17) and that approximately one-third of chronic hypnotic users could be unable to discontinue the medication (27). Relapse rates are high even for those who are able to stop (27).

It has also been observed in several studies that many patients reported a lack of knowledge or concern about the long-term use of BZRA medication (6 9). Patients perceived chronic stable BZD use, especially if they did not increase the prescribed dose, as responsive to a need and as a great benefit. In doing so, they minimized or even denied physical addictive properties or potential for misuse or inappropriate use (9).

Alternative approaches to insomnia

The majority of respondents had tried other approaches to treat insomnia besides the use of BZRA. The most common approaches, mentioned by more than half of the respondents, were the use of homeopathy, herbal medicines or food supplements and sleep hygiene techniques. This study did not ask whether these alternative approaches had been tried prior to or simultaneously with the BZRA treatment. However, it can be assumed that these patients did not find an effective alternative approach to tackle their insomnia.

A meta-synthesis on patients' perception and experience of BZRA use has identified that patients felt they had tried alternatives to medication before seeing their GP, but that these were ineffective. However, the alternatives tried were not necessarily those that would be recommended by an HCP (9). On the other hand, HCPs expressed concerns that there is a lack of alternatives to medication, and when these are available they are time-consuming and difficult to access (28).

In this study, most patients chose homeopathy, herbal medicines or food supplements as alternative approaches. Natural remedies are often perceived as safer than conventional medicinal products, although risk concerns have been raised for many supplements (29 30) and their efficacy is often questioned (3). The Domus Medica guideline does not recommend these therapies as first-line approaches to tackle sleep complaints and insomnia in adults (40).

Both European and American guidelines recommend cognitive behavioural therapy for insomnia (CBT-I) as first-line treatment for chronic insomnia in adults of any age (3 29). CBT-I usually consists of psychoeducation/sleep hygiene, relaxation training, stimulus control therapy, sleep restriction therapy and cognitive therapy. In this survey, CBT-I was not mentioned as a choice, but we can assume that it is implicitly included in "Support/therapy". Only 19% of the respondents have tried that approach.

CBT-I has many advantages as it does not have the adverse effects of hypnotics. Unfortunately, CBT services are extremely limited (particularly amongst GPs) and expensive. Moreover, hypnotic medications work quickly, and patients usually notice the effects after the

first dose. In contrast, CBT-I usually takes weeks to show effects on insomnia. Therefore, many people suffering from insomnia prefer medication in order to have a quick solution (1).

Strengths and limitations

For this study, the data were collected using a web-based (online) questionnaire. In general, surveys are suitable for measuring perceptions and emotions. They are a possible alternative for answering certain questions that cannot easily be answered with other data sources (e.g. administrative databases) for example, due to the lack of reimbursement. Online surveys are relatively simple and quick to be executed. They have a number of advantages: relatively low costs, real-time collection and access to high-quality data, the convenience for respondents to answer following their schedule, and automation with the possibility of easily incorporating logical checks and branching logic (skip patterns) (23). In particular, self-administered surveys seem to be less affected by social desirability bias and can be considered as appropriate for addressing potential sensitive topics (such as those associated with the use of sleeping pills) (14 15). Self-administered surveys are also more flexible (less time constrained) for the participants than face-to-face and telephone surveys. Furthermore, the fact that the questionnaire was distributed via the pharmacies could also have increased the level of confidence in the survey.

However, the survey shows some limitations which may have an impact on the results and should be discussed when presenting the findings.

As the sampling frame cannot be rigorously defined (we do not have access to a list of BZRA consumers in Belgium and patient participation is based on a voluntary basis), we cannot consider our sampling strategy as probability sampling. Assuming that a large number of pharmacies would participate in the survey and that pharmacists would provide the information systematically to patients over a period of three months, we anticipated the source of potential participating patients to be extensive enough to be representative of the target population (in particular for chronic users).

However, the achieved study size was far from the expected one. Several factors may have contributed to the small study size. It is possible that not all pharmacies and pharmacists may have felt committed to actively participate in patient recruitment. Also, many patients may not have been sufficiently motivated to participate in the survey (read the information on the label, open the web link, answer the questions). The impact of the COVID-19 epidemic during the survey might also have been an important determinant in explaining the low participation rate. Sciensano's second COVID-19 survey, conducted in spring 2020, shows an increased use of sleeping pills or tranquillizers in Belgium since the lockdown, and the frequentation in pharmacy has increased from 50% during lockdown. However, it can be assumed that even before lockdown it was difficult for pharmacists to talk to patients about the survey that does not concern the epidemic and for patients to be motivated to participate. Moreover, as the extension of the survey from one month to three months was not planned in advance, no new stickers were sent after the second week of the survey. All these factors might have contributed to the low number of respondents after the lockdown.

Selection bias, in particular non-response bias, is the main potential threat to the validity and the generalizability of the findings in self-administered questionnaires. People who are better educated, motivated, who properly read Dutch or French, and who have access to and feel more comfortable using the internet, are more likely to be respondents. Women are also generally more likely to respond to a survey than men (18 19), which is also reflected in this survey. Elderly are likely to be underrepresented in the study population because they feel less comfortable using or having limited access to the internet. In this survey, the age category 65+ was represented by almost one third of the respondents and this age group was not the least represented either.

Because participation rates may vary by socio-economic status, language, culture and health status, the study population (total respondents) may differ from the source (and the target) population. Moreover, this potential bias is highly likely in patients recruited in pharmacies and probably even more so in patients who were informed through other communication channels.

Online surveys are known to attract respondents with a particular interest in the subject under investigation and previous studies have shown that non-response is usually associated with pathology or health-compromising behaviours, such as substance abuse, which is more likely to be underreported (18 26). These variables were not collected and individuals presenting some of these characteristics may be less likely to respond and may therefore be underrepresented in the study population.

The effect of bias could act in opposite directions: upwards bias because the most interested and concerned patients may be participating more actively, and downward bias because of social desirability effects and concerns about confidentiality. It is difficult to determine the direction of bias, but it can be hypothesized that respondents properly follow the recommendations of use more frequently than non-respondents. As a consequence, the estimation of BZRA use may be biased and the SDS component of the questionnaire may be affected by social desirability.

Moreover, the SDS questionnaire, which was originally developed for assessing psychological dependence on drugs like heroin, cocaine, and amphetamines, was only tested in a particular setting: the population of neurotic patients attending a mental health outpatient service in the Canary Islands and who are regular users of BZD (continuous daily use for at least 3 months) (17). The ability to generalise outside this particular setting cannot be guaranteed.

Another selection bias may occur because the survey was conducted during a certain period. Only patients who entered a pharmacy during this period may have been recruited. It is possible that some time periods are perceived as being more or less favourable for consuming or stopping taking BZRA (e.g. the consumption of BZRA may decrease during the holidays, occasional consumers are more likely to stop during these periods). The impact of the coronavirus pandemic on this selection bias should also be considered.

Additionally, polypharmacy/co-medication status may also be a factor for differential recruitment, people taking multiple medicines have a higher probability to be contacted, informed and reminded about the survey. Also, BZRA abusers shopping in pharmacies (i.e. non-illicit acquisitions) are more likely to be approached to participate in the study.

There are also some structural limitations in the questionnaire. The main question focuses on the use of one BZRA. If patients took (an)other BZRA(s) in the last year, this has been collected in a secondary question, for which less details were asked. It is possible that some patients taking one specific drug have switched between different brands over time (e.g. from Stilnoct to Zolpidem EG). In these cases, it is likely that part of the exposure time is not recorded with enough detail. As a result, it would not be possible to accurately estimate the duration of use, which may be biased towards shorter periods of exposure time.

Patients in a withdrawal program have probably reported lower doses than used just recently before or not have reported BZRA use at all. For example, individuals who are under pharmacotherapy substitution for managing BZRA discontinuation (e.g. using diazepam, antidepressants, antiepileptics, …) may not have been included in the survey. This implies an underrepresentation of patients affected by the problematic abuse and dependence of BZRA.

The analysis of reported doses compared to recommended doses was based on RDD. However, the recommended doses for some more vulnerable populations (e.g. hepatic or renal impairment, respiratory problems) are lower than the RDD. As some of these patients may represent part of the studied population, it is likely that the prevalence of patients taking BZRA doses above the recommended dose have been underestimated.

Misclassification is also a concern because of potential errors or recall issues when answering the questions. However, we tried to minimize the error rate by using an online questionnaire with automatic logical checks, conditional branching and closed-ended questions.

In general, the limitations identified may lead to biases that tend to reduce the percentage of abusers and misusers.

Generalisability of results

With regard to the generalisability of the findings, the results of this study should be interpreted with caution because of the nature of the sampling method and the limited study size.

Some additional considerations affecting generalisability should also be mentioned. Only primary care patients were recruited, so the findings cannot be generalized to the institutionalized setting. Non-prescribed/illicit use was not captured. Individuals taking BZD(s) not included in the list of BZRA of interest (e.g. diazepam, alprazolam …) were not captured because these drugs were mainly indicated for anxiety and not for insomnia. However, some individuals may be using these BZD as sleeping pills (2).

Conclusions

Despite the limited study size, several findings have been made with this survey. First of all, this survey's results are consistent with other countries' findings and national data of BZRA use: ZLP is the most common BZRA prescribed for insomnia. It can be assumed that Belgian physicians still consider Z-drugs as more effective and safer compared to BZD, which is also observed in other countries (30 31 32).

This study showed in particular that recommendations, especially in terms of duration, are not followed either by patients nor by physicians who continue to prescribe these medications for a long period of time. Most patients may be unaware or in denial of the risks of dependency and long-term effects (6 9). However, these serious adverse effects have been demonstrated, making BZRA misuse/abuse an important public health issue.

The survey also showed that a majority of the respondents had tried alternative methods for treating insomnia. They mainly tried remedies often perceived as "natural" and safer than classic medicinal products, even if guidelines do not recommend them as first-line treatment for insomnia (40), because scientific evidence is lacking for most of them and risk concerns have been raised. Studies have shown that the alternatives tried by patients prior to the first consultation are not necessarily those that would be recommended by a physician (9). On the other hand, physicians express concerns about the lack of or difficulty to access to alternatives to medication (28).

It is therefore essential to target both patients and prescribers when considering methods to minimise misuse/abuse of BZRA. This strategy has already been proven to be the most successful (33).

In general, it is important to keep reminding both patients and prescribers that medication should not be considered as a first-line treatment for insomnia. It is crucial to increase the availability (accessibility and cost) of effective alternatives.

Prescribers should be encouraged to discuss the risks of BZRA with the patient, including reduced efficacy over time, rebound/withdrawal effects and tapering options. Literature review shows some patients are not concerned about the risk of addiction, while others would prefer alternative treatments and would not have started with BZRA therapy if they would have been made aware of the risk of addiction (9).

Scheduling a follow-up consultation after one week to check for effectiveness, inquire about adverse effects and review the follow-up is helpful to prevent misuse (34). By prescribing smaller boxes of BZRA (less than 30 tablets), physicians are also encouraging the patients to seek for advices if they feel the need to continue their treatment. The current supply of small pack sizes should also be expanded to allow pharmacists to respond quickly to patient's demand and comply with the physician's prescription.

Meanwhile, deprescribing of BZRA should be offered to all chronic BZRA users (34), especially

those aged 65 and older (6) given the increased risk of adverse reactions in this population. In this study, a majority of respondents have tried to stop their treatment and/or are willing to stop. HCPs might expect patients to be reluctant to stop their medication or explore alternatives, whereas patients might be open to alternatives and withdrawal solutions (35). Educating and reminding HCPs to actively discuss and empathize with the patient is thus important (28 34 35).

In conclusion, it is important to continue and improve communication and access to educational resources for both patients and HCPs when aiming to a rational use of BZRA in insomnia.

Ethics and disclosure

Consent

Participation in the study was voluntary. This was clearly stated on the introductory page of the questionnaire and by community pharmacists informing patients about the study. No personal data were collected to identify respondents. Implied consent was assumed by voluntary completion of the questionnaire.

Sponsorship

The study was funded by the FAMHP.

Research ethics approval

The survey was submitted to and approved by the ethics committee of an academic teaching hospital (Hôpital Erasme-ULB).

Privacy commission

According to the Privacy Act and the General Data Protection Regulation (GDPR), personal data are all data that directly identify or can identify an individual (e.g. person's name, phone number and email address). No identifiable data were recorded in this survey to protect subject anonymity.

The FAMHP received the survey responses, without email addresses or other personal identification data. Participants' IP addresses were not recorded in the dataset using the option for "anonymous responses" that disables the collection of IP addresses.

The FAMHP information security consultant reviewed the "privacy policy", "security policy" and the GDPR-compliance of SurveyMonkey and concluded that these were in agreement with the Privacy Act and the GDPR.

References

1. Asnis, G. M., Thomas, M. & Henderson, M. A. Pharmacotherapy treatment options for insomnia: A primer for clinicians. *Int. J. Mol. Sci.* **17**, 1–11 (2015).
2. Roehrs, Timothy, and Thomas Roth. Insomnia pharmacotherapy. *Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics* vol. **9**,4 (2012): 728-38. doi:10.1007/s13311-012-0148-3
3. Riemann, D., Baglioni, C., Bassetti, C., Bjorvatn, B., Dolenc Groselj, L., Ellis, J.G., Espie, C.A., Garcia-Borreguero, D., Gjerstad, M., Gonçalves, M., Hertenstein, E., Jansson-Fröjmark, M., Jennum, P.J., Leger, D., Nissen, C., Parrino, L., Paunio, T., Pevernagie, D., Verbraecken, J., Weeß, H.-G., Wichniak, A., Zavalko, I., Arnardottir, E.S., Deleanu, O.-C., Strazisar, B., Zoetmulder, M. and Spiegelhalder, K., European guideline for the diagnosis and treatment of insomnia. *J Sleep Res*, **26** (2017): 675-700. doi:10.1111/jsr.12594
4. Creupelandt, H. *et al.* Teaching young GPs to cope with psychosocial consultations without prescribing: A durable impact of an e-module on determinants of benzodiazepines prescribing. *BMC Med. Educ.* **17** (2017): 1–9.
5. Batlle, E., Lizano, E., Viñas, M. & Dolors Pujol, M. 1,4-Benzodiazepines and New Derivatives: Description, Analysis, and Organic Synthesis. in *Medicinal Chemistry* (2019). doi:10.5772/intechopen.79879
6. Pottie K, Thompson W, Davies S, Grenier J, Sadowski CA, Welch V, Holbrook A, Boyd C, Swenson R, Ma A, Farrell B. Deprescribing benzodiazepine receptor agonists: Evidence-based clinical practice guideline. *Can Fam Physician*. May;**64**, 5 (2018):339-351. PMID: 29760253; PMCID: PMC5951648.
7. Brandt, J. & Leong, C. Benzodiazepines and Z-Drugs: An Updated Review of Major Adverse Outcomes Reported on in Epidemiologic Research. *Drugs in R and D* **17** (2017): 493–507.
8. He, Q., Chen, X., Wu, T., Li, L. & Fei, X. Risk of dementia in long-term benzodiazepine users: Evidence from a meta-analysis of observational studies. *J. Clin. Neurol.* **15** (2019): 9–19.
9. Sirdifield, C., Chipchase, S. Y., Owen, S. & Siriwardena, A. N. A Systematic Review and Meta-Synthesis of Patients' Experiences and Perceptions of Seeking and Using Benzodiazepines and Z-Drugs: Towards Safer Prescribing. *Patient* **10**, (2017).
10. Lee JY, Farrell B, Holbrook AM. Deprescribing benzodiazepine receptor agonists taken for insomnia: a review and key messages from practice guidelines [published correction appears in Pol Arch Intern Med. Feb 28;129(2):145]. *Pol Arch Intern Med*.;**129**(1) (2019):43-49. doi:10.20452/pamw.4391
11. INCB. Psychotropic Substances 2019 – Statistics for 2018. Available online: https://www.incb.org/documents/Psychotropics/technical-publications/2019/PSY_Technical_Publication_2019.pdf
12. Gisle, L. Santé mentale. in *Enquête de santé 2013. Rapport 1: Santé et Bien-être.* (eds. Van der Heyden, J. & Charafeddine, R.) WIV-ISP, Bruxelles (2014). Disponible en ligne: https://his.wiv-isp.be/fr/Documents%20partages/WB_FR_2013.pdf
13. ANSM. Zolpidem : nouvelles conditions de prescription et de délivrance. Lettre aux professionnels de la santé. Feb. (2017). Available online : https://ansm.sante.fr/var/ansm_site/storage/original/application/8f2c0b719a543c105450a580348d0acd.pdf
14. Tourangeau R., Yan T. Sensitive questions in surveys. *Psychol Bull*. Sep; **133**(5): 859-83.(2007). doi: 10.1037/0033-2909.133.5.859.
15. Bowling A. Mode of questionnaire administration can have serious effects on data quality. *J Public Health (Oxf).*;**27**(3) (2005):281-291. doi:10.1093/pubmed/fdi031
16. Gossop, M. *et al.* The Severity of Dependence Scale (SDS): psychometric properties of the SDS in English and Australian samples of heroin, cocaine and amphetamine users. *Addiction* **90**, (1995): 607–614.
17. De Las Cuevas, C., Sanz, E. J., De La Fuente, J. A., Padilla, J. & Berenguer, J. C. The Severity of Dependence Scale (SDS) as screening test for benzodiazepine dependence: SDS validation study. *Addiction* **95**, 245–250 (2000).
18. Cheung KL, Ten Klooster PM, Smit C, de Vries H, Pieterse ME. The impact of non-response bias due to sampling in public health studies: A comparison of voluntary versus mandatory recruitment in a Dutch national survey on adolescent health. *BMC Public Health*.;17(1):276 (2017). doi:10.1186/s12889-017-4189-8
19. Smith, William. Does Gender Influence Online Survey Participation? A Record-Linkage Analysis of University Faculty Online Survey Response Behavior. Online Submission (2008).
20. Gisle L, Drieskens S, Demarest S, Van der Heyden J. Santé mentale. Enquête de santé. Bruxelles, Belgique : Sciensano ; Numéro de rapport : D/2020/14.440/3 (2018). Disponible en ligne : www.enquetesante.be
21. Federal Public Service of Health , « Somnifères et calmants, pensez d'abord aux autres solutions » . Online campaign (2018). Accessible en ligne: https://www.health.belgium.be/fr/sante/prenez-soin-de-vous/medication/somniferes-et-calmants

22. Jamila Hamdani, Sophie Kiridis, Françoise Wuillaume, Nele Maenhaut, Alain Bya, Patrick Herné, Viviane Henry, Audrey Beaujean « ZOLPIDEM: Abus et dépendance – Etat des lieux en Belgique » Oct. (2018). Not published.
23. Nayak, Mudavath & K A, Narayan. Strengths and Weakness of Online Surveys. **24** (2019): 31-38. Doi: 10.9790/0837-2405053138.
24. Victorri-Vigneau C, Dailly E, Veyrac G, Jolliet P. Evidence of zolpidem abuse and dependence :Results of the French Centre for Evaluation and Information on Pharmacodependence (CEIP) network survey. Br J Clin Pharmacol. **64**(2) (2007):198-209. DOI: 10.1111/j.1365-2125.2007.02861.x
25. Substance Abuse and Mental Health Services Administration. *The DAWN Report : Emergency Department Visits Attributed to Overmedication That Involved the Insomnia Medication Zolpidem*. (2014). Disponible : https://www.samhsa.gov/data/sites/default/files/DAWN-SR150-Zolpidem-2014/DAWN-SR150-Zolpidem-2014.pdf
26. Kypros Kypri, Ari Samaranayaka, Jennie Connor, John D. Langley, Brett Maclennan, Non-response bias in a web-based health behaviour survey of New Zealand tertiary students, Preventive Medicine, **53**, 4–5, (2011): 274-277, ISSN 0091-7435, https://doi.org/10.1016/j.ypmed.2011.07.017.
27. Ma, Andy et al. "Deprescribing of chronic benzodiazepine receptor agonists for insomnia in adults." The Cochrane Database of Systematic Reviews **7** (2019) CD013371. 3 Jul. 2019, doi:10.1002/14651858.CD013371
28. Sirdifield, C., Anthierens, S., Creupelandt, H., Chipchase, S. Y., Christiaens, T., & Siriwardena, A. N. General practitioners' experiences and perceptions of benzodiazepine prescribing: systematic review and meta-synthesis. *BMC family practice*, **14** (2013): 191. https://doi.org/10.1186/1471-2296-14-191
29. Romero, K., Goparaju, B., Russo, K., Westover, M. B., & Bianchi, M. T. Alternative remedies for insomnia: a proposed method for personalized therapeutic trials. Nature and science of sleep, **9** (2017)**:**97–108. https://doi.org/10.2147/NSS.S128095
30. Heinemann, S., Brockmöller, J., Hagmayer, Y. *et al.* Why Z-drugs are used even if doctors and nurses feel unable to judge their benefits and risks—a hospital survey. *Eur J Clin Pharmacol* **76,** (2020): 285–290 https://doi.org/10.1007/s00228-019-02783-1
31. Hoffmann F Perceptions of German GPs on benefits and risks of benzodiazepines and Z-drugs. Swiss Med Wkly 143 (2013):w13745. https://doi.org/10.4414/smw.2013.13745
32. Siriwardena AN, Qureshi Z, Gibson S, Collier S, Latham M. GPs' attitudes to benzodiazepine and 'Z-drug' prescribing: a barrier to implementation of evidence and guidance on hypnotics. *Br J Gen Pract*.**56**, 533 (2006):964-967.
33. Smith, A.J., Tett, S.E. Improving the use of benzodiazepines-Is it possible? A non-systematic review of interventions tried in the last 20 years. *BMC Health Serv Res* **10,** 321 (2010). https://doi.org/10.1186/1472-6963-10-321
34. Federal Public Service of Health , « Somnifères et calmants, pensez d'abord aux autres solutions » . Online campaign (2018). Manuel médecin
35. Dyas JV, Apekey TA, Tilling M, Ørner R, Middleton H, Siriwardena AN. Patients' and clinicians' experiences of consultations in primary care for sleep problems and insomnia: a focus group study. *Br J Gen Pract*.;60(574): (2010):e180-e200. doi:10.3399/bjgp10X484183
36. Bajaj, V., Kalra, I., Bajaj, A., Sharma, D., & Kumar, R. (2019). *A case of zolpidem dependence with extremely high daily doses. Asia-Pacific Psychiatry, e12356.* doi:10.1111/appy.12356
37. Victorri-Vigneau C, Gérardin M, Rousselet M, Guerlais M, Grall-Bronnec M, Jolliet P. An update on zolpidem abuse and dependence. J Addict Dis. 2014;33(1):15-23. doi: 10.1080/10550887.2014.882725. PMID: 24467433.
38. C. Victorri-Vigneau, M. Rousselet, S. Bulteau, M. Gerardin, M. Guerlais, F. Perrouin, H. Lomenech, M. Bronnec, P. Jolliet. ZZ drugs: are they real twins? The abuse potential and addictive properties of zolpidem and zopiclone. Le Courrier des addictions (17) – n° 3 – juillet-août septembre 2015
39. Morgane Rousselet, Fanny Feuillet, Marie Gerardin, Pascale Jolliet, Jean-Benoit Hardouin & Caroline Victorri-Vigneau (2017): The French addictovigilance network clinical assessment: Z-drugs, true false twins, Expert Opinion on Drug Safety, DOI:10.1080/14740338.2017.1346084
40. Cloetens H, Declercq T, Habraken H, et al. Aanpak van slaapklachten en insomnie bij volwassenen in de eerste lijn. EBPracticeNet Werkgroep richtlijnen eerste lijn (2018). url: https://www.ebp-guidelines.be/home
41. Cook JM, Marshall R, Masci C, Coyne JC: Physicians' perspectives onprescribing benzodiazepines for older adults: a qualitative study. J GenIntern Med 2007, 22(3):303–307.
42. Somers and Petrovic. Benzodiazepines. In: Huang AR, Mallet L, editors. Medication-related falls in older people : causative factors and management strategies. Cham, Switzerland: Springer; 2016. p. 125–33.
43. Díaz-Gutiérrez et al. Relationship between the use of benzodiazepines and falls in older adults: A systematic review. Maturitas. 2017 Jul;101:17-22.
44. McDonald et al. Benzodiazepine use and falls in older adults: is it worth the risk?" Research in gerontological nursing 12.5 (2019): 214-216

Annexes

Annex 1. Questionnaire

- Questionnaire in French : Enquête somnifères
- Questionnaire in Dutch: Bevraging slaapmiddelen

Annex 2. Letter to pharmacists

- Letter to pharmacists in French
- Letter to pharmacists in French (reminder)
- Letter to pharmacists in Dutch
- Letter to pharmacists in Dutch (reminder)

Annex 3. Primary analysis outputs

Primary analysis of completed questionnaires

Annex 4. Secondary analysis outputs

Secondary analysis of completed questionnaires