Escola Nacional de Saúde Pública

UNIVERSIDADE NOVA DE LISBOA

Strategies and interventions on responsible and rational use of benzodiazepines and derivates in the treatment of anxiety and sleep disorders

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Contents

List of acronyms and abbreviations

ATC - Anatomical Therapeutic Chemical code

BDZ - benzodiazepines and analogues

DDD - Defined Daily Dose

EU – European Union

GABA - Gamma Aminobutyric Acid

GP – General Practitioner

INRUD - International Network for the Rational Use of Drugs

MMAT – Mixed Methods Appraisal Tool

OECD - Organization for Economic Co-operation and Development

PRISMA-CI - Preferred Reporting Items for Systematic Reviews and Meta-analyses for Complex Interventions

RCT - Randomized Controlled Trials

RUM – Rational Use of Medicines/Responsible Use of Medicines

TIDier - Template for intervention description and repli- cation

WHO - World Health Organization

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Abstract

Benzodiazepines and analogues (BDZ) are anxiolytics (also known as sedatives) and hypnotics commonly used world-wide. The use of BZD, especially long-term, can result in adverse effects and represents a complex problem for some healthcare systems.

This systematic review aims to identify strategies aiming the promotion of the rational use of benzodiazepines and analogues across Organization for Economic Co-operation and Development (OECD) countries from 2000 to 2020.

We included randomized controlled trials (RCT), quasi-experimental studies, and non-randomized studies: cohort, case-control, cross-sectional, case series and reports. Government and conference reports on regulatory, administrative and educational strategies and interventions aiming the rational use of benzodiazepines and targeted to consumers, healthcare professionals, healthcare organizations and healthcare systems were also included. A relevant literature search was conducted in PubMed, Scopus, Web of Science® (Web of Knowledge), DANS (Open Grey®), OECD iLibrary and GoogleSchoolar. Two reviewers performed duplicate and independent study selection, data extraction and assessment of risk of bias.

A total of 6,308 records were identified and screened in our search, from which twenty-eight studies were included. Professionals are the preferred target of different interventions. Interventions classified, exclusively or not, as administrative were reported the most in the studies included. Most interventions have demonstrated moderate to large improvements in the prescription, dispensing or utilization of benzodiazepines and analogues.

Heterogeneity regarding the design, delivery, description and report of the strategies and interventions posed a challenge during this review and analysis.
Because strategies and interventions on the rational use of medicines have uncertain effects proper methodological and evidenced based approach should be considered in the design, description, implementation and evaluation of these interventions.

1. Introduction

Benzodiazepines and analogues (BDZ) are anxiolytics (also known as sedatives) and hypnotics[1] commonly used in the treatment of anxiety and sleep disorders. Despite their therapeutic efficacy and safety, these medicines have side effects such as tolerance (decreased efficacy to a given medicine due to repeated exposure), dependence (with changes in psychological behaviour patterns and physiological changes) and withdrawal syndrome.

The increase of prevalence consumption of BDZ may be due to the epidemiology of sleep and anxiety illnesses or indicate some disparities concerning the rational use of benzodiazepines. The wide use and misuse of BZD is a very complex problem. Some countries managed to reduce or rationalize the consumption of these medicines. Further investigation is needed, mainly focused on relating the designing and implementation of strategies and interventions with the outcomes of these measures and how they affect prescription, dispensing, consumption and use of BZD.

Understanding the strategies and interventions that aim at the rational use of BZD over the past 20 years is particularly important to ensure sustainable and effective models that can be adapted whenever and wherever needed.

2. Theorical Framework

2.1. Benzodiazepines and analogues in the treatment of anxiety and sleep-wake disorders

BDZ are indicated in the treatment of anxiety and sleep disorders. BDZ appear to promote the efficiency of GABAergic synaptic inhibition in neuronal membranes in the central nervous system, which explains its main properties and clinical indications: anxiolytic (for anxiety relief), hypnotic (for insomnia), anticonvulsant (for epilepsy), muscle relaxant (useful both in neuromuscular disorders and as component of anaesthesia), anterograde and retrograde amnesia and alcohol withdrawal (1,2).

Anxiety disorders are currently the most prevalent mental disorders worldwide and are usually associated with notable comorbidities.(3) These disorders can occur in many forms, based on psychological and behavioural characteristics. Generally, anxiety

[1]Sedative (anxiolytic) agents reduce anxiety and exert a calming effect, by depressing the central nervous system. A hypnotic drug produce drowsiness and encourage the onset and maintenance of a state of sleep, which involves a more deep depression of the central nervous system.(2)

is described by enhanced vigilance, motor tension and autonomic hyperactivity. Anxiety is often secondary to disease states (*e.g*. acute myocardial infarction) which requires specific treatment. In situational anxiety (a class of secondary anxiety states) and other disease-associated anxiety states, the short-term use of sedative-hypnotics may be adequate. (2) Generally, benzodiazepines are the first line of treatment in clinical practice for anxiety, given their efficient effect on reducing symptoms. Nonetheless, this pharmacological class has a known fatal interaction with alcohol and opioids, as well as a potential for addiction and secondary effects, that limit their use in clinical practice, something to be addressed later in this paper. This reasons the preference, and reference by some authorities, for newer antidepressants, including selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), as first-line of treatment in generalized anxiety disorders.(2,4)

Sleep-wake disorders comprehend a range of problems characterized by an alteration of the sleep-wake rhythm, with complications such as the impossibility of benefiting from rest, perceived unsatisfactory or insufficient sleep, both in quantity and quality, resulting in clinical dysfunctions (endocrine, metabolic and higher cortical function), emotional, social and occupational problems.(5–9)

These disorders are commonly a result from inadequate treatment of underlying medical or psychiatric conditions.(2) Insomnia is the most prevalent and relevant of sleep-wake disorders, as "*more than one-third of adults experience transient insomnia at some point in their lives*" and "*approximately 6% of the adults in industrialized countries suffer from chronic insomnia*".(9,10) In addition, some countries (Norway, Germany and United Kingdom) are revealing a prevalence increase up to 10% of the population in recent years.(10) Guidelines, including the Canadian Guidelines on Benzodiazepine Receptor Agonist Use Disorder Among Older Adults issued by the Canadian Coalition for Seniors' Mental Health and the European guideline for the diagnosis and treatment of insomnia from European Sleep Research Society suggest, based on evidence and expertise recommendations, that non-pharmacological psychological treatment should be the first-line of treatment for chronic insomnia.(10,11) Pharmacological interventions can be used if these are not sufficiently effective or unavailable. BDZ and antidepressants are effective in short-term treatment (less than 4 weeks), and generally preferred over barbiturates (such as pentobarbital and secobarbital).(2,10) The main goal of the pharmacological intervention is the efficacy in treating a particular sleeping problem, to which the clinical criteria of to select the drug is

either to promote decreased sleep latency and/or sleep duration. Most BDZ can help to achieve this, however the side effects that must be monitored and accounted for.(2)

As stated before, regarding the use of benzodiazepines in anxiety and sleep disorders, there are recommended non-pharmacological interventions as the first approach (*e.g.* psychotherapy). When used, treatment should start with the lowest recommended dose possible and the duration of use should be as short as possible, not exceeding eight to twelve weeks for anxiety or four weeks for insomnia, including the tapering off process(10–13). Despite their therapeutic efficacy and safety, these medicines have side effects such as tolerance (decreased efficacy to a given medicine due to repeated exposure), dependence (with changes in psychological behaviour patterns and physiological changes) and withdrawal syndrome. In the case of benzodiazepines and analogues, this syndrome is characterized by increased anxiety, insomnia and even seizures. The degree of dependence and magnitude of withdrawal symptoms, directly depends on the intensity and dose of the medicine taken. (2).

There are some consequences, besides tolerance, dependence and withdrawal syndrome. These adverse consequences of benzodiazepines (*e.g.* anterograde amnesia, poor concentration and memory and confusion) are usually dose-related and predictable. Long-term regular use in therapeutic dosage and from self-prescription or recreational use in excessive doses can result in more serious adverse effects, especially in the elderly, that are more sensitive to the central nervous system effects of BDZ.(1,12,14,15) Nevertheless, these medicines have more favourable safety profiles, since they have flatter dose-responses curves(2), and efficacy, especially when compared with other pharmacological groups, *e.g*. barbiturates, with which drug withdrawal rebound phenomenon associated with many hypnotics is less frequently seen with benzodiazepines.(16)

The concerns about over-prescription of these drugs are no novelty, given their widespread availability and reports of illegal street use in various countries (benzodiazepines were addressed on the "*6th review of psychoactive substances for international control*" in 1982)(16).

2.1.1. Trends and context of benzodiazepines and analogues worldwide

Health can be defined as "*a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity*"(17). As such, mental health is an integral part of health and well-being, and crucial for a happy, fulfilled and productive

life.(18,19) Mental health requires a range of comprehensive strategies for promotion, prevention, treatment and recovery, and can be impacted and impact social health determinants.(18) Mental health problems include many illnesses, such as anxiety and sleep disorders. The burden of mental health worldwide, both in morbidity and mortality, is highly concerning, especially considering the aggravation caused by COVID-19 pandemic. Consequently, authorities worldwide are prioritizing this matter and calling action on Universal Health Coverage for Mental Health(20).

According to the Institute for Health Metrics and Evaluation (IHME) the most common mental disorders in 2016, across EU countries, were anxiety disorders with an estimated 25 million people suffering from it (5,4% of the population).(19) Even higher statistics were released by the same institution years after. The mean proportion of total prevalent cases of anxiety disorders in countries across OECD is 4,38%. Portugal, New Zealand, Netherlands, Ireland, Switzerland and Norway present higher results (from 7,5% to 9% of total anxiety disorders cases).(21) Figure 1 depicts the variation across OECD countries.

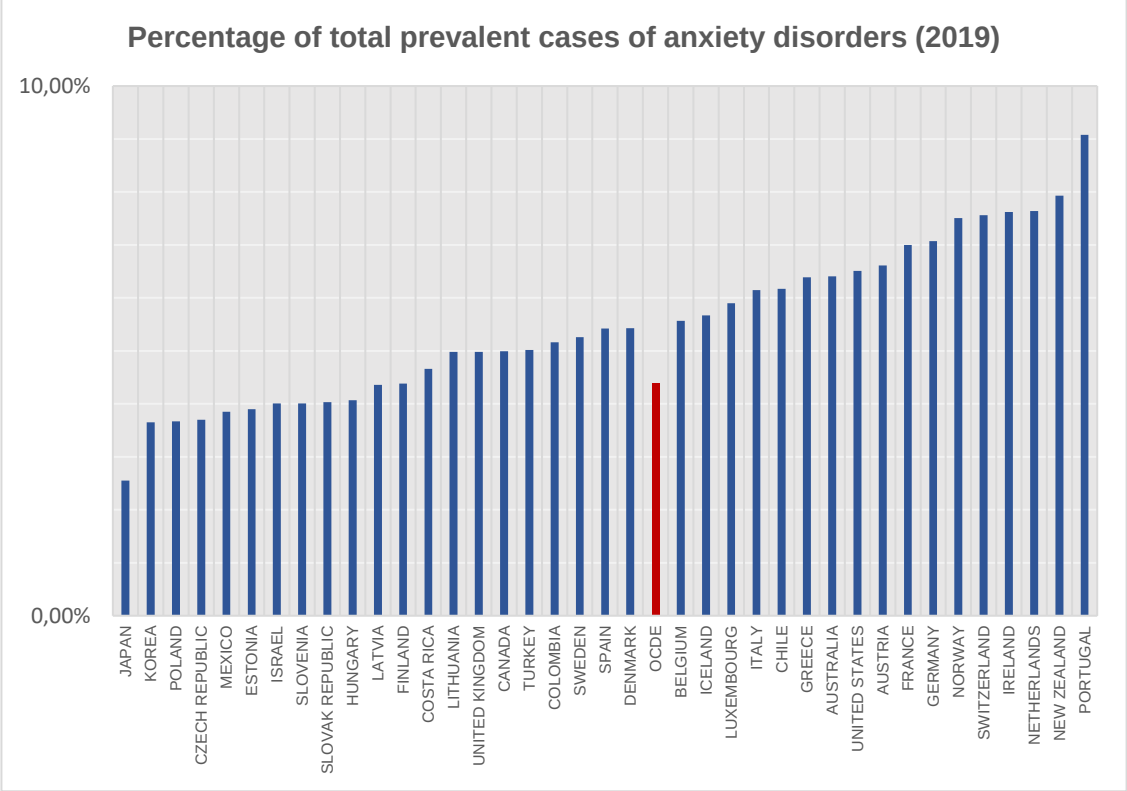


Figure 1 Percent of total prevalent cases of anxiety disorders in OECD (%). 2019. Adapted from Institute for Health Metrics and Evaluation (IHME)(19)

Regarding insomnia, data suggests that around 6% of adults from industrialized countries suffer from chronic insomnia as a disorder(22) with recent data indicating an increase in prevalence to about 10% (*e.g*. Norway, UK and Germany).(10) In the United States, short-term insomnia has an estimated prevalence of 9.5%, of which 1 in 5 cases transitions to chronic insomnia.(23,24)

It is also worth mentioning that there are many described studies, with differences in methodological approaches and quality and consequently there are variations in and between countries.(10) The between-country variation can also be due to cultural differences and perceptions towards sleep and sleep problems.(25) Even if the various dimensions and depth of anxiety and sleep disorders (especially insomnia) are not fully comprehended, evidence and experience illustrate that these are relevant problems that should be addressed.

The prevalence consumption of BDZ worldwide may be due to the epidemiology of sleep and anxiety illnesses or indicate some disparities concerning the rational use of benzodiazepines. In several OCDE countries, there is a highly reported consumption of anxiolytic (ATC N05B) and sedative-hypnotics (ATC N05C). In most of them, there has been a tendency to diminish, with some relevant exceptions as Portugal and Spain in anxiolytic (ATC N05B) consumption (Figure 2) and the northern European countries in sedative-hypnotic (ATC N05C) (Figure 3), while the data fluctuates across countries. Part of this can be explained by different reimbursement and prescribing policies for benzodiazepines, as well as possible differences in disease prevalence and treatment guidelines. We do not discard varieties due to diverse methodological approaches to the consumption OECD report on this pharmaceutical group. For example Austria, Latvia, Estonia, Portugal, Spain and Sweden include data for primary care physicians only, while others include data from other providers.(26)

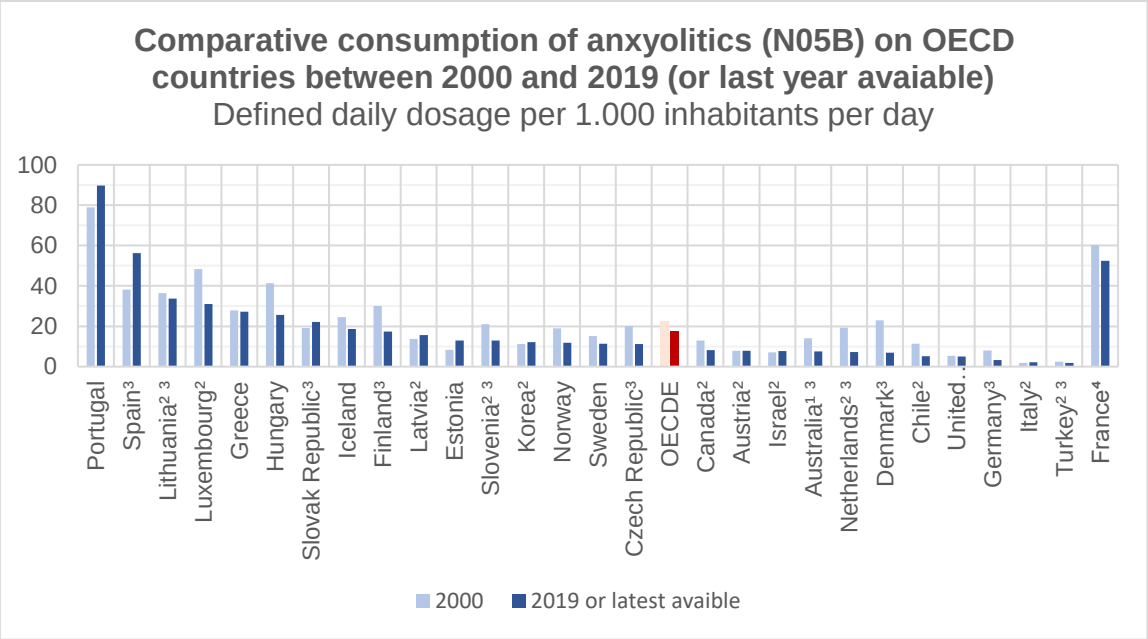


Figure 2 Comparative consumption of anxiolytics (N05B) on OECD countries between 2000 and 2019 (or last year available).

Adapted from OECD.Stat. (1) Data from Australia was reported with differences in methodology. (2) Lithuania, Luxembourg, Latvia, Slovenia, Korea, Canada, Austria, Israel, Netherlands, Chile, United Kingdom, Italy and Turkey only had data first reported after 2000. (3) Lithuania, Slovak Republic, Slovenia, Czech Republic, Australia, Netherlands, Denmark, United Kingdom, Germany and Turkey did not report the consumption data of hypnotics and sedatives on year 2019; the information of this country refers to the last year available, mostly 2018. (4) France latest information dates from the year 2009.

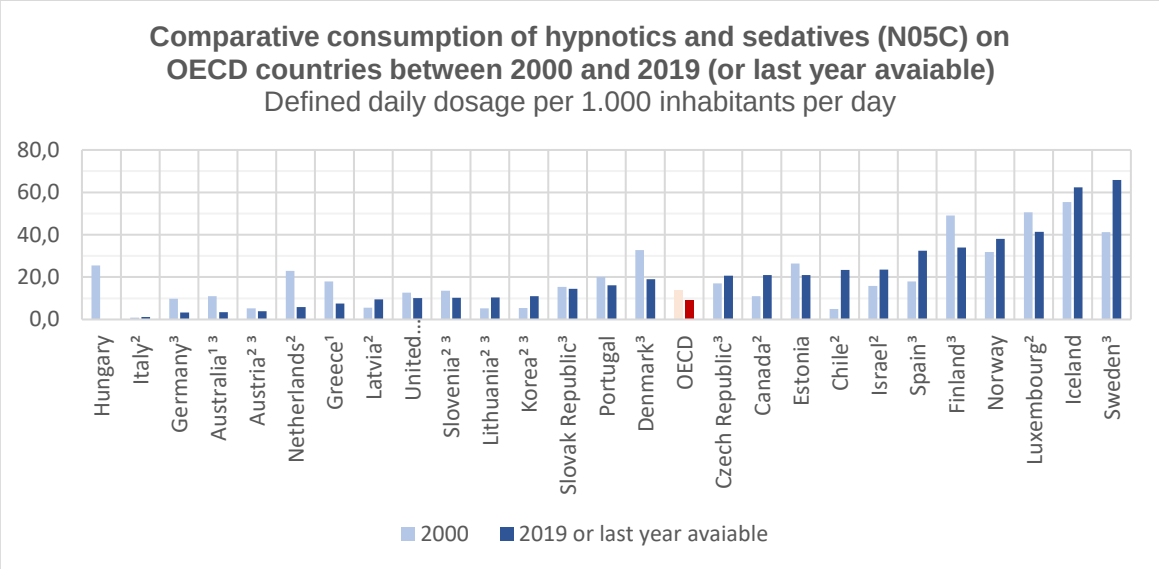


Figure 3 Comparative consumption of hypnotics and sedatives (N05C) on OECD countries between 2000 and 2019 (or last year available).

Adapted from OECD.Stat. (1) Data from Australia and Greece were reported with differences in methodology. (2) Italy, Austria, Netherlands, Latvia, Slovenia, Lithuania, Korea, Canada, Chile, Israel and Luxembourg only had data first reported after 2000. (3) Germany, Australia, Austria, United Kingdom, Slovenia, Lithuania, Korea, Slovak Republic, Denmark, Czech Republic, Spain, Finland and Sweden did not report the consumption data of

hypnotics and sedatives on year 2019; the information of this country refers to the last year available, mostly 2018.

Despite the known adverse effects, mentioned above, long-term use of BDZ can also lead to falls in elder people and dementia. This also inflicts additional and potentially avoidable costs on health systems.(1,19) In addition, this problem is particularly relevant when we focus on prolonged use and the types of BZD prescribed (as stated before, consensus establishes that prescription and utilization of benzodiazepines should be for the shorter period possible, not exceeding eight to twelve weeks for anxiety or four weeks for insomnia). (12,19) Data from countries available (Figure 4) emphasizes variations in rates of BZD long-term prescribing and the prescribing of long-acting BZD in people aged over 65 years.(19,27)

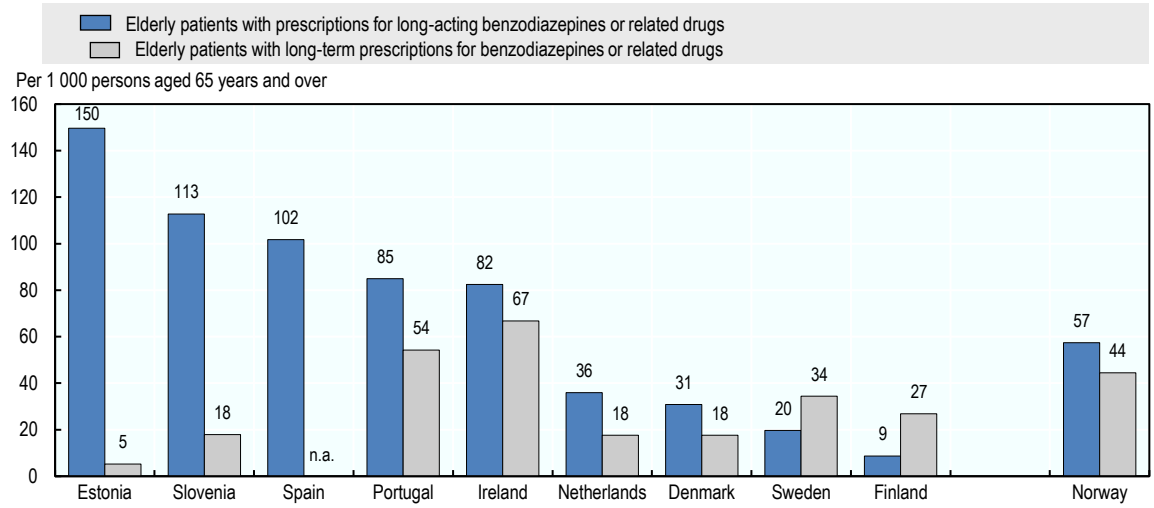


Figure 4 Elderly patients with prescriptions for benzodiazepines or related drugs, number per 1 000 patients aged 65 and over, 2015 or nearest year.
Source: OECD Health Statistics 2018.

By associating the wide levels of use and prescribing of BDZ with the prescription of antidepressants, the population ageing, the burden of mental health illnesses and the increasing of polimedication we get a potential worldwide public health problem.(28)

On other hand, variations between countries may raise the question of which factors might influence the utilization of BZD. Although hypothesis regarding cultural differences might be plausible (WHO recognises that people with mental health condition can experience discrimination and stigma), further research is needed regarding perceptions and responses towards sleep and anxiety illnesses and the existence or effectiveness of different reimbursement, prescribing, dispensing, use policies for BZD.(18,20,26,28)

Future trends in medication use for anxiety and insomnia, BZD, must be taken into consideration. The COVID-19 pandemic caused direct and indirect consequences impacted mental health conditions and disrupted services and interventions on mental, neurological and substance use disorders.(29,30) For instance, numbers from the United States showed a rise of prescription of medication for anxiety (34,1%) and for insomnia (14,8%) between mid-February to mid-March of 2020.(31) The effects of the pandemic may broadening changes in patterns of use of BZD, including increase in prescription in order to treat insomnia and anxiety consequential of the demands and pressure on people lives.(32)

2.1.2. Use and abuse of benzodiazepines and analogues

Besides the risk of over-prescription and misuse of BZD in the treatment of its clinical indications, illegal actions involving benzodiazepines are also concerning, as this is one of the groups substances most commonly used to commit drug facilitated crimes (in particular, drug-facilitated sexual assaults, like flunitrazepam). Frequent and excessive use, in concomitance with stimulants, hallucinogens and opioids, are also reported. The consumption of BZD to enhance and prolong the effects of opioids and other drugs, or to avoid withdrawal symptoms is very common.(32) With even some new “street” benzodiazepines produced by organized crime, being in circulation, and often involved in drug related deaths.(33)

2.1.2.1. Inappropriate use of benzodiazepines

As stated before, BZD have six main clinical indications: anxiety, insomnia, epilepsy, muscle spasms, sedation (prior or during surgical procedures) and to manage withdrawal symptoms of alcohol.(2,32) Despite having similar clinical effects, there are important pharmacodynamic and pharmacokinetic characteristics that influences the drug choice and its dose, both in insomnia and anxiety.(2,32,34)

Guidelines (*e.g.* the NICE British National Formulary and the Portuguese Directorate General of Health) establish that pharmacological treatment with BZD should start with the lowest recommended dose possible. The duration of treatment must be as short as possible, not exceeding eight to twelve weeks for anxiety or four weeks for insomnia with tapering off process included.(12,13,35) In fact, in the treatment of insomnia, when BZD drugs use exceeds this period, benefits diminish. With long-term use being associated with worsening of sleep quality, disruption of sleep patterns and an increased arousal during the night.(27)

Inappropriate use of medicines occur whenever any of the conditions and/or principles for the rational use of medicines is not met ("*Patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community*.").(36,37) Although several definitions and concepts are proposed in literature, we can categorize three patterns of inappropriate prescription and utilization of BZD (28):

i. Inappropriate dose or duration, called overuse, that is defined by a prescription that is not, or no longer, necessary;
ii. Misuse, characterized by an unfavourable benefit/risk balance that when detected requires withdrawal or replacement. For instance, a prescription of a long half-life BZD in the elderly even for less than 30 days is not recommended and constitutes a misuse;
iii. Underuse, that refers to omission of potentially beneficial medications. For example, the utilization of BZD for anxiety disorders can be a misuse, but the absence of antidepressant treatment in this context constitutes an underuse.

Numerous factors can contribute to the inappropriate use of BZD. Table 1 lists some of the reasons that may lead to the use of BZD for longer periods than recommended (or overuse).(12,38–40)

"Effectiveness in eliminating or reducing symptoms";
"Patients' fear of withdrawal symptoms";
"Patients' desire for rapid symptoms relieve puts more pressure on medical prescription";
"Difficult access to psychotherapy, which may indicate that this type of health care needs is not being met";
"Unavailability of integrated mental health care services or mental health care providers with relevant skills";
"Lack of patients' awareness regarding the risks of BZD use";
"«Medicalization» of human daily worries";
"The over-optimistic safety profile of BZD, also promoted by pharmaceutic industry (when first launched in the market in the '60s)."

Table 1 Summarized reasons that lead to the use of BZD for longer periods than recommended.
Source: from J. Oliveira, I. Neves, M. Fernandes et al.(12)

Additionally, there is a common preconception among clinicians, who preferer taking the risk of maintaining a treatment of which the patient can be strongly addicted rather that favouring its withdrawal.(28)

2.1.2.2. Toxicological effects

BZD potentiates the inhibitory actions of GABA receptors by enhancing receptor binding and consequently leads to a postsynaptic hyperpolarization by an increased flow of chloride ions trough the GABA ion channel.(2,41)

The isolated consumption of BZD in toxic doses rarely causes a significant toxicological response since they have flatter dose-response curves. Studies on drug-related deaths indicate this assumption (0.3 deaths per million tablets of diazepam prescribed).(2,41) However, this toxic response varies within these drugs, with alprazolam being, supposedly more toxic in overdose than other benzodiazepines.(2) When isolated benzodiazepine overdose happens, it will comprise a central nervous system depression with normal or near-normal vital signs. With great probability of patients presenting slurred speech, ataxia and altered mental status. But this can vary, from mild drowsiness to coma-like states. Respiratory compromise/depression is more frequently associated with the co-ingestion of benzodiazepines with alcohol or other drugs. This response depends on multiple factors, such as individual characteristics (tolerance, weight, age), dosage and co-ingestant. Severe cases can achieve comatose states and urgent treatment may require mechanical ventilation.(41) This evidentiate that the presence of other central nervous system depressants, including ethanol and opioid analgesics, influences the pharmacological action of these drugs. More serious cases of overdosage, intentional or accidental, involve polypharmacy or drug combinations.(2,28) Treatment in more extreme conditions is further complicated by aspiration of gastric contents (more likely if ethanol is co-ingested) and cardiovascular depression.(2)

Cases of hypersensitivity reaction, including skin rashes, can occur occasionally with these drugs. There are also reports of teratogenicity leading to fetal deformation, following the use of certain benzodiazepines (FDA even reclassified individual benzodiazepines in terms of pregnancy risk).(2)

2.1.2.3. Elderly people as a vulnerable population

Insomnia (as the most common sleep disorder) and anxiety are highly prevalent in older people and associated with distress and morbidities in this group.(42,43) Concurrently BDZs are one of the most common drug reported as potentially inappropriate in older persons, with approximately only a third being appropriately prescribed (12,44,45) being commonly associated with preventable adverse drug events.(46) It should be also highlighted that continuation of long-term prescriptions accounts for much of the growth in prescription rates.(19,27)

High school education, higher chronic disease score, higher levels of self-reported pain and stress are reportedly factors significantly associated with benzodiazepine use among older adults.(47)

Due to both pharmacodynamic and pharmacokinetic modifications, elderly people are more sensitive to the effects of sedative-hypnotics.(48) One of the main modifications is the oxidative pathway of liver metabolism (cytochrome P450 metabolism). A majority of benzodiazepines are metabolized this way (Phase I metabolism), conjugated with glucuronidation (Phase II metabolism).(2,49). Lorazepam (a high-potent BZD that displays short-acting characteristics) is an exception since it exclusively undergoes direct glucuronidation. Lorazepam is regarded as a safer BZD to elderly people, especially with hepatic or renal dysfunctions, because this metabolic pathway is not affected by ageing.(49,50)

Generally BZD utilization in this age group, and especially when used inappropriately, is often associated with confusional states, worsen delirium states and other cognitive effects, increased fall risk (and consequently hip fracture) and adverse outcomes in people with other diseases (such as chronic obstructive pulmonary disease).(44,51–53) As mentioned above, long-term use of BZD leads and aggravates cognitive impairment.(54) Literature also highlights that BZD are commonly prescribed for older people, especially with residential and nursing care setting patients that are approximately three times more likely to be prescribed BZD than non-care home residents. Nonetheless, BZD exposure rises with increasing age.(55)

2.1.2.4. Benzodiazepines discontinuation

Besides preventing the utilization of benzodiazepines beyond recommended time, especially on low-dose regimens intended for shorter periods (<4 weeks), there is a fundamental question on how to recognize justified long-term use from suggestive chronic dependence that must be treated with therapeutical discontinuation. This must always include tapering.(56)

Evidence suggests that a gradual tapering should take eight to twelve weeks. With a decrease between 10% and 25% of the baseline dose approximately every two to three weeks. Serious reactions from BZD tapering are considered to be rare.(49,57–60) But the following symptoms have been often reported: "*irritability, insomnia, poor concentration, poor memory, restlessness, increased anxiety, perceptual disturbances, tremors, diaphoresis, nausea, diarrhoea, confusion, psychosis, and seizure".*(61)

2.2. Responsible and rational use of medicines

2.2.1. The concept of rational use of medicines

WHO defines rational use of medicines as "*patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community*" .(62) Or in a simpler way responsible use of medicines means that patients receive the right medicine, including its dosage, at the right time, at the right cost and use them appropriately and benefit from them. This recognizes the challenge of resources sustainability and stakeholder responsibility all across the healthcare systems.(63) Irrational (inappropriate, improper, incorrect) use of medicines is when one or more of these conditions is not met.(64)

The rational use of medicines aims to ensure that:

- A medicine is only used when necessary and appropriately chosen based on the most recent scientific or clinic evidence in order to be as effective as possible and less likely to cause any harm. The choice of medicines should always consider patient's preferences and the best use of available resources possible.
- There is availability and timely access to quality medicines and that these are adequately administered and monitored for their effectiveness and safety.
- A multidisciplinary collaborative approach is used, covering citizens, households and caregivers, in addition to health professionals who assist the patients under their care.(65)

In order to promote the rational use of medicines a comprehensive, sustainable, national and sector-wide approach is required, as well the active involvement of governments, health professionals and civil society.(66) Promoting quality use of essential medicines leads to better health outcomes and can achieve considerable efficiencies.(67)

2.2.2. Addressing the rational use of medicines and frameworks of interventions

Since the eighties that WHO and international organizations are actively working towards the rational use of medicines. The present definition of the rational use was consensualized and disseminated for the first time at an WHO international conference

in 1985. The foundation of the International Network for Rational Use of Drugs (INRUD), and WHO continuing advocacy, resulted in a global research agenda for the rational use of medicines that ensued the evidence development on interventions and policies to promote the rational use of medicines that allowed the identification and evaluation of interventions and strategies.(36,37)

One crucial element for a healthcare system or organization is how to measure and assess the rational use of medicines. The components of rational or irrational use of medicines are multidimensional and multifactorial.(36,68) For example, medicine use encounters occur in many environments, including health facilities and the community. And the environment is linked to the individual medicine use behaviour(69–71). Problems in identifying, classifying, and quantifying medicines can also be highlighted as measurement issues, as the same medicine is often available under different names, forms and dosages. (72) This is also true for the characterization of the appropriateness of use for benzodiazepines, and therefore what is meant by an improvement of use. (73)

There are several well-established methods to measure the type and degree of rational/irrational use, as the methods published by WHO on investigation medicine use in health facilities (WHO/DAP 1993) and the community (Hardo, Hodgkin and Fresle, 2004). (36,70–72). These can be either quantitative, preferred to gather numerical data of the problem or qualitative used to describe the behaviours, beliefs and motivations of those involved in medicine use. Some of these methods (*e.g.* the manual produced by WHO and INRUD) provide core indicators, valid and reliable, that are highly standardized and often do not need any national adaptations. As so, they serve as a simple tool to assess the quality of use of medicines (often referred as “rational medicine use”).(72) We summarized some examples of the indicators or criteria in Table 2. Over time other ranges of performance, quality, and safety indicators have been introduced and increasingly used. Normally associated with the improvement of quality of care.(69)

Evaluation of the effectiveness of different strategies and interventions depends on many factors, including the type of intervention, time, setting, and the implementation process. And by looking for both intended and unintended changes in specific outcomes previously determined.(72)

Table 2 Examples of medicine use indicators are described in the literature.

Adapted from Elseviers et al., 2016 and WHO, 1993).(70,71)

Aggregate-level data: reflect the total amount of medicines in a system and carry no information on how these medicines are distributed among individuals	
Defined daily dose (DDD)	suitable for addressing total aggregated use, and especially useful in ambulatory care, and also widely used to measure medicine use in the hospital and long-term care institutions as well
Prescribed daily dose (PDD):	the average daily amount of medicine that is prescribed to patients. It can be determined from clinical data.
Prevalence proportion	the proportion of a population that uses medicine or group of medicines at a given point in time.
Incidence rate	count of new users divided by the person-time at risk for becoming a new user.
Duration of drug use	Is the total exposure (usually measured in days) to medication, requiring the need to know not only when a medicine is started but also how long a person is exposed to the medicine.
Average daily dose	the average daily amount of medication that is used by patients.
Pharmaceutical expenditure	provides a measure of the economic importance of medicines. It is affected by both volume and price and is used in national and cross-national statistics and for pharmaceutical policy analyses
WHO/DAP 1993: Core medicine use indicators developed to be used as measures of performance in general areas related to the rational use of medicines in primary health care facilities	
Prescribing Indicators (36,70)**:**	The average number of medicines prescribed *per* patient encounter. % medicines prescribed by generic name % medicines prescribed from essential medicines list or formulary % prescriptions in accordance with clinical guidelines
Patient Care Indicators(36,70)**:**	Average consultation time Average dispensing time % medicines actually dispensed % medicines adequately labelled % Patients with knowledge of correct doses
Facility Indicators (36,70)**:**	Availability of essential medicines list or formulary to practitioners. Availability of clinical guidelines % key medicines available.
Complementary medicine-use indicators	Percentage of patients treated without medicines. Average pharmaceutical cost *per* encounter. Prescription in accordance with treatment guidelines. Percentage of patients satisfied with the care they received. Percentage of health care facilities with access to impartial pharmaceutical information.

3. Purpose and objectives of this research

Many studies describe the use of BZD, as well as risk factors, consequences, and management of their misuse. Some even address psychosocial and pharmacological interventions to reduce the use of these medicines in specific indications.(74–76) However, few studies focusses policy and system-level intervention (educational, regulatory, administrative, etc.) aiming at rational use of BZD and targeting regulation, medicine policies and financing, healthcare professionals, healthcare institutions or population. Even less relate the implementation of these measures with their outcomes. The wide use and misuse of BZD is a very complex problem. Some countries managed to reduce or rationalize the consumption of these medicines. Further

investigation is needed, mainly focused on relating the designing and implementation of strategies and interventions with the outcomes of these measures and how they affect prescription, dispensing, consumption and use of BZD

Understanding the strategies and interventions that aim at the rational use of BZD in the past 20 years is particularly important to ensure sustainable and effective models that can be adapted whenever and wherever needed.

3.1. Objectives

To identify and assess strategies and interventions designed and implemented to promote the rational use of benzodiazepines and analogues in anxiety and sleep disorders that targeted health systems, institutions, healthcare professionals and citizens in the OCDE countries in the last 20 years. To this end, a systematic review was conducted aiming to answer the following research questions:

i. Which strategies, policies and interventions aiming at the rational use of benzodiazepines and analogues in sleep and anxiety disorders were implemented in OCDE countries between 2000 and 2020?
ii. What targets are commonly aimed with these interventions and strategies (health systems, healthcare professionals, institutions or organizations, financing, patients, or citizens)?
iii. Did the different strategies or interventions affect the use of benzodiazepines and analogues in sleep and anxiety disorders in the countries, healthcare systems, healthcare facilities or communities where they were implemented?

4. Methods

4.1. Methodology

Systematic literature review including published studies and grey literature reporting the design or implementation of strategies and interventions to promote the rational use of benzodiazepines and analogues in OECD countries in the last 20 years (from 2000 to 2020).

4.1.1. Systematic Review Protocol

The process of this systematic review will follow the extension of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting methods and results of “complex-interventions” – PRISMA-CI – complemented

with and adapted use of the Template for Intervention Description and Replication (TIDier) checklist for describing interventions.(77–81)

4.1.2. Eligibility criteria

Studies will be selected according to the criteria outlined below.

i. Study designs

This review will include randomized (RCT) and non-randomized (non-RCT) controlled trials, including quasi-experimental studies, cohort studies, case-control studies and cross-sectional. Grey literature is a source of important contributions to systematic reviews.(82) We will include the following grey literature: committee reports, government reports and conference reports, if published by an official institution or agency.

ii. Types of participants

For the purpose of this review, we will adopt the definition of "rational use of medicines" accepted by WHO at the Nairobi conference in 1985: *"patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community*."(62) Aiming for the rational or responsible use of medicines implies that activities, capabilities and resources of health system stakeholders are aligned to guarantee that people receive the right medicines, at the right time, use them appropriately and benefit from them. As so, there is an individual and collective responsibility towards this goal.(63)Taking this into account, we established four recipients or targets of interventions (unit of analysis) in which the scope of our review will focus on:

a. Consumer-level

We will include studies reporting interventions targeting consumers, defined as any person using a benzodiazepine or analogue(s) for anxiety or sleep disorders, either a patient, caregiver or both and targeted as individuals or as groups.(83) Community-based interventions will also be included as a consumer-level setting or intervention. A community is defined as a specific group of people living in a defined geographical area, arranged in a social structure and exhibiting some awareness of their identity as a group and shared common needs.(84)

b. Healthcare professional-level

Studies addressing interventions targeting healthcare professionals who prescribed, dispensed, administered, and monitored benzodiazepines or analogues will also be included.

c. Healthcare organization- level

Organizations, facilities or institutions that deliver health care goods and services as their primary activity, regardless of their legal, accounting, organisational and operating structures.(85) Studies addressing interventions that wittingly or consequently affect the organization or functioning of healthcare services or institutions and cooperation between stakeholders will be considered.

d. Health care system-level

We also will seek strategies and interventions targeted to the healthcare systems. Health care systems are defined as "*the combination of all the resources, organizations and institutions that are dedicated to improving personal health through preventive, promotive, curative and rehabilitative health actions and interventions*" provided by both state and non-state stakeholders (86,87). We admit different levels of administrative or jurisdictional organization of health care systems, such as local, district, regional, state, national and international. Strategies and interventions that directly or indirectly influence healthcare system function or articulation will be considered.

iii. Types of interventions

Irrational or non-rational use is defined as the use of medicines in a way that is not compliant with rational as defined by WHO, 1985.(36) Examples include the use of inadequate dosages or non-adherence to dosing regimens, failure to prescribe in accordance with clinical guidelines, inappropriate self-medication and use of too many medicines per patient ("poly-pharmacy").(63,88)

Countless factors contribute and influence how medicines are used.(36) A lot of emphasis is placed on prescribers, dispensers and consumers as key stakeholders to achieve a rational use of medicines. But other fundamental challenges must be taken into consideration such as access to health care, the integration of care delivery, appropriate healthcare financing and its model, market regulation, medicines and health policies and partnerships and stakeholders involvement.(63,72)

Since the components of RUM are multidimensional, and although many gaps remain in our knowledge, there are several strategies and interventions to change medicine use practices and behaviours.(36,68,72)

In this review, we will solely focus on educational, administrative, and regulatory strategies and interventions. Table 3 frames the different intervention categories, considered by The International Network for Rational Use of Drugs (INRUD) in 1991 and adopted in this review. (36,89,90).

Table 3 Strategies and Intervention categories.
Adapted from Quick, Laing and Ross-Degnan(89) **and WHO**(36)**.**

Category	Definition	Examples
Educational	*Based on changing pharmaceutical use patterns through education and persuasion*	Training professionals involved in prescription, dispensing, monitoring, and administering medicines. Public education and media campaigns. Independent medicines information. Problem-based pharmacotherapy training in undergraduate curricula.
Administrative	*Influence usage by better structuring decision-making processes*	Use of standard diagnosis and treatment protocol and guidelines. Essential medicines list based on treatments of choice. Implementation or modification of referral between healthcare professionals' protocols or procedures. Institutionalization or modification of healthcare services
Regulatory	*Orienting and restricting provider and consumer decisions.* *Set of laws, rules, procedures and incentives designed to improve the safe and effective use of medicines.*(69)	Banning unsafe medicines. Limitation of the number of medicines per prescription or per dispensing. Financial incentives or changes in reimbursement schemes. Sufficient government expenditure to ensure availability and access of medicines, workforce and care.

Psychological and pharmacological treatments or interventions, solely used or in combination, will not be considered in the scope of this review as these are focused on work undertaken extensively in the literature. (74–76,91)

Only strategies and interventions aiming the improvement of the use of medicines included in the Anatomical Therapeutic Chemical (ATC) classification system groups N05BA (benzodiazepine derivates used in the treatment of neuroses and psychosomatic disorders associated with anxiety and tension) and N05CD (benzodiazepines derivates used mainly in sleeping disorders) will be considered. (92) (Table 4 lists the medicines included in the ATC groups N05BA and N05CD).

Table 4 List of medicines included in The Anatomical Therapeutic Chemical (ATC) classification system groups N05BA and N05CD.

ATC Group	Name
N05BA - Benzodiazepine derivates used in the treatment of neuroses and psychosomatic disorders associated with anxiety and tension	Diazepam, chlordiazepoxide, medazepam, oxazepam, potassium clorazepate, lorazepam, adinazolam, bromazepam, clobazam, ketazolam, prazepam, alprazolam, halazepam, pinazepam, camazepam, nordazepam, fludiazepam, ethyl loflazepate, etizolam, clotiazepam, cloxazolam, tofisopam, bentazepam, lorazepam combinations
N05CD - Benzodiazepines derivates used mainly in sleeping disorders	flurazepam, nitrazepam, flunitrazepam, estazolam, triazolam, lormetazepam, temazepam, midazolam, brotizolam, quazepam, loprazolam, doxefazepam, cinolazepam, remimazolam, nimetazepam

iv. Outcomes

For the purposes of this research, an improvement in the use of benzodiazepines will be defined by each study's pre-determined criteria or outcomes, if any exists. The results will be reported in the same format as they were presented in the original source. For example, the authors can define a decrease in units prescribed or the duration of the use of benzodiazepines as an outcome for the intervention.

v. Timing

Only studies and literature that report on the design or implementation of policies and interventions that took place between 2000 and 2020 will be selected and included.

vi. Setting

Strategies and interventions designed and/or implemented within a large jurisdiction or healthcare system in OCDE countries. Jurisdictions can be regional, national or international OCDE countries in any health context.

The following healthcare settings will also be considered and each study setting will be included in the data collection process: Primary Care (including community pharmacies), Hospital Care and Long-term care.

vii. Language

Articles, reports, and other documents written in English, Spanish, and Portuguese.

viii. Information sources

Literature search strategies will be developed using research descriptors limited to the variables that result from the research question. We will search PubMed, Cochrane Library and Web of Science. The search of grey literature will be conducted in Open Grey (www.opengrey.eu) database. We will also conduct research on government and institutional sources from OCDE iLibrary and GoogleSchoolar. The literature search will be limited to the English language.

ix. Search strategy

A relevant literature search will be conducted in PubMed, Scopus, Web of Science® (Web of Knowledge), DANS (Open Grey®), OECD iLibrary and GoogleSchoolar.

The following query as developed and refined in PuMed and later on adapted to other information sources:

("Pharmaceutical Preparations"[Mesh] OR "Prescription Drugs"[Mesh] OR "drug" OR "pharmaceutical production") AND ("Drug Utilization"[Mesh] OR "therapeutic use" OR "Prescription Drug Misuse" [Mesh] OR "Substance Abuse, Oral"[Mesh] OR "Substance-Related Disorders"[Mesh] OR "Inappropriate Prescribing" [Mesh] OR "Health Services Misuse"[Mesh] OR "rational" OR "abuse" OR "misuse") AND ("Anxiety"[Mesh] OR "Sleep Wake Disorders"[Mesh]) AND "Benzodiazepines"[Mesh] NOT "Alcohol"[Title/abstract].

Detailed search queries can be consulted in Appendix B. The definition and refinement of the search strategy were performed with the collaboration of the Documentation and Information Services / Library of the National School of Public Health.

4.1.3. Study Records

i. Data management

The process of recording and selection of literature will be managed using reference management software. This will allow the organization of references in different groups (included or excluded), duplicates removal and sharing between the reviewers' team.

ii. Selection process

The selection of literature will be independently conducted by two reviewers strictly based on the inclusion and exclusion criteria in Table 5. First, duplicates will be removed. After duplicates are removed, titles and abstracts will be screened, and the full text afterwards. Excluded articles will be recorded with an explanation for exclusion. Any inconsistencies among the reviewers will be settled by discussion and resolved with a final consensus.

Table 5 Inclusion and Exclusion Criteria Summary

Criteria	Inclusion	Exclusion
Study Designs	Randomized and non-randomized controlled trials, including quasi-experimental studies, cohort studies, case-control studies, cross-sectional, case series and reports	Systematic reviews and meta-analysis, narrative reviews, editorials, research protocols, thesis and dissertations, newsletters and bulletins, fact sheets, policy statements.
	Grey literature committee and government reports and conference reports if published by an official institution or agency	
Publication Language	English, Spanish or Portuguese	All others
Publication date	From 2000 to 2021	
Years considered	Policies and interventions that took place between 2000 and 2020	
Setting	OCDE Countries	-
Study Population	Interventions that aim, mainly or secondly, to promote the rational use of medicines are included in the ATC system groups N05BA and N05CD and that explicitly target primary recipients consumers, health professionals, institutions or health systems.	Non described or not clear
Interventions	Educational, administrative, and regulatory strategies and interventions purposing, mainly or secondly, for the rational use of benzodiazepines and analogues (aiming at the reduction or control of use, abuse or misuse)	Studies reporting psychological and pharmacological treatments singly or combined. Studies including only part of the intervention. Non described or not clear.
Outcomes	Pre-determined criteria or outcomes in each study	-

iii. Data collection process

The data for each included study will be extracted to a data extraction sheet using Microsoft Excel. This will be developed based on Cochrane Collaboration Data's data collection form.

Extraction will be carried out by two independent reviewers and any disagreements should be reconciled. If there is no consensus, a third party can be consulted.

iv. Outcomes and prioritization

For the purposes of this research, an improvement in the use of benzodiazepines will be defined by each study's pre-determined criteria or outcomes, if any exists. Whenever possible, the results will be reported in the same format as they were presented in the original article using the Template for Intervention Description and Replication (TIDieR) checklist and guide.

The characterization of the appropriateness of use for benzodiazepines, and therefore what is meant by an improvement of use, can be defined as an issue. (34) On the other hand, interventions on the use of medicines can bring both intended and unintended changes in specific outcomes previously determined. (23) We expect to find one or more performance, quality, and safety indicators for medicine use, defined in each study. Such as prescribing, dispensing, cost, patient care and facility indicators (*e.g.* the number of dispensed units in the hospital). Other secondary outcomes may also be described.

v. Risk of bias in individual studies

A critical assessment of the quality of the risk of bias of the studies will be performed using the Mixed Methods Appraisal Tool (MMAT), version 2018. This is designed for the appraisal stage of systematic mixed studies reviews, allowing to appraise the methodological quality of five categories to studies: qualitative research, randomized controlled trials, non-randomized studies, quantitative descriptive studies, and mixed methods studies.(93)

vi. Data synthesis

A systematic narrative synthesis will be presented with the information presented in the text and tables to summarize and explain the characteristics and findings of the included studies. To improve the completeness of information and reporting of each

study review, we choose to use an adapted form of the Template for Intervention Description and Replication (TIDieR) checklist and guide.

5. Results

5.1. Description of studies

A total of 6 308 articles were identified and screened from which ninety-six were eligible for full text assessment. After full-text review, twenty-seven records met inclusion criteria and were included in this review. An interrupted time series analysis from Stoker et. al. was included after hand search. Appendix A depicts the study retrieving and selection flow of articles, including main reasons for exclusion (some records could be excluded for multiple reasons). A grey literature screening was also performed but with no relevant results. Appendix B summarizes search queries used. Appendix C summarizes the studies included in the present systematic literature review.

11 out of 28 studies were *quasi-experimental* study design. Six were randomized controlled trial (from which 2 single-blind studies), five were interrupted time series, three retrospective cohort studies (two case-control and one observational), two prospective cohort studies and one cross-sectional study (as shown in Table 6).

Table 6 Study design distribution

Study Design	No. of articles
Quasi-experimental study	13
Randomized controlled trial	6
Interrupted time series	5
Retrospective cohort study	2
Before-and-after study	1
Cross-sectional study	1
TOTAL	**28**

The articles included in this review were published between 2004 and 2021. The year of 2012 was the year with more published articles included (Figure 5).

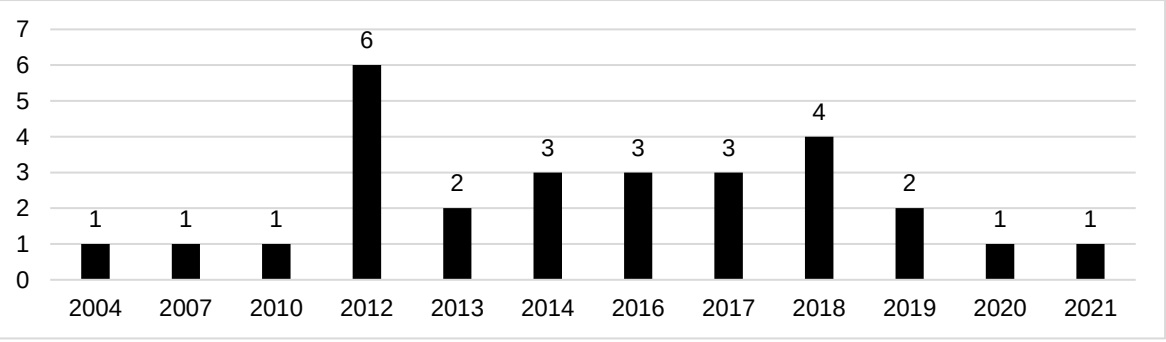


Figure 5 Reviewed articles by publishing year

All studies reported interventions based in OCDE countries. Eight studies were from information or data provided in the United States of America, followed by Netherlands (four). A distribution of the countries mentioned or included in the records assessed is shown in Table 7.

Table 7 Countries in included studies

Country	Number of Publications
USA	8
The Netherlands	4
Ireland	3
France	3
Spain	3
Canada	2
Denmark	2
Finland	2
United Kingdom	2
Australia	1
Belgium	1
Japan	1
Greece	1
Norway	1
Switzerland	1
Sweden	1

5.2. Characteristics of setting and providers of the intervention

Nine studies were conducted in the primary care setting, five in hospital care and four in long-term care or nursing homes. Six studies referred to interventions that were transversally settled, and four in specific settings (*e.g.* prisons).

As for providers, defined as the main or supporter agent involved in the intervention delivery, medical doctors were the professionals mostly reported in the included studies (n= 16), followed by pharmacists (n=12). In some studies medical doctors were specifically mentioned by their speciality. General practitioners were the most specified ones (n=5) followed by geriatricians (n=4) and psychiatrists (n=3). Psychologists and nurses were both mentioned once. Governmental Authorities' interventions were mentioned in 7 different studies.

Figure 6 Interventions' providers mention in the assessed records

Interventions' providers	No. of studies mentioned
Medical Doctors	16
Pharmacists	12
Governmental Authorities	7
Psycologists	1
Nurses	1
Other staff	1

5.3. Intervention's types and targets of the intervention

The interventions and strategies addressed in the included studies were categorized in three types: administrative, educational and regulatory (definitions are detailed in Table 8). In eleven studies, the intervention was classified into more than one category. In these cases, one intervention counted in two or three categories. Administrative interventions were most often reported: eighteen times (only seven exclusively). Sixteen interventions were classified was educational (five exclusively). Six interventions had regulatory characteristics (five fell exclusively into this category).

Many interventions (n=13) were based or required a multidisciplinary collaboration between healthcare providers, usually accompanied with changes in functioning of the organization or in the relation and articulation with stakeholders. In five interventions there were some forms of prescription audit and feedback, peer review and group processes in which health professionals identified a medicine use problem and developed, implemented and/or evaluated the strategy or intervention to address the problem. In six studies, it was observed interventions based on definition of clinical guidelines (standard treatment guidelines, prescribing policies), consisting of developed statements or rules (nationally, regionally or locally) to help or to rule prescribers about appropriate treatment or decisions. Additionally, Cadogan, Bradley and Bennet reported modifications on drug legislation and regulations that introduced requirements to benzodiazepines prescribing.(94) Eight interventions reported in the studies foresaw education about the use of benzodiazepines to the public based on campaigns or direct contact with healthcare professionals. And four reported education activities directed to healthcare professionals.

Studies were also labelled during the review accordingly to the direct or indirect targets of interventions as: consumer-level, professional-level, organizational-level and system-level. It was previously considered that the same intervention could affect, directly or indirectly, more than one target. Healthcare professionals were the most

prevalent target of the intervention with eighteen studies reporting strategies and interventions directly or indirectly designed and implemented to address the prescription, dispensing, administration or monitorization of benzodiazepines.

Nine studies addressed interventions that required or affected the normal functioning of healthcare organizations. Most of these included the creation or modification of services to enable or enhance multidisciplinary collaboration, to set new services (*e.g.* medicines review by pharmacists on a daily basis) or local procedures or rules regarding prescription.

At consumer-level 10 studies reported interventions that influenced the use of benzodiazepines and analogues. A majority had an educational dimension. Three of them implied changes in reimbursement of BZD.

Lastly, six studies described interventions designed to influence the use of benzodiazepines at the system-level. Interventions in this category consisted in changes of reimbursement, national legislation modification and state implementation of a prescription monitoring program.

Appendix C provides a detailed summary of studies included in the present systematic literature review with brief descriptions and key findings of the reported interventions. In complement, Appendix D synthesizes the intervention delivery and rational based on the template for intervention description and replication (TIDieR) checklist and guide.

We characterized and profiled the interventions reported in the studies included in this review. In thirteen studies the interventions described were assigned to more than one intervention.

Table 8 Summary of the interventions reported in the studies included in this review

Interventions described	No. of studies
Multidisciplinary collaboration	**13**
Public education about medicines	**8**
Development, modification and implementation of clinical guidelines and/or internal procedures	**6**
Professional education (continuing in-service professional development)	**5**
Financial and reimbursement policies	**5**
Supervision, audit and feedback	**5**
Appropriate and enforced legislation or regulation	**1**

5.4. Interventions outcomes and results

All included studies had the outcomes defined *a priori*. The great majority of the records assessed (n=19) took general indicators as outcomes such as incidence or prevalence of diagnoses or benzodiazepines use or proportion of patients treated with BZD. In eleven records the defined outcomes were refined and specific as medicine use indicators and/or found in literature (*e.g.* Defined daily dose (DDD), Medication Appropriateness Index, Average equivalent diazepam doses). In six studies, process indicators were used as outcomes such as the number of professional interventions or recommendations issued. In five records clinical outcomes were also used, usually measured with a validated tool. Three studies measured the patient perceptions on their health and quality of life or drug self-use. Only one study pre-defined cost indicators as an outcome. In Appendix E detailed results and key findings of each study can be found.

In each study and considering the outcomes predefined criteria, we assessed the reported drug use improvements. Secondary and non-expected results were also considered. Each study was graded from 0 to 3 (0: no improvements or worsening in use; 1: minor improvements; 2: moderate improvements; 3: large improvements). Table 9 lists the studies assigned to each score. Most of the studies included in this review described moderate (eight studies) or large (seven) improvements in the prescription, dispensing or utilization of benzodiazepines and analogues. Six studies referred minor improvements and six described no improvement or a negative influence on the benzodiazepine's utilization. No grading was attributed to Martin *et. al*(95) study since the outcomes defined and measured were the change of risk perception, beliefs and knowledge regarding the use of BZD.

Table 9 Synthesis of results according to improvements in drug use

Studies, by Author(s)		Drug use improvements
Bachhuber, Marcus A. et al.; Azermai, M. et al.; Navy, H.J. et al.;	Rat, C. et al.; Rowntree, R. et al.; Cadogan, C.A., Bradley, C.P. and Bennet, K.;	**0**
Dolan, C. et al.; Stoker, Lennart Jan et al.; Velert Vila, Josefina et al. (1); Gemelli, Maria Grazia; Yockel, Katherine; Hohmeier, Kenneth C.;	Furbish, Shannon M.L. et al.; Chen, Y. C.; Kreling, D. H;	**1**
Crotty, M. et al.; Mestres Gonzalvo, C. et al.; Velert Vila, Josefina et al. (2); Hoebert, Joëlle M. et al.;	Lang, P.O. et al.; Cabelguenne, D. et al.; Clay, Emilie et al.; Mondielllo, T. B.; Stutzman, L. A. ;	**2**
Salonoja, M. et al.; Reeves, Rusty; Geka, M. et al.; Davidson, S., Thomson, C., Prescott, G.;	Jørgensen, V. R. K; Tannenbaum, Cara et al.; Badr, A.F. et al.;	**3**
From studies own results and key findings the drug use improvements were assessed and graded accordingly to this scale: 0 – None, 1 - Minor, 2- Moderate, 3 – Large. Martin, P. et al. measured the participants perceived risk from consumption of benzodiazepines and therefore was excluded from any assessment for drug use improvement as that was not the study objective.		

Figure 7 shows the distribution of scores for drug improvement use according to the setting of the intervention. Nine of the studies including in this review occurred at the primary care. Two thirds of the interventions in this setting registered moderate to large improvements in BZD utilization. Five studies were developed at the hospital setting, with two registering large improvements and one moderate. At the long-term care setting two studies reported moderate improvements, one minor and one no improvements at all. In this review two studies that reported interventions at prison setting were also included, with moderate and large improvements in benzodiazepines' use. Six studies had been conducted across two or more settings, with some of them describing collaborative interventions, such as between primary care, e.g. pharmacies, and hospital care.

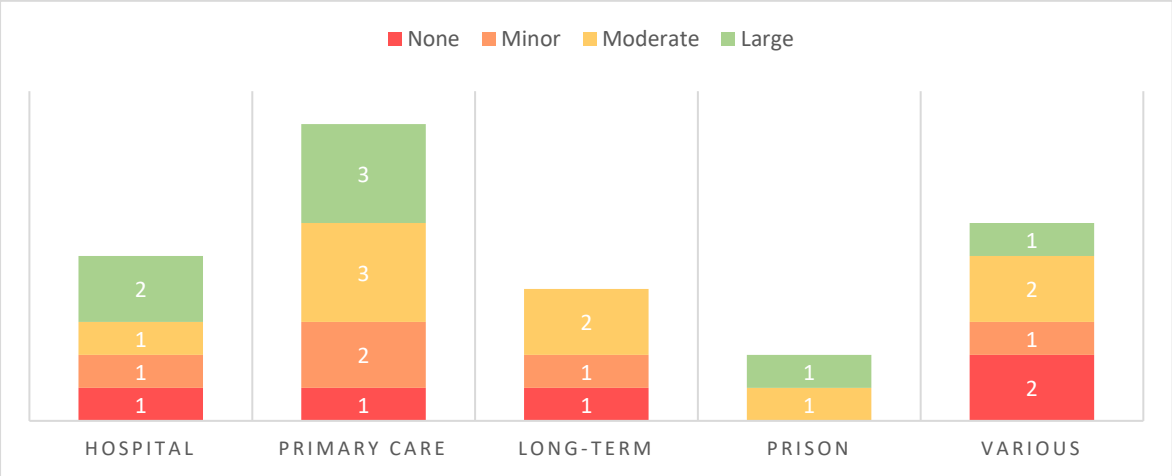


Figure 7 Drug improvement use score distribution by setting of intervention

Figure 8 illustrates drug improvement use score distribution according to the intervention's target(s). A majority of the interventions were designed and implemented to modify or influence the process of prescribing, dispensing and administration of benzodiazepines at professional-level. Half of the interventions that directly or indirectly targeted healthcare professionals registered moderate improvements in the BZD use. 37,5% of these interventions had minor or no improvements at all. And only three studies have reported large improvements.

Interventions targeting consumers exclusively, or not, were reported in six studies. Two thirds registered moderate and large improvements with the rest reporting minor (two studies) or no improvement (one study).

Similar results could be found regarding interventions, directly or indirectly, at organizational level. With more than 75% of these interventions having moderate to large results.

Only four studies reported interventions at system-level. Only in one study the designed intervention was exclusively aiming systemic modifications. Interventions aiming systemic modifications included in this review are also targeting consumers and professionals. Studies targeting at this level only registered moderate improvements (in three studies) and minor improvements (one study).

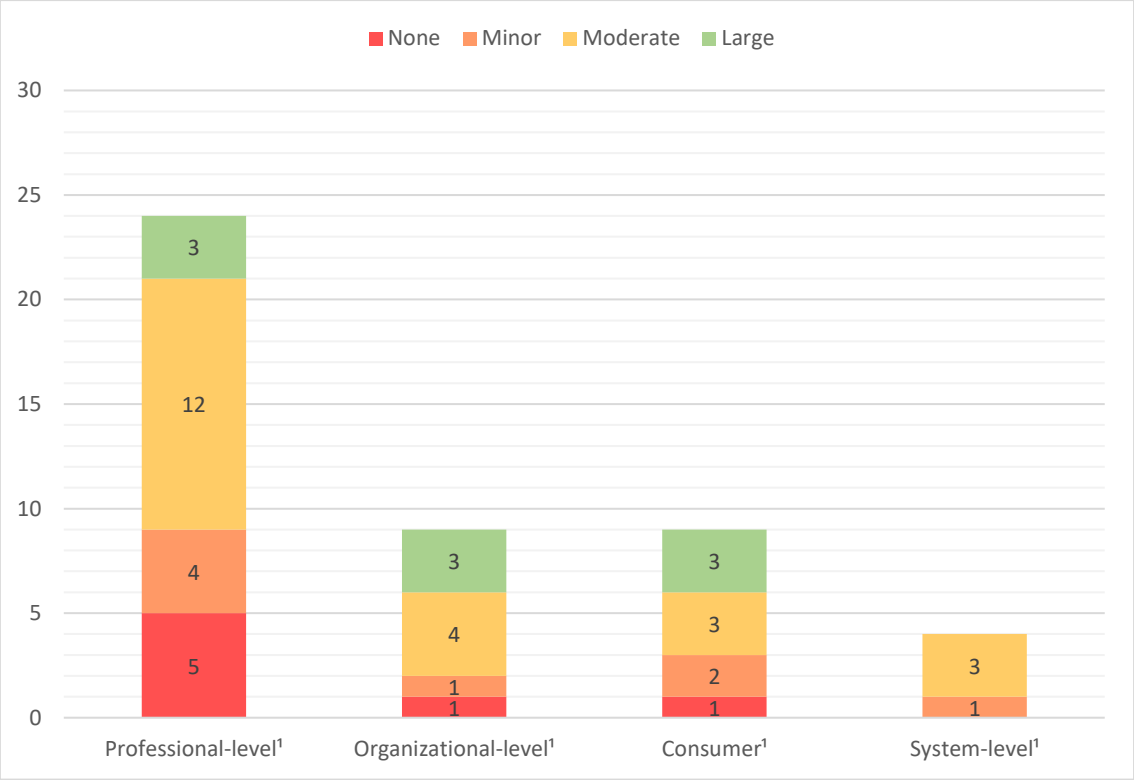


Figure 8 Drug improvement use score distribution according the intervention's target(s).

[1]An intervention aimed for two or more targets categories was counted once in each correspondent category.

Figure 9 evidentiate the distribution of drug improvements scores in accordance with the type of intervention category. Combined administrative and educational interventions were the most common (ten in twenty-seven) with homogeneous results regarding the improvement of BZD utilization. Three studies reported large improvements, two moderate, three minor and two no improvements at all. Exclusively administrative interventions amounted to seven interventions in total, with three studies reporting moderate improvements and two large improvements. Four studies focused on educational interventions in exclusive. Two of these have reported large improvements, one moderate and one no improvements. Regulatory counted for five interventions in total with two presenting no improvements, one minor and two registering moderate improvements. In the regulator category no interventions with large improvements were

registered. A single study reported an intervention assigned at all three categories with moderate results on BZD use.

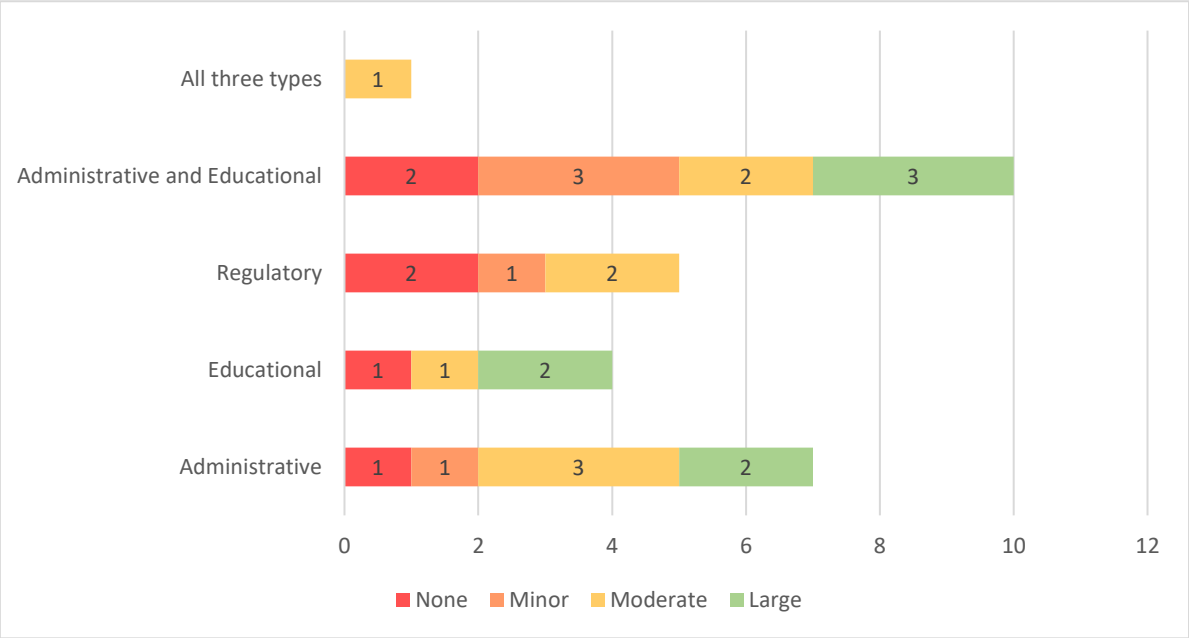


Figure 9 Drug improvement use score distribution by type of intervention

Figure 10 shows the drug improvement use score distribution according to providers, that is, defined as the main or supporter agent involved in the intervention delivery. As so, the interventions could involve one or more providers at the same time. Collaborative interventions – involving two or more providers – were counted once in each correspondent provider.

As mentioned before medical doctors were the professionals mostly reported in the included studies (n= 16). Medical doctors were sometimes specified by their speciality. General practitioners were the most mentioned ones (n=5) followed by geriatricians (n=4), and psychiatrists (n=3). In interventions with general practitioners as providers three reported large, and one moderate, improvements in BZD use. In all studies with geriatricians and/or psychiatrists participating as providers were registered improvements.

Pharmacists participated as providers in twelve studies. One third with large improvements use, being the professional category with more participations in interventions with this kind of results. In four studies moderate results were reported. And in three only minor improvements were registered. In one study involving this profession no improvements happened following the interventions.

Psychologists and nurses were both mentioned in Azermai *et. al* study(96). This was a continuing in-service professional development intervention with no improvements in benzodiazepine use.

Governmental Authorities' interventions were mentioned in 7 different studies. In three of these no improvements in BZD use were made. In three moderate results were registered and in the last, only minor results were reported.

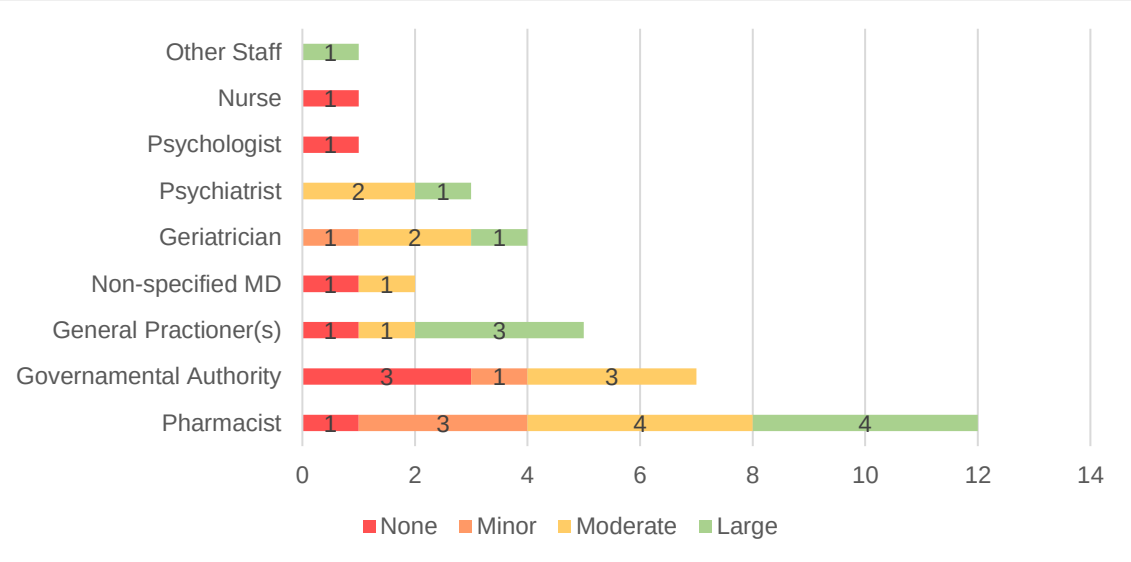


Figure 10 Drug improvement use score distribution according providers, solely or in cooperation.
[1]An intervention involving two or more providers was counted once in each correspondent provider.

A majority of the interventions were delivered by one provider only. As seen in Figure 11, almost 65% of the studies of this category registered minor (five studies) and moderate (six studies) improvements in drug use. Only three studies counted for large improvements.

As for the interventions with two or more providers involved, 70% of the studies included reported moderate (three) and large (four) improvements in benzodiazepine use.

In both the categories three studies with no improvements were counted for as seen below.

Provider(s)	0	1	2	3	Total
One Provider	3	5	6	3	**17**
Two or more providers	3		3	4	**10**

Figure 11 Drug improvement use score distribution according to providers collaboration or exclusive participation

5.5. Risk of bias in included studies

Foreseeing some heterogeneity on the study designs and methodologies and the possibility of finding qualitative and mixed methods studies and interventions we used the MMAT tool (version 2018). This tool allows the appraisal of most common types of studies methodologies and designs and can be used the quality of empirical studies.(93,97)

After selection of eligible studies only two main categories of study designs were found, accordingly to the criteria underlined by the developers of this tool: quantitative randomized controlled trials and quantitative non-randomized controlled trials. For each chosen category the methodological quality criteria questions were rated in “Yes”, “No”, and “Can’t tell”. No studies were excluded based on their methodological quality as recommended by the developers of the MMAT tool. A summary of the rating for each study can be found in Appendix F. No score was calculated since this is discouraged in the MMAT utilization.

None of studies included in the randomized control trial category (six in total) and evaluated predicted the blinding of the outcome assessors. Blinding of outcome assessors, aims to avoid bias in measuring the outcome. This can be difficult or impossible in some contexts. In most of the interventions included in this review the researchers – assuming the role of outcome assessors – directly or indirectly participated in the intervention delivery. Understandably, this makes blinding impracticable. As result some deviations from intended interventions can lead to bias in the estimated effects of planned intervention or its adherence.(98) On the participants adherence to the intervention only Navy et al.(99) described deviations on the planned interventions. Mainly because participants had the option to contact their prescribers after receiving the outreach letter (which was part of the planned intervention) and because authors promoted physicians (intervention providers) autonomy and avoided to interfere with the patient-provider relationship.

About participants representativeness on the non-randomized studies, Reeves(100), Rowntree *et al*.(101) and Bachhuber *et al.*(102) did not provide any description of the target population. This was due to the fact that part of the interventions reported in these studies consisted of medication chart and prescription reviews or simply, in the last of them, an estimation of rates of emergency department visits involving benzodiazepines.

In the non-randomized category, a transversal aspect of all studies was the strong possibility of the existence or influence of confounding bias. Cofounders were not clearly accounted for in the design and analysis of the intervention, with the exception of Hoebert et. al(103) and Stoker et. al.(104) Some of them took note on some participants' characteristics as age, gender, other medication and comorbidities at baseline during participants description. But in general, they all lacked the report or description of methods to control for confounders or did not address potential ones at all at the results or the study limitations. Accurate identification and measure of confounders is crucial in all types of health outcomes research. Any inaccuracy can lead to bias or residual confounding.(69) These findings can be justified by the complexity of the interventions or of the settings that may rise difficulties to a complete identification and measurement of potential confounders. In healthcare settings or systems, at the very limit, there are multiple factors that can influence outcomes on medication utilization.

Overall, most of the studies assessed in the non-randomized category did have report on the intervention integrity. Meaning, that the intervention was delivered or administered as initially intended. However, in six of them (Reeves(100), Clay et al.(105) Bachhuber et al.(102), Mondiello et al.(106), Cabelguenee et al.(107) and Geka et al.(108)) that was not clearly defined. Again, it must be underlined that complexity of some interventions and settings can explain this. Or even the study aim itself. For example, Clay et al. described and compared the effects of anti-BZD campaigns and/or the introduction of prolonged-release melatonin in the pharmaceutical market in nine european countries.(105) Which makes it difficult to ensure that the different interventions were delivered as intended. Only Furbish et al. noted that the study intervention and participants follow-up did not occur as initially idealized which was a severe limitation for a study that was based on voluntary adherence in intercollaborative service aiming to improve the use of benzodiazepines.(109)

6. Discussion

The present systematic review was conducted to identify and assess strategies and interventions designed and implemented to promote and ensure the rational use of benzodiazepines and analogues in anxiety and sleep disorders. Three main categories of intervention were focussed on this review: educational, administrative and regulatory interventions. The targets or objects of these interventions and strategies were also outlined and previously defined: consumer-level, professional-level, organizational-level and system-level.

6.1. Consumer-level interventions

Ten out of twenty-eight studies reported interventions which targeted consumers both directly and indirectly. All but one of the studies reported interventions that were solely educational or both educational and administrative. Focusing on these the studies of Davidson, Thomson and Prescott(110), Salonoja et al.(111), Velert Vila et al.(50,112) and Navy et al.(99) involved an educational approach with or without multidisciplinary collaboration approach with an active participation of pharmacists in medication reviews and counselling processes (in Salonoja *et al*. it was a geriatrician who collaborated with general practitioners).

In two of those studies participants received a mail or letter about precautions and dangers of prolonged use of benzodiazepines and with advice to attend a specific appointment to receive support on tapering.(99,110) These studies reported very different drug use improvements between. While the study of Davidson, S., Thomson, C. and Prescott, G reported major improvements with "*durable reduction in overall diazepam prescribing by using a minimal intervention strategy and maintaining a collaborative, proactive relationship between primary and secondary care providers"*(110), Navy et al found no significant improvements on benzodiazepine use. This may be due to the procedures and intervention delivery. In the Davidson's study the prescriptions were dispensed weekly, hereby compelling participants to maintaining a regular contact with the pharmacists responsible for monitoring the tapering regime. The providers were also aligned with consensus guidelines that helped harmonization between interventions. Tannenbaum et al. also resorted on an educational tool mailed to participants.(113) This tool was constructed among various professionals and pretended to "*create cognitive dissonance about the safety of benzodiazepine use, education about drug interactions, peer champion stories intended to augment self-efficacy, suggestions for equally or more effective therapeutic substitutes for insomnia and/or anxiety, and stepwise tapering recommendations*"(113) and maintain a tapering off regime.

Other two studies highlighted the role of pharmacists in the interdisciplinary or multidisciplinary teamwork. Velert Vila et al. randomized control trials determined that "*pharmacists intervened whenever medication-related problems (MRP) or negative results of the medication (NRM) of necessity, efficacy or safety appeared, giving the patient information on the correct use of BZD referring to the physician referring if it was intended to eliminate the medication from the therapeutical care, decrease dose or switch to lorazepam when there was any problem of interaction with other medications*

used or when adverse drug reactions appeared"(112). In this pharmaceutical care follow-up whenever patients refused to attend to the physician consultation after referral, pharmacists did propose a tapering off regime and kept up with patients. Those interventions brought minor to moderate improvements to the use of BZD. Both studies are similarly designed, and interventions implemented alike. It must be noted that one of these focused more in the measurement of processes (*e.g*. the number of pharmacists' interventions and recommendations) instead of results. One must highlight the fact that in both these studies procedures of referral to physicians were clearly defined and based on collaboration between primary and secondary care (making these interventions also administrative). Both these records suggested that pharmacists led-medication review have positive effectiveness to reduce medicine problems and unnecessary medicines, like reported in Dudley et al. systematic review.(114)

A similar study was reported by Salonoja et al. where a geriatrician assessed the appropriateness of each drug of every participant through medicine review and an individual interview. Changes in therapeutical regimen were discussed and plan defined and provided to the users to stepwise reduction. This was followed by a co-intervention that consisted in 1-hour lecture to the general population.(111) Salonoja *et al*. study pointed out major improvements in medication use. All these experiences are aligned with some evidence that's support the provision of counselling of patients and/or physicians by pharmacists to improve adherence.(114)

It must be underlined that all these, exclusive or not, educational interventions were specially designed to the reduction and cessation of benzodiazepine use. A meta-analysis from Parr *et al*. on the effectiveness of current treatment approaches for benzodiazepine discontinuation stated that "*providing individuals with advice to cease benzodiazepine use or with a more extensive intervention increases cessation rates significantly in comparison with routine care"*.(115) Ryan *et al*. in an overview of systematic reviews conclude that interventions that provided "*information or education as a single component may be ineffective to improve adherence or clinical outcomes*". It also underlines that here is not sufficient evidence to determine whether educational interventions, when delivered alone, reduce adverse effects, but the existent evidence suggested that it may improve knowledge.(116) Martin *et al*. study corroborates this conclusion. In this intervention a "*home-based educational program consisting of a document mailed to participants demonstrated significant effects on medication knowledge, beliefs and risk perception in a cohort of older benzodiazepine users*".(95)

Three studies focused on the elimination or reduction of the reimbursement of benzodiazepines (103,104,117) with minor and moderate improvements on medicines use mainly in benzodiazepines initiation. Financial incentives and pharmaceutical policies aimed at influence consumers are effective, with mixed results.(114) This underlines the importance of viewing policy changes outcomes in a broader perspective. A regulator change may lead to the desired goal but may create an unexpected outcome. Therefore careful attention is required before and after policy implementation when determining the effects of regulatory changes.(103)

6.2. Professional-level interventions

Eighteen studies reporting strategies and interventions directly or indirectly targeted to healthcare professionals. These were designed to modulate the process of prescribing, dispensing and administration.

In five of these studies supervision, audit and feedback was the core intervention with none to moderate improvements on benzodiazepine use.(101,102,106,118,119) Accordingly to the literature audit and feedback usually lead to small but potentially important improvements in professional practice. The effects are generally small to moderate. The intensity, delivery and provision of audit feedback and the baseline performance are predictive factors on audit and feedback effectiveness.(120,121) Mondiello *et al*. evidenced moderate results. In this intervention an online tool was designed to improve psychotropic medication prescribing. Patients were identified and a schedule appointed. Pharmacists conducted medication reviews and provided recommendations to prescribers.(106) The adoption of the online tool had the potential to change the providers behaviours (122) and may explain the positive results in this study. As stated before, the pharmacists' involvement on medication review and collaboration with the prescribers are also positive predictive factors on benzodiazepines use.

In eleven of the records assessed aiming for healthcare professionals one of the interventions' cores was the institution multidisciplinary collaboration on healthcare services organizations or in healthcare delivery. Generally, a multidisciplinary approach had minor to large benzodiazepine use improvements. Pharmacists direct participation on team meetings, implementation of medication review processes and issuing of recommendations to prescribers have shown favourable results.(108,123) These results corroborate that pharmacy services to reduce suboptimal prescribing shows promising and noteworthy improvements.(124) Bachhuber *et. al* presented a retrospective study

on a state-owned implementation of a prescription monitoring program in the USA with no evidence on improvements in benzodiazepine use. Similar results on these programs in literature, being stated that these programs are an important tool for minimizing potential harm.(125,126) The lesser results of these intervention could be due to the outcomes definition for this study that was the rates of Emergency Department visits involving benzodiazepine misuse.

Rat *et al* reported a national-wide intervention in France in which general practitioners were enrolled on a new pay-per-performance payment system. The implementation of these strategy did not affect the prescription of long half-life benzodiazepines, while the number of prescriptions of short half-life drugs increase.(127) Literature on financial incentives effectiveness in changing professional practice has methodological limitations and evidence of patient's health improvement is still poor. It is also stated that financial incentives for physicians are usually ineffective for improving compliance with guideline outcomes.(128,129)

A cross-sectional study reported the effects of a new controlled drugs legislation that introduced new and tighter requirements for the prescription of benzodiazepines. However, with no improvements on the medicines use.(94)

Four studies addressed educational interventions, combined with other dimensions already mentioned, targeting to healthcare professionals with mixed results. Azermai *et al.* reported a governmental-funded quality improvement project where two nursing homes received educational courses, complemented with a co-intervention consisting in professional support aiming a transition towards person-centred care.(96) No improvements in the use of benzodiazepines was found. In contrast, in Reeves' study a guideline was issued, followed by an audit and educational sessions where prescribers could compare prescription trends with significant and time-persistent reduction of benzodiazepine prescription.(100) As stated before, single component educational interventions have been proven ineffective to improve adherence or clinical outcomes. Reeves' study suggested that guideline, education, and peer comparison techniques should be used together more often. A critical literature review suggested that personalization of educational strategies or interventions promotes the effectiveness on the improvement of drug prescription. It also concluded that the combination of active and passive strategies results in reduced rates of failure.(130)

6.3. Organizational-level interventions

Nine studies issued interventions with components that had healthcare organizations as recipients of those interventions. All except one were based on a multidisciplinary approach with minor to large benzodiazepine use improvements. Many of these collaborations forced changes in the way organizations work with the implementation of online tools(106) and medicine review services within organizations or based on cooperations with local stakeholders.(107,109) One example of these collaborations effectiveness is the retrospective study of Geka *et al*. in Japan. In this study, pharmacists decided to convene multidisciplinary clinical team meetings where they could effectively share information on BZD use and discuss their prescription recommendations with other clinical team members.(108) Major and time-resilient improvements in benzodiazepines prescription and use resulted from this day-to-day collaboration and change in those wards that indicated that improved communication between multidisciplinary team may be important in avoiding and reverting long-term BZD use.(131) Evidence sustains that the expansion of multidisciplinary collaboration to cooperation between organizations, and even healthcare settings can promote a better utilization of BZD, as around 40% of BZD prescriptions are initiated during hospital admissions and are followed by continued prescription at primary care. (131)

Internal procedures and clinical guideline are relevant aspect of these results. Jørgensen's study portrays an intervention that consisted in changes in prescription and consultations rules with elimination of telephone prescription, the issuing of single prescriptions only following consultation and limited for a single month's use only, and discussion at consultation regarding future treatment requirements as well as a possible phased reduction of treatments. Educational sessions complemented this intervention. On other hand, Mestres Gonzalvo *et al*. described the implementation of a clinical rule, through a business intelligence software to screen patients that had been using BZD for longer than 4 weeks.(132) These two interventions had large and moderate impact on drug use. These results may sustain the importance of clinical guidelines and organizational standardized procedures as a way of improving health care processes, outcomes and costs. Some examples of perceived benefits of guideline implementation were increased clinical efficiency and reduction of inappropriate care. Moreover, guidelines are perceived as the most important key intervention to enhance the rational use of medicines.(133)

There are some barriers and factors that affect guidelines implementation – such as sufficient funding for development and active dissemination – that consequently

justifies the mixed results on this method to improve medicines use. (133,134) The use of the clinical rule in Mestres Gonzalvo's study can be considered as a technological support system. These have proven to have consistently resulted in significant practice improvements.(122,135)

6.4. System-level interventions

A total of six studies assessed reported interventions targeted to healthcare systems, of which five were within regulatory category (one also had educational and administrative dimensions). Chen and Kreling studied the effects of the exclusion of benzodiazepines from Medicare Part D, a US federal government program to help beneficiaries pay for prescription drugs, with minor impact on BZD use improvement, since for some individuals the change in reimbursement coverage did cause them to switch from BZD to an alternate agent.(117) A review from Green *et al*. stated that this behaviour occurs whenever drugs are interchangeable and consequently prescription and utilization decreases.(136)

Hoebert *et. al.* and Stoker *et. al.* described the benzodiazepine exclusion from the Dutch reimbursement list occurred in 2009 with minor to moderate improvements. (103,104) Hoebert *et. al* focused on general practice data (primary care) and found out an increase of the number of reimbursed prescriptions (BZD only were not reimbursed when used as anxiolytic, hypnotic and sedative). Even so, BZD "*disappeared from the top 10 most-prescribed medicines and were among the top 10 medications with the steepest decrease in number of prescriptions".* This was a result of a positive "*effect on the decrease of incident diagnosis"* (not having had this diagnosis in the 365 days before the diagnosis of interest) *"and initiation of BZD use in patients with newly diagnosed anxiety or sleeping disorder"*. Simultaneously, the proportion of patients of patients receiving prescription for benzodiazepines decreased.(103) Stoker *et al.* described a moderate decrease on volume, incidence and prevalence of use of benzodiazepine. It must be underlined that in this study were assessed and reviewed a random sample of benzodiazepines dispensing.

The retrospective study from Clay *et al.* aimed to evaluate the impact of campaigns on BZD and Z drugs (BZD/Z) rational use and the availability of an alternative pharmacotherapy (prolonged released melatonin) and respective reimbursement. The annual sales from Finland, Norway, Denmark, Sweden, Greece, France, the Netherlands, Spain and the United Kingdom were extracted to analyse the use of BZD/Z-

drugs. The authors grouped all the countries in three main groups accordingly to BZD/Z-drugs consumption trends, even if each country had a particular experience and conditions. In Greece, for example, there was no anti-BZD campaign. This kept the consumption of these drugs until the introduction of prolonged release melatonin in the market, which provoked a drop of 14.5% over three years. This decrease was not inferior in Finland and Denmark where the reduction of BZD/Z-drugs seemed to be associated with the combined effects of anti-BZD campaigns and the launch of a therapeutic alternative. However, the decrease in these two countries were not higher than in Greece (where there was no campaign). In Norway, the Netherlands and the UK the anti-BZD campaigns appeared effective but have firstly resulted in a shift in prescriptions patterns towards Z-drugs. The authors tried to propose different hypothesis to explain this and further changes that occurred in those countries. In Norway the introduction of therapeutic alternatives (prolonged release melatonin) later reverted the shift to Z-drugs. However, the shift reversion was not observed in the UK. As for the Netherlands they propose that the reimbursement status(103,104) is a considerable factor to explain the later decrease in BZD sales, establishing that consumption in this country is price sensitive.(105) It is known that reimbursement policies can greatly impact consumption.(137) A third group of countries displayed no variations on BZD sales and an increase on Z-drugs use despite the intense and long lasting campaigns: France, Spain and Sweden. Those findings can be explained by the reimbursement policies in force, especially in price and reimbursement-sensitive pharmaceuticals market, such as Spain, or the availability and reimbursement of melatonin.(105,138,139) Overall, Clay *et. al* concluded that campaigns aiming to promote the reduction of BZD/Z-drugs sales and consumption and achieve discontinuation of longer use, tend to fail if they are not associated with the availability of pharmacotherapeutic alternative. Reimbursement policies should also be considered, bearing in mind that the non-reimbursement of BZD/Z-drugs have not shown any effect on Z-drugs consumption.(105)

Additionally, a study described the implementation and effects of a controlled drugs legislation that introduced new and tighter requirements for the prescription of benzodiazepines. However, with no improvements on the medicines use.(94)

6.5. Strategies and interventions characteristics and cores as predictive factors for the rational use of medicines

In this review different strategies and interventions aiming for the rational use of benzodiazepines and analogues were identified. Mixed administrative and educational interventions were the most common type of intervention found. Followed by exclusively

administrative, exclusively educational and regulatory. The preferable target or recipient of implemented interventions are healthcare professionals, especially prescribers and pharmacists. Overall, the interventions' cores described, in order of decreasing frequency were i. Multidisciplinary collaboration; ii. Public education about medicines; iii. Development, modification, and implementation of clinical guidelines and/or internal procedures; iv. Professional education (continuing in-service professional development); v. Financial and reimbursement policies; vi. Supervision, audit and feedback; vii. Appropriate and enforced legislation or regulation. These are in line with the core interventions to promote more rational use of medicines postulated by WHO and INRUD.(36,68,72) Fifteen studies reported multifaceted interventions, that is, with more than one core component. Previous study found that multifaceted interventions aimed at changing benzodiazepine prescribing and use tend to be more effective in comparison with single-faceted interventions.(140,141) Additionally it must be underlined that clinical, social and cultural factors related to all interveners impact benzodiazepine prescribing, dispensing and utilization.(142) As so, the existence of multifaceted interventions is comprehensible and desirable. In the studies included in this review, generally, the focus of the interventions identified was on the discontinuation of long-term therapeutics instead of prevention, for example, on promoting the risk-benefit analysis by providers before prescribing.

One goal of this study was to characterize the influence of different strategies and interventions on the use of benzodiazepines. Therefore, in this review we assessed and graded the improvement of BZD utilization accordingly to each study criteria, outcome and results. Even if there are several well-established methods to measure the type and degree of rational and irrational, almost every study defined their own outcomes.(36,70–72) Clinical and economic outcomes were seldom reported in interventions to reduce sedative use, which was previously found in other review.(143) The heterogeneity of outcomes and criteria adopted in each study hindered the association between benzodiazepine utilization improvement and interventions characteristics, like setting, provider, interventions' type and core. Sixteen studies have demonstrated moderate to large improvements in the prescription, dispensing or utilization of benzodiazepines and analogues. And six more reported minor improvements. Even if this review could not establish any association or conclusion regarding the interventions' characteristics as predictive factors on the rational use of medicine it did identify the more common interventions used.

Because strategies and interventions on the rational use of medicines have uncertain effects, and since the components of rational use of medicines are multidimensional, proper methodological and evidenced based approach should be considered in the design, description, implementation and evaluation of these interventions.

6.6. Strengths and limitations

Previous systematic reviews assessed factors associated to the misuse of benzodiazepines and analogues. Some have focused on the characterization of the benzodiazepine misuse, general practitioners' experiences and perceptions of benzodiazepine prescribing and patients' experiences, perceptions and influencing factors on benzodiazepine use.(144–146) Others in interventions to reduce de use or promote deprescribing and tapering, specially focused on psychological and pharmacological interventions.(74,76,91,147) The present review stands out from others for its comprehensive approach on the rational use of benzodiazepines, highlighting interventions on prescribing, dispensing and use of benzodiazepines, at different settings and levels of the healthcare system. It is focused on educational, administrative and regulatory interventions that are at hand of healthcare professionals, decision and policymakers and stakeholders to prevent, to control and to reverse benzodiazepine overconsumption.

The comprehensiveness of this study allowed the review and assessment of different strategies and interventions of several natures in OCDE countries. However, a segmented review on the different intervention categories – educational, administrative and regulatory – could provide more results and an in-depth analysis and review.

There is a wide recognition that RCTs are considered a gold standard study design for evaluation interventions effectiveness, since other designs may be more prone to bias.(83) In this review one in every five studies is a RCT. Nonetheless, the aim of our review is to provide practical and useful information. The inclusion of quasi-experimental studies – and other non-randomized studies – can provide valid causal effect estimates. The exclusion of these may reduce the value of evidence synthesis.(148) However the heterogeneity across studies regarding design and methods used must underlined.

Heterogeneity can also be highlighted regarding the design, delivery, description and report of the interventions. As stated by Hoffman *et al.,* the quality of descriptions of interventions in publications remains remarkably poor, with key features and

components being often missing or poorly described.(79) This impacted deeply the data collection, synthesis and analysis in this review, despite the use of PRISMA-CI and TIDieR guidelines and checklist on data collection and synthesis. This apparent heterogeneity may be a reflection of the influence of complex interplays of individual characteristics, social determinants, the healthcare delivery systems and the interventions themselves on the effectiveness outcome.(81) Systematic reviews focusing on interventions' effectiveness in health systems or public health setting can potentially benefit from framing interventions as complex interventions. These involve, at minimum, multiple components and a complex pathway. Oversimplification may limit the usability of review findings.(78)

On the other hand, countless factors can contribute and influence how medicines are used and that affect the effectiveness of strategies and interventions.(36) That can cause intended or unintended changes in outcomes. This was reflected in interventions that fitted in the postulated definition of Guise *et al*.[2](81)**.** We believe that our review benefitted from the utilization of specific guidance on systematic reviews of "complex interventions" in order to address this complexity in most stages of this research. This effort was complemented with the use of the TIDieR guidance. If we consider the different elements and components necessary to assess an intervention (Population, Intervention, Comparison, Outcome; "PICO"), TIDieR must be accounted as an guide for reporting and comparing interventions.(79) Studies included in this review seldom reported the use of any guidance or tool to report their interventions, which impacted the review process. In the great majority of the records assessed, there was no fidelity assessments by the authors or researchers. Intervention fidelity can be defined as "*the degree to which an intervention happened in the way the investigators intended it to*". The assessment of intervention fidelity is relevant to understand and measure of how and why a given intervention work.(149)

We used the MMAT tool on the appraisal of evidence. However, it is recommended some experience and training for the utilization of this tool and its domains, something that the reviewers lacked. Additionally, the methodological

[2] "*All complex interventions have two common characteristics: they have multiple components (intervention complexity) and complicated/multiple causal pathways, feedback loops, synergies, and/or mediators and moderators of effect (pathway complexity). In addition, they may also have one or more of the following three additional characteristics: target multiple participants, groups, or organizational levels (population complexity); require multifaceted adoption, uptake, or integration strategies (implementation complexity); or work in a dynamic multidimensional environment (contextual complexity)"***.**(81)

approach on this tool highly discourages the exclusion of low methodological studies from the review. This limitation can influence the quality of evidence on this review and may contribute to disparities within the results and on the assessment and grading of the drug use improvement reported in each study.(93,97)

It was also noticed a lack of consistency on outcomes definition, measurement and reporting. This difficulted the assessment of effectiveness of interventions with objectiveness needed. A score was outlined and assigned to each study regarding the medicines use improvement. This was an important qualitative and comparative exercise that aimed to standardize and illustrate effectiveness, although is naturally subjective and susceptible to bias.

A search for studies in grey literature was carried out. However, this retrieved no results. Even if some interventions, especially organization-level ones, are usually associated with research and healthcare institutions, where publication is encouraged and desired, it is likely that governmental policies, strategies and actions were not covered in our search of grey literature. A more comprehensive and in-depth search in each countries government databases would probably result in more resources. Specifically, legislation, policies, guidelines and projects aiming the control of benzodiazepines and other drugs. This would benefit from the segmentation of this review by the three categories of interventions: regulatory, administrative and educational.

7. Conclusions

Although considered safe and effective, long-term regular use in therapeutic dosage or occasional use in excessive doses of benzodiazepines and analogues can have adverse effects that must be accounted for. Trends for benzodiazepines use worldwide may rise some concerns or at least questions regarding the rational use of benzodiazepines.

In this review different strategies and interventions aiming for the rational use of benzodiazepines and analogues were identified. Although an extensive literature search was performed, additional studies could be available in other databases and in grey literature, especially internal government reports that could not be identified in our screening.

Mixed administrative and educational interventions were the most common type of intervention found. Followed by exclusively administrative, exclusively educational and

regulatory. The preferable target or recipient of implemented interventions are healthcare professionals, especially prescribers and pharmacists.

Overall, the interventions described, in order of decreasing frequency were i. Multidisciplinary collaboration; ii. Public education about medicines; iii. Development, modification, and implementation of clinical guidelines and/or internal procedures; iv. Professional education (continuing in-service professional development); v. Financial and reimbursement policies; vi. Supervision, audit and feedback; vii. Appropriate and enforced legislation or regulation. A great number of interventions aimed to design, facilitate or promote multidisciplinary collaboration within the institution or even between healthcare settings.

We assessed the improvement in the prescription, dispensing and consumption of benzodiazepines and analogues. This assessment was mode through the attribution of a grade accordingly the criteria and outcomes defined, and results of each study as reported. Most studies reported moderate to large improvements in benzodiazepine use. No clear association was found between the measured improvement and the outlined intervention characteristics: setting, type of intervention, target of the intervention and provider. This may be due to the heterogeneity of outcomes and criteria adopted in each study. Because strategies and interventions on the rational use of medicines have uncertain effects, and since the components of rational use of medicines are multidimensional, proper methodological and evidenced based approach should be considered in the design, description, implementation and evaluation of these interventions.

8. Recommendations

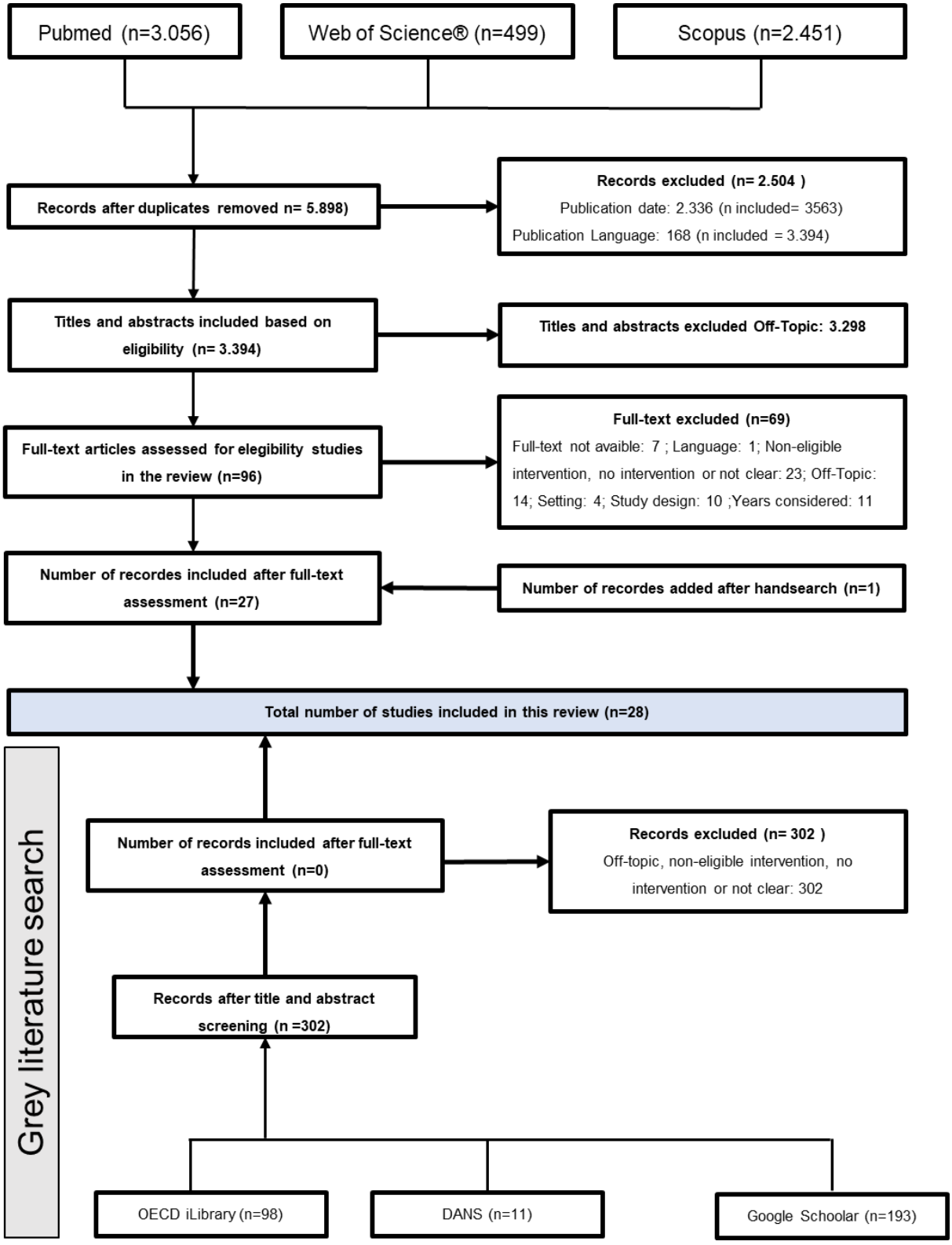
The prevalence of anxiety and sleep disorders across different countries highlights the importance of developing consistent and evidence-based interventions on the rational use of benzodiazepines and analogues. Even more when insomnia, anxiety and depression are public and relevant health concerns that were heightened due to the COVID-19 pandemic.(150) A study in United States outlined a significant decline in benzodiazepines prescriptions indicating a large treatment gap as a direct consequence of access to healthcare restrictions due to the pandemic.(151) This may lead to a rebound effect on BZD consumption in the near future.

Public health prevention programs are needed to prevent chronicity of BZD use in some countries. As well as interventions aimed to reduce the already verified long-term consumers.

There is a significant variation in the design and reporting of strategies and interventions, simple or complex, regarding the rational use of BZD. Which causes mixed results in literature for some kinds of interventions. The predictive factors for this behaviour can be addressed in future research. Further studies should address the effectiveness of complex and combined interventions, mainly those aimed for healthcare systems.

Appendix A

Flowchart for the selection of eligible studies



Appendix B

Detailed search queries

Pubmed search query
("Pharmaceutical Preparations"[Mesh] OR "Prescription Drugs"[Mesh] OR "drug" OR "pharmaceutical production") AND ("Drug Utilization"[Mesh] OR "therapeutic use" OR "Prescription Drug Misuse" [Mesh] OR "Substance Abuse, Oral"[Mesh] OR "Substance-Related Disorders"[Mesh] OR "Inappropriate Prescribing" [Mesh] OR "Health Services Misuse"[Mesh] OR "rational" OR "abuse" OR "misuse") AND ("Anxiety"[Mesh] OR "Sleep Wake Disorders"[Mesh]) AND "Benzodiazepines"[Mesh] NOT "Alcohol"[Title/abstract]

Scopus search query
ALL ("drug") OR ALL ("prescription drugs") OR ALL ("pharmaceutical preparation") OR ALL ("pharmaceutical product") AND ALL ("Substance-Related Disorders") OR ALL ("Inappropriate Prescribing") OR ALL ("Health Services Misuse") OR ALL ("rational") OR ALL ("abuse") OR ALL ("misuse") AND ALL ("anxiety") OR ALL ("sleep disorder*") AND ALL ("benzodiazepin*") AND ALL ("intervention*") OR ALL ("strateg*") AND NOT ALL ("alcohol")

Web of Science® search query
(ALL=(drug) OR ALL=(prescription drugs) OR ALL=(pharmaceutical preparation*) OR ALL=(pharmaceutical product)) AND (ALL=(Substance Abuse, Oral) OR ALL=(Substance-Related Disorders) OR ALL=(Inappropriate Prescribing) OR ALL=(Health Services Misuse) OR ALL=(rational) OR ALL=(abuse) OR ALL=(misuse)) AND ((ALL=(anxiety) OR ALL=(sleep disorder*)) AND (ALL=Benzodiazepin*) NOT ALL=(alcohol))

Google Schoolar search query
"benzodiazepine" policy intervention strategy rational use abuse misuse oecd

DANS EASY search query
Benzodiazepine*

OECD *iLibrary*
from (All Fields contains '"benzodiazepin*"') from (Language contains 'en') **AND** from (All Fields contains '"intervention*"') **OR** from (All Fields contains '"strateg*"') **OR** from (All Fields contains '"polic*"') **AND** from (All Fields contains 'prescribing') **AND** from (IGO collection contains '"igo/oecd"') **AND** from (Content type contains '"Workingpaper"') **OR** from (All Fields contains 'miuse') **AND** from (Theme contains 'Social Issues/Migration/Health') **AND** from (Language contains '"en"') with type(s) subtype/workingpaperseries OR subtype/workingpaper

Appendix C

Summary table of studies included in the present systematic literature review and narrative description

Autor(s)	Year(s) Considered	Study Design	Country	Setting	Participants Type, n.o	Intervention(s) Target(s)[1]	Type of Intervention[1]	Intervention brief description	Provider(s)
Crotty, M. et al.(152)	2000	Randomized controlled trial	Australia	Long-term care	154 residents with medication problems and/or challenging behaviours	Healthcare professional-level	Educational	Two multidisciplinary case conferences involving the resident's general practitioner, a geriatrician, a pharmacist and residential care staff were held at the nursing home for each resident.	General Practitioner (GP) Geriatrician Pharmacist
Jørgensen, V. R. K(153)	2005-2006	Interrupted time series	Denmark	Primary care	13 medical practitioners w/ a total patient base during the study of 18 513 patients receiving BZD or cyclopyrrolones	Healthcare organization-level	Administrative Educational	Changes in prescription and consultations rules with elimination of telephone prescription, the issuing of single prescriptions only following consultation, the prescription of medicine sufficient for a single month's use only; and discussion at consultation regarding future treatment requirements as well as a possible phased reduction of treatments	General Practitioner (GP) Other staff
Salonoja, M. et al.(111)	2003-2005	Randomized controlled trial	Finland	Various	591 community-dwelling people aged 65 or older participated	Consumer-level	Educational	Review of the medication by the geriatrician and one-time counselling and discussion with patient on practical instructions of plans to facilitate stepwise reduction A co-intervention consisting in a 1-hour lecture about adverse effects of BZD, other psychotropics and other fall-risk-increasing drugs (FRID).	Geriatrician
Dolan, C. et al.(118)	2008	Interrupted time series	Ireland	Hospital care	70 patients aged 65 years or older	Healthcare professional-level	Educational Administrative	Medication use audit cycle and feedback. After audit results were disseminated together with consensus guidelines on the prescribing of these medications in older adult population to all general practitioners. Two educational sessions, one for doctors and one for nurses, were held for general hospital staff	Geriatrician
Hoebert, Joëlle M. et al.(103)	2008-2009	Retrospective cohort study	Netherlands	Primary Care	13,596 patients aged 18 years and older with incident diagnoses of sleep disturbance and anxiety disorder in 2008 and 2009	Healthcare system-level	Regulatory	Change in the reimbursement status of benzodiazepines, announced mid-2008, that came into force on January 1, 2009. From that date on, benzodiazepines were excluded from the Dutch reimbursement list (full reimbursement, regardless of diagnosis or other restriction) when used as anxiolytic, hypnotic or sedative. Cover remained for a limited number of indications (e.g. epilepsy)	Governmental Authorities
Lang, P.O. et al.(154)	2008	Before-and-after study	Switzerland	Hospital care	150 elderly individuals (aged ≥ 65 years old) admitted for an acute condition and with behavioural and psychological symptoms related to dementia	Healthcare professional-level Healthcare organization-level	Administrative	From admission to discharge, daily collaboration provided by senior geriatrician and psychiatrist working in a usual geriatric interdisciplinary care team.	Psychiatrist Geriatrician
Velert Vila, Josefina et al. (1)(50)	2006-2007	Randomized controlled trial (single blind)	Spain	Primary care	314 patients aged ≥ 65 years old continuously using BZD for the treatment of insomnia and anxiety that frequently visited the 11 pharmacies included in the study	Consumer-level Healthcare professional-level	Administrative Educational	Interviews and pharmaceutical care (with pharmacotherapeutic follow-up). Interdisciplinary collaboration between the pharmacist and the physician.	Pharmacists
Velert Vila, Josefina et al. (2)(112)	2006-2008	Randomized controlled trial (single blind)	Spain	Primary care	337 patients aged ≥ 65 years old to whom BZD for the treatment of insomnia and anxiety were frequently dispensed within the 12 pharmacies included in the study	Consumer-level Healthcare professional-level	Administrative Educational	Interviews and pharmaceutical care (with pharmacotherapeutic follow-up). Interdisciplinary collaboration between the pharmacist and the physician.	Pharmacists
Reeves, Rusty(100)	2008-2009	*Quasi*-Experimental Study	USA	Prison	36 psychiatrists working in prisons	Healthcare professional-level	Administrative Educational	Guideline, education, and physician profiling using peer comparison to achieve lasting changes in prescribing among correctional psychiatrists.	Psychiatrists
Clay, Emilie et al.(105)	2007-2011	Interrupted time series	Finland, Norway, Denmark, Sweden, Greece, France, the Netherlands, Spain and the United Kingdom.	Various	Not applicable	Healthcare system-level	Educational Administrative Regulatory	Anti-BZD government driven campaign and/or launch of Prolonged-release melatonin (an alternative to BZD/Z drugs in the treatment of insomnia). Anti-BZD/Z-Drugs Campaigns could include the issuing or modifications of guidelines in treatment of insomnia and reimbursement changes both for BZD/Z-Drugs and PR-Melatonin	Governmental Authorities

Martin, P. et al.(95)	2012	Quasi-experimental study	Canada	Community	144 community-dwelling men and women aged 65 years and older, consuming at least five prescription medications including a benzodiazepine dispensed for at least three consecutive months.	Consumer-level	Educational	Development of an educational tool for older adults that increases risk perception about benzodiazepines through knowledge acquisition and change in beliefs mailed to previously recruited BZD users	Physicians/Pharmacists
Chen, Y. C.; Kreling, D. H(117)	2005-2006	Quasi-experimental study	USA	Various	250 subjects who changed from private coverage to Part D (reimbursement scheme) and 216 who had continuous private coverage were included in the intervention and comparison groups	Consumer-level Healthcare system-level	Regulatory	Exclusion of benzodiazepine from Medicare Part D, a federal governement program to help beneficiaries pay for prescription drugs	Governmental Authorities
Rat, C. et al. (127)	2011-2012	Quasi-Experimental study	France	Primary care	41,436 and 42,042 patients that initiated benzodiazepine treatment in 2011 and 2012, respectively.	Healthcare professional-level	Regulatory	Enrollement of General Practictioners (GPs) on a new pay-per-performance payment system. GPs were asked to decrease the proportion of patients who continued their benzodiazepine treatment 12 weeks after its initiation and to decrease the proportion of patients older than 65 who were prescribed long half-life benzodiazepines. In return, GPs could expect an extra payment of up to 490 euros per year.	Governmental Authorities General Practitioners
Tannenbaum, Cara et al.(113)	2010-2012	Randomized controlled trial	Canada	Primary care	303 long-term users of benzodiazepine medication aged 65-95 years, recruited from 30 community pharmacies	Consumer-level	Educational	Development of an educational tool with tapering recommendations mailed to previously recruited BZD users	General Practitioners (GP) Pharmacists
Bachhuber, Marcus A. et al. (102)	2004-2011	Interrupted time series	USA	Various	Not applicable	Healthcare professional-level Healthcare system-level	Administrative	State implementation of prescriber-accessible Prescription Monitoring Programs (PMPs) to help providers to identify individuals filling prescription from multiple providers. PMPs promotes benzodiazepine safety, avoiding, among others, Emergency department visits involving benzodiazepines	Governmental Authorities Physician
Gemelli, Maria Grazia; Yockel, Katherine; Hohmeier, Kenneth C.;(119)	2014-Not specified	Quasi-experimental study	USA	Long-term care	64 residents in 11 long-term care facilites aged ≥ 65 years old with diagnosis of insomnia	Healthcare professional-level	Educational Administrative	Medication use audit and feedback. Following medicine review pharmacists documented recommendations on interventions for the prescribers regarding re-evaluation of patients, discontinuation or tapering of medication and prescribing of alternative therapy (melatonin).	Pharmacists
Azermai, M. et al.(96)	2013-2014	Quasi-experimental study	Belgium	Long-term care	393 polymedicated residents	Healthcare professional-level	Educational	Government-funded quality improvement project. Two nursing homes received three educational courses. In the intervention nursing home (INH) additionally, a transition towards person-centred care through professional support was applied.	Psychologist/Nurse
Furbish, Shannon M.L. et al.(109)	2015	Quasi-experimental study	USA	Primary care	29 patients prescribed with a BZD for anxiety disorder or sleep disturbance receiving primary care at a clinic	Healthcare professional-level Healthcare organization-level	Administrative	Implementation of a collaborative team-based benzodiazepine service. Motivational interviewing was implemented according to patients' individual stage of change as assessed by the transtheoretical model of change. The pharmacy team collaboratively managed benzodiazepines and medications under collaborative drug therapy management (CDTM) agreement. The CDTMs included evidence-based treatment algorithms and were developed by a team of pharmacists and physicians.	Pharmacists
Mondiellllo, T. B.; Stutzman, L. A.(106)	2015-2016	Quasi-experimental study	USA	Primary care	Thirteen patients 75 years of age and older	Healthcare professional-level Healthcare organization-level	Administrative Educational	Implementation of an online tool designed to improve psychotropic medication prescribing. Patients were identified and an schedule appointed. Pharmacists conducted medication reviews through review of electronic records 7 to 14 days prior to each patient's appointment to assess dosing and duration of high-risk medications as well as omissions of care, incomplete medications monitoring and a duplicate pharmacotherapy. Recommendations were made to providers by pharmacists in the electronic medical record to optimize prescribing for each individual patient	Pharmacists
Badr, A.F. et al.(123)	2014-2015	Quasi-experimental study	USA	Hospital care	197 adults aged 18 years and older admitted to a communitty hospital and prescribed medication for the treatment of in-hospital insomnia	Healthcare professional-level Healthcare organization-level	Administrative	Daily orders were reviewed by one pharmacy resident and recommendations made to discontinue any unnecessary, newly prescribed sedative/hypnotic orders when appropriate. The pharmacist interventions included recommending discontinuation of the newly prescribed sedative/hypnotics verbally during inpatient team rounds or by contacting the prescribing physicians via the hospital paging system that resulted in further discussions over the phone. A brief reasoning behind the recommendation was provided, emphasizing potential risks of these agents, before recommending discontinuation of the order. All interventions were documented and monitored for change 24 h post-recommendation.	Pharmacists
Mestres Gonzalvo, C. et al.(132)	2016	Quasi-experimental study	Netherlands	Long-term care	161 patients admitted into a nursing home and with chronic use of BZD/Z	Healthcare professional-level Healthcare organization-level	Administrative	A clinical rule was created to generate a report, through a business intelligence application, whenever a patient had been using a BZ/Z for longer than 4 weeks. An advisory for each patient was generated whenever a patient had chronically been using BZ/Z. After assessment these recommendations were digitally sent to the nursing homes physicians whom were requested to indicate whether the advisory was followed or not. Follow-up on BZ/Z use was performed during the period 4 months after the physicians had reacted.	Physicians
Cabelguenne, D. et al.(107)	2000, 2004, 2008, 2012 and 2016	Quasi-experimental study	France	Prison	1249 patients that were adult male prisoners in Lyon's prisons in 2000, 2004, 2008, 2012 and 2016	Healthcare professional-level Healthcare organization-level	Administrative	The institutionalization of a Programme based on teamwork between psychiatrists and pharmacists in prisons with BZD prescriptions being systematically review by pharmacists after prescription and before administration and implementation of coproduced guidelines.	Psychiatrists Pharmacists

Navy, H.J. et al.(99)	2016-2017	Randomized controlled trial	USA	Integrated care	326 patients with 65 years of age and older who resided at home, had a current supply of alprazolam and had four outpatient dispensings of alprazolam during the previous 12 months.	Consumer-level Healthcare organization-level	Educational Administrative	Educational outreach regarding alprazolam use reduction via a mailed letter to patients and consultation and supervised tapering with clinical pharmacist	Pharmacists
Rowntree, R. et al.(101)	2015-Not specified	Quasi-experimental study	Ireland	Hospital care	Physicians working in the psychiatric unit	Healthcare professional-level	Educational Administrative	Medication use audit and feedback. After audit results were mailed and presented to medical practitioners and an educational session provided around best practice guidelines for the prescribing of BZD/Z drugs.	Physicians
Geka, M. et al.(108)	2013-2015	Retrospective cohort study	Japan	Hospital care	273 patients confined in the hospital's psychiatric wards	Healthcare professional-level Healthcare organization-level	Administrative	Multidisciplinary clinical team meetings where pharmacists can effectively share information on the current status of Benzodiazepine receptor agonists (BZRA) use and their prescription recommendations with other clinical team members can lead to reduced BZRA dosages	Pharmacists
Stoker, Lennart Jan et al.(104)	2002-2015	Interrupted time series	Netherlands	Various	2 500 800 benzodiazepine prescriptions from 128 603 patients	Healthcare system-level	Regulatory	Dutch Ministry of Healthcare determined that BZDs were no longer reimbursed when used as anxiolytic, hypnotic or sedative in the Netherlands. The purpose of this policy change was to reduce chronic use and lower healthcare expenses. Coverage remained in case of epilepsy, palliative sedation and multiple psychiatric disorders, under the condition that the physician considered that no alternative treatment was suitable for the patient at hand.	Governmental Authorities
Davidson, S.; Thomson, C.; Prescott, G.;(110)	2014-2017	Quasi-experimental study	UK	Primary care	92 patients with repeat prescription of diazempam identified using the primary care IT system	Consumer-level	Educational Administrative	Patients were sent a specific review appointment letter according to the appointment capacity. This letter advised the patients about the importance of attending the review appointment to allow appropriate diazepam prescribing, to receive support, and to discuss any difficulties with their GP. Tapering regimes were formulated by the pharmacist prescriber or the medication technician based on current best practice. Dose reduction grids for each patient facilitated a down-ward titration of 1 mg each wk/mo depending upon the individual circumstances. The pharmacy team determined the exact quantities and doses of tablets for the patient while liaising with the local dispensaries. All the prescriptions were dispensed weekly, based on current recommendations.	General Practitioners (GP) Pharmacists
Cadogan, C.A.; Bradley, C.P.; Bennet, K.(94)	2016-2019	Cross-sectional study	Ireland	Various	9,474,555 prescription claims for benzodiazepines	Healthcare professional-level Healthcare system-level	Regulatory	New controlled drugs that extended the scope of the Misuse of Drugs Regulations to include zopiclone and zolpidem and introduced new requirements for the prescription of these drugs and some benzodiazepines that included full identification of prescriber, including first name and registration number and the specification of the total quantity to be supplied in both words and figures	Governmental Authorities

Appendix D

Interventions delivery description based on the template for intervention description and replication (TIDieR) checklist and guide.

Autor(s)	Rationale	Intervention Delivery	Location of intervention	Tailoring	Modifications	Planned Intervention adherence or fidelity assessment	Actual intervention adherence or fidelity assessment
Crotty, M. et al.(152)	Evidence from Canada suggests that 40% of residents in aged care facilities are on at least one inappropriate drug with 10% receiving two or more inappropriate medication orders concurrently. Using multidisciplinary case conferences as an intervention to change the use of potentially inappropriate medications has been investigated previously with disappointing results. A study found that only 25% of the case conference recommendations were accepted by the resident's physician. However, the physician was not present at the conference and received the recommendations by mail. Another trial reported that despite the acceptance of many of the recommendations in the management plan, non-significant reductions in medication orders, medication costs and mortality were achieved in the reviewed group.	General Practitioners (GPs) were advised that facility staff had nominated their patient for the study and they were invited to attend two multidisciplinary case conferences conducted 6–12 weeks apart. The times of the case conference were negotiated around the GP needs. The resident's GP, a geriatrician, a pharmacist, residential care staff and a representative of the Alzheimer's Association of South Australia attended the case conferences, which were held at the facility. Residential care staff expanded on any issues in the case notes that case conferences, which were held at the facility. Residential care staff expanded on any issues in the case notes that required discussion and the Alzheimer's Association of South Australia representative discussed non-pharmacological management of dementia-related behaviour. Each case conference was chaired by the GP, who used their medical records in addition to case notes from the facility. A problem list was developed by the GP in conjunction with the care staff and a medication review was conducted prior to each case conference. All facilities in the study, including those in the control group, received a half-day workshop provided by the Alzheimer's Association of South Australia, which examined the use of a toolkit in the management of challenging behaviours.	10 Long Term Care Facilities	NE	NE	NE	NE
Jørgensen, V. R. K(155)	In Ringkjøbing county, Denmark, efforts over the last 6 years have focused on reducin the use of benzodiazepines and cyclopyrrolone drugs in general practice. Information and education seminars have been held. Supervisory groups have been initiated, and counselling on the part of medical practioners has been implemented, as well psychotherapeutic counselling by specialist consultants. The Danish regional medical health officers have intesified their attempts to identify practioners having patients with a large turnover of dependece-producing drugs. The practioners in question have subsequently been asked to explain how they intend to reduce their use of dependence-producing drugs. The total reduction in use of dependence-producing drugs as a result of these joint efforts was 4% between 2003 and 2004. This reduction was more than twice the level of reduction reported for the rest of the country.	The intervention consisted of: (i) the elimination of telephone prescriptions for benzodiazepine and cyclopyrrolone drugs; (ii) the issuing of single prescriptions only, following consultation; (iii) the prescription of medicine sufficient for a single month's use only; and (iv) discussion at consultation regarding future treatment requirements as well as a possible phased reduction of treatments. A guide and poster was developed for the benefit of patients and staff. The staff guide described the intervention, the drugs inclueded, the reasoning, guidelines for initial consultation, rules for the initial prescription and rules for the allocation of compulsory consultations priori to the ordination of prescriptions A number of meetings were held in order to implement the intervention: i. a 2.5-hour meeting, including a 2-hour PowerPoint lecture. The meeting was held to motivate the participantes in the project. The invited delegates were practitioners as well as pharmacists with staff; ii. a 1-hour afternoon meeting with practitioners where it was decided when and how the intervention would be implemented iii. a 2-hour briefing session primarily aimed at the homecare services as well as the other key persons, such as local psychiatrist.	10 General Practices in Lemvig Municipality, Denmark	The intervention was adapted from a previous initiative held in two Danish General Practices in Thyborøn. The implementation of the reported intervention was done with the collaboration of the Ringkjøbing Public Health Department. The intervention was carried with full support and cooperation of the involved practitioners, and was headed by the author in his capacity as Medical Advisor to the Medicine Team, Region Midtjylland. During intervention, a number of meetings were held in order to implement the intervention. The professionals involvement and degree of participation was arranged accordingly with their expected participation in the intervention.	NE	NE	NE
Dolan, C. et al.(118)	Audit of all aspects of medication use is a recognised means of monitoring and improving the quality and safe use of medication. Behaviour is unlikely to be altered via audit by itself, but information provided by audit will help guide educational strategies to correct identified deficiencies in prescribing practice.	Two-day period for initial audit followed by the intervention, that consisted of sending feedback letters of the audit results together with consensus guidelines on benzodiazepine and Z-drug prescribing to all general practitioners in County Sligo. Moreover, two educational sessions, one for doctors and one for nurses, were held. A re-audit was conducted after 6 months period.	Sligo General Hospital (SGH), Ireland	Two different educational sessios were held, one for doctors and one for nurses. No information on topics or organization of these sessions.	NE	NE	NE

Salonoja, M. et al.(111)	Discontinuation of the long-term usage of BZD has been done by advising participants to quit these drugs on their own (minimal intervention), by single tapering off programmes, by augmentation with cognitive-behavioural therapy or with support of different medications. In a recent meta-analysis, evidence was found for the efficacy of minimal interventions followed by a systematic discontinuation. However, there is a clear need for simple and efficient methods for withdrawal of the long-term use of BZD.	At baseline and after the 12-month intervention, the geriatrician collected the data about drugs by interviewing the participants and from the medical records. All participants were asked to take the prescriptions and pillboxes of regularly or irregularly used drugs to the interviews. Drugs were coded using a modified Anatomical Therapeutic Chemical (ATC) The cause of the use of every drug was asked by interviewing and by taking into account the diagnosed diseases. Based on this information, the geriatrician assessed the appropriateness of each drug of every participant in the intervention group and proposed necessary changes. To reduce the use of psychotropics and other fall-risk-increasing drugs (FRID) in the intervention group, plans were provided to the users of these drugs to facilitate stepwise reduction over some future months. The needs and practical instructions relating to the changes were discussed with the participants. However, a new drug was prescribed if the interviews and clinical examinations showed a new or inappropriately treated disease. The participants in the intervention group paid only one visit to the geriatrician, where they received these oral instructions supported with written ones. The changes were entered in the medical records of each participant, where the general practitioners could read the proposals made. The fall prevention consisted also of counselling about risk factors and prevention of falls, physical exercises in groups and at home (aimed to improve muscle strength and balance), psychosocial groups for all and separately for depressive participants and home hazard assessment and modification. The control programme consisted of one counselling session about prevention of falls.	Satakunta Hospital District, Finland	NE	NE	NE	NE
Hoebert, Joëlle M. et al.(103)	The rationale for this restriction was to reduce the use of these medicines to a few specific patient subpopulations, to avoid irregular (chronic) use of benzodiazepines, and to limit the health care costs. Although costs per prescription are €12 to €16, macro-level costs were high because of the volume of benzodiazepine use. Several studies have shown the importance of studying the effects of restrictions on reimbursement for pharmaceuticals. Policy measures may not always be successful if patients shift to other (costly) treatments or measures do not necessarily lead to clinical benefits, as shown by previous studies.	In the Netherlands the coverage of pharmaceutical care is regulated by the Health Insurance Act. The Ministry of Health, Welfare and Sport and the Healthcare Insti- tute of the Netherlands decide which drugs fall under the mandatory health insurance package. Registered medicines have to be assessed before they can be included in the Medicines Reimbursement System (GVS). Medicines listed in the GVS are fully or partially reimbursed by health insurers. Once a year the Ministry of Health, Welfare and Sport evaluates and actualises the list in order to keep healthcare affordable. In January 2009, Dutch Ministry of Healthcare determined that BZDs were no longer reimbursed when used as anxiolytic, hypnotic or sedative in the Netherlands. The purpose of this policy change was to reduce chronic use and lower healthcare expenses. Coverage remained in case of epilepsy, palliative sedation and multiple psychiatric disorders, under the condition that the physician considered that no alternative treatment was suitable for the patient at hand.	Netherlands	NE	NE	NE	The Dutch Foundation for Pharmaceutical Statistics showed a 16% reduction in overall use of benzodiazepines and 14.5% fewer chronic users in 2009 compared with previous years.
Reeves, Rusty(100)	The author hypothesized that when, in the context of the issuing of a guideline for the evaluation and treatment of insomnia, psychiatrists were educated about the shortcomings of benzodiazepines and quetiapine and allowed these psychiatrists to compare their prescribing practices with those of their peers, the psychiatrists would decrease their prescriptions of benzodiazepines and low-dose quetiapine.	Before the study began, the NJDOC issued a guideline for the evaluation and treatment of insomnia. This guideline encouraged the nonpharmacological treatment of insomnia. Psychiatrists were instructed to refer inmates with simple insomnia, with or without mild anxiety or depression related to adjustment to prison, to sleep hygiene groups and brief psychotherapy, rather than to start medication. An institutional guideline for the evaluation and treatment of insominia was issued, encouraging nonpharmacological treatment. The number of Patients on a Benzodiazepine per FTE Psychiatrist was assessed and the professionals were ranked accordingly to the frequency of prescribed. The results were coded and individually emailed. The psychiatrists were given the reasons why the prescription of a benzodiazepine for treatment of anxiety or insomnia in the prison is not the preferred choice, accordingly to the guideline issued. The psychiatrists were asked to minimize this use and to refer inmates to non-pharmacological treatments. Psychiatrists were informed that outliers remaining at the second assessment would be individually counselled. New assessments were conducted 7 and 20 months after the initial one and compared the prescribing practices of each psychiatrist. Those were not informed about the third assessment (20 months)	13 Prisons of the New Jersey Department of Corrections (NJDOC)	Individual counselling to outliers remaining in the second assessment was planned. No further information is given about this.	NE	NE	NE

Velert Vila, Josefina et al. (1) (50)	According to the Spanish Medicines Agency (AGEMED), BZDs should not be used for more than one month for insomnia or more than 3 months for anxiety, including the time of gradual drug withdrawal. The intervention of the pharmacist in a multidisciplinary way with the doctor has been shown to improve the adequacy of treatments, health education, compliance, inadequate prescription, detection of ADRs and pharmacological interactions, patient satisfaction, decrease in morbidity and mortality and the overall cost of care.	Pharmacists intervened whenever medication-related problems (MRP) or negative results of the medication (NRM) of necessity, efficacy or safety appeared, giving the patient information on the correct use of BZD referring to the physician referring if it was intended to eliminate the medication from the therapeutical care, decrease dose or switch to lorazepam when there was any problem of interaction with other medications used or when adverse drug reactions appeared (adverse drug reactions were screened by reference of the patient through a questionnaire that contains the most frequent ADRs attributed to BZDs). In case that the patient refused to go to the physician but wished to stop using the BZD, the pharmacist recommended the tapering of to avoid rebound effect. In summary, the intervention(s) carried out were: a) pharmacist-physician-patient through a written document addressed to the physician in those cases in which the BZD used by the patient was intermediate-acting (other than lorazepam) or long-acting, and when, even with intermediate-short action, the usage time was longer than that indicated by the Spanish Medicines Agency to try to reduce dose and if possible eliminate the drug, b) pharmacist-patient intervention in those situations in which the patient refused to the intervention with the physician, for fear that he would withdraw the BZD prescription The intervention group was followed up every 3 months until completing a year. During the second year no new patients were included, only the follow-up. Patients in the control group only underwent the initial and final interview, after one year.	11 pharmacies in the Community of Valencia	Pharmacists' recommendations (intervention) whenever medication-related problems (MRP) or negative results of the medication(NRM) of necessity, effecacy or safety appeared after individual assessement. Information provided to patients and physician are assumed to be specific and personalised.	NE	NE	NE
Velert Vila, Josefina et al. (2)(112)	According to the Spanish Medicines Agency (AGEMED), BZDs should not be used for more than one month for insomnia or more than 3 months for anxiety, including the time of gradual drug withdrawal. The intervention of the pharmacist in a multidisciplinary way with the doctor has been shown to improve the adequacy of treatments, health education, compliance, inadequate prescription, detection of ADRs and pharmacological interactions, patient satisfaction, decrease in morbidity and mortality and the overall cost of care.	Pharmacists intervened whenever medication-related problems (MRP) or negative results of the medication (NRM) of necessity, efficacy or safety appeared, giving the patient information on the correct use of BZD referring to the physician referring if it was intended to eliminate the medication from the therapeutical care, decrease dose or switch to lorazepam when there was any problem of interaction with other medications used or when adverse drug reactions appeared (adverse drug reactions were screened by reference of the patient through a questionnaire that contains the most frequent ADRs attributed to BZDs). In case that the patient refused to go to the physician but wished to stop using the BZD, the pharmacist recommended the tapering of to avoid rebound effect. In summary, the intervention(s) carried out were: a) pharmacist-physician-patient through a written document addressed to the physician in those cases in which the BZD used by the patient was intermediate-acting (other than lorazepam) or long-acting, and when, even with intermediate-short action, the usage time was longer than that indicated by the Spanish Medicines Agency to try to reduce dose and if possible eliminate the drug, b) pharmacist-patient intervention in those situations in which the patient refused to the intervention with the physician, for fear that he would withdraw the BZD prescription The intervention group was followed up every 3 months until completing a year. During the second year no new patients were included, only the follow-up. Patients in the control group only underwent the initial and final interview, after one year.	12 pharmacies in the Community of Valencia	Pharmacists' recommendations (intervention) whenever medication-related problems (MRP) or negative results of the medication(NRM) of necessity, effecacy or safety appeared after individual assessement. Information provided to patients and physician are assumed to be specific and personalised.	NE	NE	NE
Lang, P.O. et al.(154)	The authors hypothesized that the integration of a senior psychiatrist and 2 clinical nurses specialized in mental health into the usual geriatric care team would provide more specialized and more comprehensive care to patients, thus leading to a better continuum of care. It was postulated that effective and daily collaboration between senior geriatricians and psychiatrists should enable the prescribing physician to appraise older patients in the context of their concurrent diagnoses. This could also favor pharmacological management of both somatic or mental comorbid conditions.	This interdisciplinary team designed, implemented, and monitored comprehensive care and discharge plans for patients with mental comorbidities across a care continuum. This approach included a therapeutic plan with the aims of (1) limiting harmful effects from drug-drug or drug-disease interactions; (2) ensuring the prescription of medications at the right doses and for the correct durations; (3) systematically balancing the clinical benefit and the risk of ADE associated with any prescription with the patient's needs, quality of life, and expectations; and (4) reducing the rate of omission of indicated medications with proven efficacy according to the patient's level of functionality and life expectancy. This intervention is based on good communication and reciprocal interaction between the psychiatrist and the geriatrician in the clinical decision making to prescribing medications. Only the geriatrician was prescribing/writing orders for medications. The 2 senior physicians were present on the unit daily, participated in daily medical rounds and once-weekly interdisciplinary meetings, and had direct contact with both patients and caregivers.	Geriatric Hospital (HOGER) of the academic department of internal medicine, rehabilitation and geriatrics (DMIRG) of the Geneva university hospitals, Switzerland	Cases were discussed among the interdisciplinary team. A personalized plan of care was designed, implemented and monitored.	NE	NE	NE

Clay, Emilie et al.(105)	It has also been demonstrated that in some countries such as France, BZD and Z-drugs are overused and prescribed for a much longer time than the indicated 4 weeks. As a result, more and more health authorities in Europe are initiating policies and recommendations to decrease the consumption of BZD and Z-drugs. However, the anti-BZD and Z-drug campaigns initiated in most countries have been unsuccessful, and despite the guidelines and national recommendations, the use of BZD and especially Z-drugs has continued to increase. Several clinical trials demonstrated that PR- melatonin could help reduce BZD and Z-drugs consumption. As PR-melatonin was launched in many European markets in 2008, it was interesting to evaluate how campaigns to decrease BZD and Z-drugs prescriptions affected consumption of these drugs in real life, with or without market uptake of PR-melatonin.	The authors analyzed and evalatued the impact of anti-BZD campaigns and the availability of alternative pharmacotherapy (PR-melatonin) on the consumption of BZD and Z-drugs in several European countries. The evolution of BZD/Z-drug sales volumes (together and separately) 3 years prior to the launch of PR-melatonin (at the end of 2007) and then 4 years after the launch of PR-melatonin (2011), as well as the evolution of PR-melatonin sales volumes were studied. Additional parameters considered in the interpretation of the data were: the launch strategy of PR-melatonin (actively promoted/not promoted), product positioning and key messages, national or regional anti-BZD/Z-drugs campaigns (the type of campaign, their target and the recommendations), the penetration rate of PR-melatonin in 2011 and its reimbursement status compared to BZD/Z-drugs. Anti-BZD/Z-Drugs Campaigns could include the issuing or modifications of guidelines in treatment of insomnia and reimbursement chagens both for BZD/Z-Drugs and PR-Melatonin.	Finland, Norway, Denmark, Sweden, Greece, France, the Netherlands, Spain and the United Kingdom.	Anti-BZD/Z-Drugs Campaigns could include the issuing or modifications of guidelines in treatment of insomnia and reimbursement chagens both for BZD/Z-Drugs and PR-Melatonin	NE	NE	NE
Martin, P. et al.(95)	Social cognitive theory, which consists of health promotion through social cognitive means, guided the development of the intervention. The specific learning model that was applied was constructivist learning. Constructivist learning theory aims to promote active learning through creation of knowledge that seeks to make sense out of the material presented. The goal of this approach is to create an environment where the learner can interact with academic material, fostering their own selecting, organizing and information integrating processes. Such theories have already proven successful in other health promotion interventions such as in educational materials for smoking cessation.	An educational intervention for reducing benzodiazepine use was developed to create cognitive dissonance, a critical component of constructivist learning theory. A self-assessment component was also introduced. Textual content of the intervention was based on a systematic review of the evidence as well as guidelines concerning the use of benzodiazepines in the elderly. A geriatrician and graduate student drafted the initial content of the tool, which was then validated by a panel of colleagues with expertise in geriatric pharmacy and reviewed by a health librarian to ensure that the wording met standards for patient literacy at the Grade 6 level. The tool was developed in English, and backward and forward translated into French. The tool was field-tested in six focus groups. The final educational intervention consisted of a seven-page letter-size paper brochure written in 14-point font. The cover page of the brochure states ‘‘You May Be At Risk’’ with a picture of a pillbox with several medications in it, followed by ‘‘You are currently taking (name of the patient’s benzodiazepine)’’. The first page of the intervention is entitled ‘‘Test Your Knowledge’’ and consists of four true or false questions on the use of the benzodiazepines. The second page lists the correct answers. Elements of constructivist learning theory are incorporated into the answers to create cognitive dissonance and challenge the patient’s beliefs for each incorrect answer. The third page incorporates self-assessment and education about potential inappropriate use, side effects, drug-drug interactions and information about physiologic changes that occur with age that affect drug metabolism. The fourth and fifth pages present evidence-based risks associated with benzodiazepine use in the elderly and suggestions for equally or more effective therapeutic substitutes. The sixth page describes a case scenario highlighting one woman’s success at weaning herself off benzodiazepines. The last page outlines a simple 21-week tapering program. The reader is encouraged on four occasions and is warned in large, red lettering to ‘‘Please Consult your Doctor or Pharmacist Before Stopping Any Medication.’’ The educational tool was mailed to BZD users previsously recruted from community pharmacies	Montreal, Canada	NE	NE	The tool was field-tested with a convenience sample of older adults to determine the readability and comprehension of the information. Six focus-groups (n = 60 adults) were conducted.	NE
Chen, Y. C.; Kreling, D. H(117)	With ongoing concerns and debate about benzodiazepine use, particularly among elders, when the prescription drug benefit was added to Medicare, benzodiazepines were removed altogether from coverage. Although potentially merely a blunt instrument to affect change, the exclusion policy introduced a financial disincentive for benzodiazepine use among elders.	Exclusion of benzodiazepine from U.S. Medicare Part D drug coverage, a federal governement program to help beneficiaries pay for prescription drugs.	USA	NE	NE	NE	NE
Rat, C. et al. (127)	In 2011, French policy makers speculated that a pay-for-performance intervention might motivate GPs to improve their practices. As part of a national agreement with the French National Ministry of Health and the federations of French GPs, four different priorities were defined: medical surgery organization, quality of chronic disease management, prevention practices, and medical and economic efficiency.	The pay-for-performance intervention that was evaluated in this study was implemented as a nationwide strategy in a country in which these drugs are extensively prescribed. As part of the pay-for-performance intervention, General Practitioners were asked to decrease the proportion of patients who continued their benzodiazepine treatment 12 weeks after its initiation to 12% and to decrease the proportion of patients older than 65 who were prescribed long half-life benzodiazepines to 5%. Benzodiazepine prescribing practices were assessed based on these two indicators with a related specific extra-payment amount of 490 euros. The global extra-payment amount for each GP was estimated at 5000 euros, based on a grading scale assessing 29 indicators.	Pays de la Loire geographic area (French West Coast)	NE	NE	NE	NE

Tannenbaum, Cara et al.(113)	Direct-to-consumer advertising of prescription drugs by the pharmaceutical industry has clearly been shown to influence patient demand for medicines. Educational interventions aimed at achieving patient empowerment around medication overtreatment has potential to catalyze shared decision making to deprescribe. Patient empowerment is a process that aims to “help people gain control, which includes people taking the initiative, solving problems, and making decisions, and can be applied to different settings in health and social care and self-management.”	The patient empowerment intervention consisted of an 8-page booklet based on social constructivist learning and self- efficacy theory, and its development and testing have been previously detailed. The intervention comprises a self-assessment component about the risks of benzodiazepine use, presentation of the evidence for benzodiazepine-induced harms, knowledge statements designed to create cognitive dissonance about the safety of benzodiazepine use, education about drug interactions, peer champion stories intended to augment self-efficacy, suggestions for equally or more effective therapeutic substitutes for insomnia and/or anxiety, and stepwise tapering recommendations. Tapering recommendations consist of a visual 21-week tapering protocol showing a picture-based diminishing schedule of full-pill, half-pill, and quarter-pill consumption. The visual schematic for the deprescribing protocol was proposed by consumers during the development and usability testing of the intervention to enable application to any benzodiazepine, regardless of dose. The intervention asks participants to discuss the deprescribing recommendations with their physician and/or pharmacist. The information is included in a letter-size paper handbook, with the language set at a sixth grade reading level and written in 14-point font to facilitate accessibility to the material. The intervention was mailed to the intervention group within 1 week of group allocation while the usual care (wait list) group received the educational tool 6 months following group allocation.	30 community pharmacies (cluster units) at Montreal, Canda	The intervention was personalized according to the participant’s pharmacy profile to include the name of the specific benzodiazepine the participants was taking.	NE	NE	NE
Rowntree, R. et al.(101)	Best practice guidelines advise short-term use (<4 weeks), using the lowest dose possible and only after alternate therapies have been tried. Regular audit of benzodiazepine prescribing has been shown to improve prescribing practices.	Over a 1-week period, 50 inpatient prescriptions in the three wards (acute, sub-acute and psychiatry for the elderly) of the psychiatric unit of a city center hospital were reviewed by the researchers. If benzodiazepines or z-hypnotics were prescribed, it was noted whether they were regular or ‘as required’, initiated before or during admission and any withdrawal attempts made. The benzodiazepine or z-hypnotic type was also recorded. Benzodiazepine doses were converted to diazepam-equivalents. In respect of ‘as required’ medications indication, maximum dose and review/cessation date were noted. It was documented how often ‘as required’ medications had been administered in the week before. The results of the first part of the audit cycle were presented at a local audit meeting attended by both consultant and non-consultant hospital doctors working in the psychiatric unit. At this, education was provided around best practice guidelines for the prescribing of benzodiazepine and z-hypnotic medications and areas of need from the audit data were highlighted. This feedback was also emailed to all medical practitioners, including those newly employed during the interim period.	Three wards of an inpatient psychiatric unit	NE	NE	NE	NE
Gemelli, Maria Grazia; Yockel, Katherine; Hohmeier, Kenneth C.;(119)	In a recent review the results of a pharmacist’s impact on sedative/hypnotic use have been mixed, and there has subsequently been a call for future studies establishing pharmacists’ clinical utility in the appropriate use of sedative/hypnotics.	Pharmacists’ interventions making a recommendation to the prescriber were conducted at each of the 11 long-term care facilities. Residents’ insomnia diagnoses and medications were verified through manual chart reviews, and interventions were documented and subsequently placed in the residents’ charts to ensure physician retrieval. Interventions specifically stated how long patients were receiving the targeted medication, typical durations of therapy, and adverse effects associated with long-term therapy. Within the interventions, recommendations were made to consider psychiatric re-evaluation for patients, discontinue/taper the medication if appropriate, and consider alternate therapy (melatonin), if desired. For convenience, timing of interventions was chosen to coincide with Centers for Medicare & Medicaid Services required monthly scheduled	11 regional long-term care facilities located within northeastern Tennessee, USA	NE	NE	NE	NE
Bachhuber, Marcus A. et al. (102)	Prescription Monitoring Programs (PMPs) aim to improve prescription safety by helping providers to identify individuals filling prescriptions from multiple providers or pharmacies (i.e., “doctor shopping” or “pharmacy shopping”), which has previously been documented among some people taking benzodiazepines. The impact of prescriber-accessible PMPs on benzodiazepine safety, specifically ED visits involving benzodiazepine misuse, is unknown.	State implementation of prescriber-accessible Prescription Monitoring Programs. In the United States, prescription monitoring programs (PMPs) are state-level registries of prescriptions for controlled substances. These programs aim to improve prescription safety by helping providers to identify individuals filling prescriptions from multiple providers or pharmacies (i.e., “doctor shopping” or “pharmacy shopping”), which has previously been documented among some people taking benzodiazepines.	11 metropolitan areas in the United States	NE	NE	NE	NE

Furbish, Shannon M.L. et al.(109)	As the medication experts, clinical pharmacists are well positioned to collaborate with an interdisciplinary team of PCPs to optimize appropriate benzodiazepine use, improve patient safety, and improve anxiety symptom control. Although studies have clearly described the benefits of pharmacists collaborating to improve suboptimal medication use and outcomes in many settings none have assessed the impact of pharmacists integrated in primary care working to improve high-risk benzodiazepine use.	Implementation of a benzodiazepine service. Screening tools were applied to assess symptoms. Motivational interviewing was implemented according to patients' individual stage of change as assessed by the transtheoretical model of change. The pharmacy team collaboratively managed benzodiazepines and medications under collaborative drug therapy management (CDTM) agreement. The CDTMs included evidence-based treatment algorithms and were developed by a team of pharmacists and physicians. Given the clinic is housed within the hospital, the CDTM was also approved by the hospital's pharmacy and therapeutics committee, as well as the clinic's medical director. Medication changes were made by the clinical pharmacist and were limited to those indicated in the CDTM. For needed changes that did not fall within the purview of the CDTM, the pharmacy team made recommendations and obtained approval from a PCP prior to making any changes. Efforts were made to discuss recommendations with the responsible PCP, but in situations where this was not possible, a partner PCP was consulted. Per the CDTM, all patients received education on nonpharmacological therapies (eg, avoiding stimulants and triggers, meditation, sleep hygiene, exercise) and were offered referrals to mental health specialists. Access to specialist care was dependent on patient payer source and availability. Per CDTM, the clinical pharmacist ordered pertinent laboratories as necessary to monitor for safe medication use and to screen for secondary causes of anxiety or sleep disturbance (eg, thyroid function, serum creatinine, liver function tests, electrolytes).	Anschutz Internal Medicine Clinic at the University of Colorado Hospital	Pharmacist recommendantions were based on a complete medication review. Interventions can be considered personalized.	NE	NE	NE
Mondiellllo, T. B.; Stutzman, L. A.(106)	Suboptimal prescribing in geriatric patients can lead to drug-related problems (DRPs), which has been identified as a significant quality-of-care problem in the elderly. Pharmacists carry the unique training of medication expertise. Consultation with pharmacists has been shown to have a positive impact on medication use in the geriatric patient population. Previous studies demonstrated that clinical pharmacy interventions have reduced the occurrence of DRPs in the elderly.	Patients were identified using na online dashboard that included a "real-time" tool designed to improve psychotropic medication prescribing. And had a cheduled appointment with a primary care provider. An initial complete medication review (CMR) was conducted by a pharmacist through review of the patients eletronic medical records 7 to 14 days prior to each patient's appointment to assess dosing an duration of high-risk medications as well as omissions of care, incomplete medication monitoring, and a duplicate pharmacotherapy. Recommendations were made to providers by the pharmacistis to optimize prescribing for each individual patient. These recommendations were entered as a progress note in the patient's eletronic medical record and included recommendations for safely tapering high-risk medications as well as alternative pharmacologic and nonpharmacologic interventions. In addition to the progress note, pharmacists communicated with the providers via face-to-face interactions, in encrypted eletronic mail messages, or both. Pharmacists conducted a subsequent follow-up CMR at the end of the study period to assess if recommendations were accepted and determine the change in outcomes.	Coatesville Veterans Affaris Medical Center in Coatesville, Pennsylvania, USA	Pharmacist recommendantions were based on a complete medication review. Interventions can be consdiered personalized.	NE	NE	NE
Azermai, M. et al.(96)	A reduction in the use of psychotropic drugs has been found to be more feasible in nursing homes with a ‘person-centered culture’. In a person-centered culture the needs centered of patients are heard and the care for patients is tailored to their needs. Patient tailored care sees patients as individuals, and considers person’s desires, values, lifestyle, family and social situation. This finding reinforces the need for multifaceted interventions and multidisciplinary collaborative care. In Belgium, general practitioners (GPs) still supervise their patients who have moved from their own home environment to a nursing home, resulting in an average of consulting GPs per nursing home. Efforts are needed to reduce this variability in management strategies of behavioural problems which often lead to prescribing of psychotropics in nursing homes	Before receiving the educational courses, only the intervention nursing home received an ‘awareness-campaign’ to inform the nursing home staff, the residents and their relatives to increase awareness regarding the project. Therefore, a period of 3 months (October 2013– December 2013) before the actual start of the project (January 2014–October 2014) was considered to increase awareness of nurses or allied health personnel and to reduce resistance of residents and their relatives. This was realized through flyers, posters and the nursing home’s own newspaper. This ‘awareness-campaign’ was not implemented in the control nursing home which simulated ‘every day’s reality’. Three educational courses were organized separately for GPs and for nurses/nurse assistants. Each session dealt with a particular topic related to one of the psychotropic drug classes: depression and the use of antidepressants; sleeping/anxiety problems and the use of hypno-sedatives; behavioural and psychological symptoms of dementia (BPSD) and the use antipsychotics. The courses were given by experts in the field (GP, psychologist, old age psychiatrist, geriatrician and pharmacist, the last two with the background in clinical pharmacology) and lasted approximately two hours each. The content of the courses was focused on evidence-based practice, reduction of psychotropic drug use and non-pharmacological alternatives. In contrast to the control nursing home (CNH), the intervention nursing home (INH) offered person-centered professional support in addition to the educational courses, during the project (10 months). The budget allowed two part-time project staff-members (a psychologist and a nurse) to be involved in the project. Their main tasks included field work in the nursing home, reducing resistance from the floor and to promoting the ‘change in psychotropic use and prescribing culture’. This was realized by stimulating multidisciplinary collaboration, more communication with the treating GP, by recording the medication (psychotropic drug) use and finally by offering person-centered care. The person-centered care was offered by reaching to the nursing staff (often also on their request) and by searching together for and offering tailored and plausible alternatives for a particular resident.	Two Nursing homes in East Flanders, Belgium	NE	NE	NE	NE

Cabelguenne, D. et al. (107)	BZD consumption is particularly frequent in prison, where approximately 20% of male prisoners are treated by BZDs. Limiting BZD consumption is necessary to avoid psychological and physical dependence, particularly in prison. A pharmacotherapy programme was therefore initiated by pharmacists in 2001 in the prisons of Lyon, France. In a first retrospective study, the positive impact of this collaboration was demonstrated: prescribed doses of BZD significantly decreased. But one limitation of this study was the lack of data about the durability of this effect.	Teamwork between psychiatrists and pharmacists in the prisons of Lyon (population of 850 male and female adult inmates) was initiated in April 2001. BZD prescriptions were systematically reviewed by pharmacists after prescription and before administration. When necessary, a pharmaceutical opinion was notified to the psychiatrists in order to revise the prescription depending on the clinical picture of the patient. In the meantime, monthly meetings were initiated between pharmacists and physicians to develop common guidelines. The aim of this programme was to reduce prescribed doses and to limit the number of patients taking BZD. Prescription guidelines and a table of maximum daily doses for BZD were drawn up. Initially, the maximum daily dose was 40 mg of diazepam dose equivalent (DE). After 2008, this dose was updated and increased to 60 mg DE, according to the BZD conversion table adapted from literature. Psychiatrists were allowed to exceed these maximum daily doses when they considered the patient atypical (medical history of drug abuse, risk of withdrawal syndrome, violence and nervousness), but were required to inform the pharmacist.	All Lyon's prisons, France	NE	NE	NE	NE
Navy, H.J. et al.(99)	Reduction of benzodiazepine use poses considerable challenges to health care providers as patients may not agree with reduction of treatment, experience withdrawal symptoms, or fear that their symptoms will return. Trials that sent an informational letter, a low-cost strategy that can allow for mass targeting, to educate patients on the inappropriateness of benzodiazepine use were found to be effective in engaging patients to discuss medication-use reduction recommendations with their physician and/or community pharmacist and, ultimately, resulting in benzodiazepine discontinuation.	An intervention letter was developed with input from the institution geriatric clinical pharmacist and the medical director of geriatrics and Medicare. The letter was addressed to the patient and outlined: 1) the reason for it being sent (i.e., the patient was prescribed alprazolam), 2) that there are risks to taking alprazolam, 3) organizations that recommend against taking alprazolam, 4) alprazolam's side effects, 5) possible alternate treatments, 6) a request to call the study clinical pharmacist to discuss treatment options, 7) not to stop taking alprazolam without speaking to the study clinical pharmacist, and 8) the telephone number and times to call the study clinical pharmacist. After the letter was drafted, reading level analysis was performed by the institution corporate communications department, and the letter was edited subsequently to a fifth grade reading level. If a patient called the study clinical pharmacist, usual care was provided. During the usual care discussion, the study clinical pharmacist assessed the patient's decisional capacity to understand and follow instructions. If the patient could not comprehend the information provided or make a reasoned choice regarding alprazolam dose reduction or discontinuation, the study clinical pharmacist did not proceed with study information or recruitment unless a legally authorized representative (LAR) was identified and brought to the telephone. Following the usual care conversation, the study details, consent process, and request to participate in the study was offered to the patient/LAR. For patients who agreed to participate, alternate treatment options were discussed on a case-by-case basis. If the patient was agreeable, the study clinical pharmacist collaborated with the patient's primary care provider (PCP) to develop an individualized alprazolam taper plan. The study clinical pharmacist would then monitor the patient for withdrawal symptoms by telephone follow-up throughout the duration of the taper. For patients who did not agree to study participation, usual care was provided; however, clinical outcome assessment was not performed per IRB requireme	Kaiser Permanente Colorado (KPCO) integrated healthcare, USA	NE	NE	NE	NE
Badr, A.F. et al.(123)	Hospitalization is a major cause of sleeping pattern disturbance, which can contribute to insomnia in many patients. Insomnia is usually treated symptomatically during hospitalization. There are currently no standard guidelines for managing acute in-hospital insomnia, which could lead to overt misuse or over-use of the sedative/hypnotic agents in this setting. There is evidence that when pharmacists monitor therapy, there is improved prescribing and administration of sedative/hypnotics in multiple settings.	Data on sedative/hypnotic use was collected retrospectively for a 2-month period and a sample of 100 patients was randomly selected for analysis. A 2-month prospective phase followed, during which a hospital-wide daily orders report on sedative/hypnotic agents was generated and monitored. The report captured the list of the medications that were identified in the retrospective phase of the study when ordered as needed for sleep (prn insomnia). The pharmacist interventions were made and documented by a pharmacy practice resident training at the hospital. The intervention was performed during the days the pharmacy resident was physically at the hospital, and thus excluded weekends. The pharmacist interventions included recommending discontinuation of the newly prescribed sedative/hypnotics verbally during inpatient team rounds or by contacting the prescribing physicians via the hospital paging system that resulted in further discussions over the phone. A brief reasoning behind the recommendation was provided, emphasizing potential risks of these agents, before recommending discontinuation of the order. All interventions were documented and monitored for change 24 h post-recommendation.	A community hospital in Boston, Massachusetts, USA	NE	NE	NE	NE

Mestres Gonzalvo, C. et al.(132)	European studies show a prevalence of chronic BZ/Z use in the nursing home population of between 28 and 50%. Furthermore, based on different criteria, such as the Beers or the STOPP/START criteria (screening tool of older people's prescriptions (STOPP) and screening tools to alert to the right treatment (START)), benzodiazepines have been identified as inappropriate medications; they should be avoided in patients 65 years and older, independent of diagnosis or condition. A clinical rule was created to generate an alert whenever a patient used a BZ/Z for longer than 4 weeks, as described in STOPP criteria. A clinical rule is a real-time decision support module that focuses on medication safety and medication optimization.	A clinical rule was created to generate a report whenever a patient had been using a BZ/Z for longer than 4 weeks. An extraction of the medication information (drug, dosage, start date and Stop date) was obtained using a business intelligence application. The clinical rule screened the extraction and generated a report creating an alert for patients who had used a BZ/Z for longer than 4 weeks. For these patients, the indication of BZ/Z was established afterwards by considering the information on the medication record and/or the time the medication was given, the assuming that a single night dose was indicated to treat insomnia. Establishing the indication was performed manually by medication record review by two of the authors. An advisory for each patient was generated whenever a patient had chronically been using BZ/Z. After the indication was assessed, these advisories were digitally sent to the respective nursing home (NH) physician (n = 12) as a list. The advisory consisted in a recommendation for phasing out BZ/Z use and eventually stopping it. After the BZ/Z has been completely stopped, a minimum of 2 weeks resting period should be granted before evaluating whether there was still an indication for BZ/Z usage. The nursing home physicians were requested to indicate whether the advisory to phase out BZ/Z and eventually stop it was followed or not. When the advisory was not adhered to, they were asked to specify the reason by indicating one of the following options: – Patient/family resistance – It has already been tried before without success – It is not necessary: BZ/Z use is only as needed – Indication is still present The NH physicians returned the digital list along with a reply to the question of whether they had followed the given advisory. Follow-up on BZ/Z use was performed during the period 4 months after the NH physicians had reacted in order to evaluate whether, in cases of following the advisory, BZ/Z had been successfully stopped.	15 Zuyderland nursing homes, Netherlands	Advisories for each patient were generated.	NE	NE	NE
Geka, M. et al.(108)	Pharmacists at the psychiatric wards of the Tokyo Women's Medical University Hospital have been assessing BZRA use based on specific clinical criteria and have been offering prescription recommendations to attending psychiatrists. By recording their assessments, recommendations, and instructions for patients in medical charts, the pharmacists aimed to collectively share the information with multidisciplinary clincal teams. However, because of the highly specialized nature of the written information, everyone on the team could not easily acquire a shared understanding of the information. Further, there are no clearly established standards for continuing or discontinuing BZRA administration. Therefore, various members of a team tended to offer different recommendations to psychiatrists, which made it difficult for the psychiatrists to define policies for BZRA administration. Since the appropriate BZRA use was obstructed by their action, the pharmacists realized the need for a more effective information-sharing strategy to raise awareness, reinforce the goal of reducing BZRA dosages, and promote the appropriate use of these drugs. With this objective in mind, the pharmacists decided to convene multidisciplinary clinical team meetings where various members of medical staff could exchange views.	At multidisciplinary clinical team (psychiatrists, pharmacists, nurses, therapists and psychologists) meetings the pharmacists screened out patients, who, based on predefined clinical criteria, presented their prescription recommendations aimed at dosage reduction, and made time for explaining how to assess BZRAs. Thus, the pharmacists continued to provide the team opportunities for considering appropriate BZRA use. If patients taking the same BZRA dosage were present before the next conference, the pharmacists announced it again. This intervention was commenced on Floor A in 2014 and on Floor B in 2015.	Psychiatric unit of the Tokyo Women's Medical University Hospital	Each case was assessed by the pharmacists and discussed at the multidisciplinary clinical team.	NE	NE	NE
Davidson, S.; Thomson, C.; Prescott, G.;(110)	NICE (The National Institute for Health and Care Excellence) recommends the use of benzodiazepines as a short-term measure during crisis in generalized anxiety disorder (GAD), and not routinely for longer than a month. Repeat prescriptions should be avoided in patients with major personality disorders or a history of substance misuse. Minimal intervention strategies have been demonstrated to increase the odds of a patient stopping their benzodiazepine by threefold. These odds are further doubled by creation of systematic reduction strategies.	Patients were sent a specific review appointment letter according to the appointment capacity. This letter advised the patients about the importance of attending the review appointment to allow appropriate diazepam prescribing, to receive support, and to discuss any difficulties with their GP. Tapering regimes were formulated by the pharmacist prescriber or the medication technician based on current best practice. Dose reduction grids for each patient facilitated a downward titration of 1 mg each wk/mo depending upon the individual circumstances. The pharmacy team determined the exact quantities and doses of tablets for the patient while liaising with the local dispensaries. All the prescriptions were dispensed weekly, based on current recommendations.	Linkwood Medical general practice, Elgin, United Kingdom	Patients could attend a review appointment to allow appropppriate prescribing.	NE	NE	NE

Cadogan, C.A.; Bradley, C.P.; Bennet, K.(94)	In 2002, the Benzodiazepine Committee (established by the Irish Minister for Health) published a detailed report with various recommendations relating to the prescribing and monitoring of BZRA use in Ireland, as well as prescribing guidelines. In May 2017, new controlled drugs legislation was implemented in Ireland. This legislation included specific provisions with direct implications for the prescribing of all con-trolled drugs including BZRAs, opioids and stimulants (e.g. lisdexamfetamine), as well as other less commonly used drugs (e.g. phenobarbitone, selegiline). The legislation addressed one of the Benzodiazepine Committee's previous recommendations by extending the scope of the Misuse of Drugs Regulations to include zopiclone and zolpidem. The 2017 legislation introduced additional requirements for most BZRAs which were also assigned a new controlled drug schedule.	New controlled drugs that extended the scope of the Misuse of Drugs Regulations to include zopiclone and zolpidem and introduced new requirements for the prescription of these drugs and some benzodiazepines that included full identification of prescriber, including first name and registration number and the specification of the total quantity to be supplied in both words and figures	Ireland	NE	During the period of the study (2018) there were unexpected parallel modifications to the condicions of GMS shceme with a reduction from 2.5EUR to 2.00EUR per item in co-payment for prescripition medications	NE	NE
Stoker, Lennart Jan et al. (104)	Worldwide different strategies have been used to reduce the use of BZDs. One of these strategies is to influence behaviour of patients, physicians and/or pharmacists by introduction of financial incentives, like pay for performance, copayments and restriction or termination of reimbursement. Since January 2009, BZDs are no longer reimbursed when used as anxiolytic, hypnotic or sedative in the Netherlands. The purpose of this policy change was to reduce chronic use and lower healthcare expenses.	In the Netherlands the coverage of pharmaceutical care is regulated by the Health Insurance Act. The Ministry of Health, Welfare and Sport and the Healthcare Insti- tute of the Netherlands decide which drugs fall under the mandatory health insurance package. Registered medicines have to be assessed before they can be included in the Medicines Reimbursement System (GVS). Medicines listed in the GVS are fully or partially reimbursed by health insurers. Once a year the Ministry of Health, Welfare and Sport evaluates and actualises the list in order to keep healthcare affordable. In January 2009, Dutch Ministry of Healthcare determined that BZDs were no longer reimbursed when used as anxiolytic, hypnotic or sedative in the Netherlands. The purpose of this policy change was to reduce chronic use and lower healthcare expenses. Coverage remained in case of epilepsy, palliative sedation and multiple psychiatric disorders, under the condition that the physician considered that no alternative treatment was suitable for the patient at hand.	Netherlands	NE	NE	NE	NE

NE - non-specified or non-existent

Appendix E

Summary table of studies' results and key findings

Autor(s)	Results	Key Findings	Drug use improvements
Crotty, M. et al.	There was a significant difference in the change in Medication Appropriateness Index (MAI) score between the groups (P < 0.001), with the change in the intervention group significantly different to the change in the control group (P = 0.004). Overall, there was a significant difference between groups in the reduction in MAI scores for benzodiazepines (P = 0.009) as well as for the comparison between intervention and control (mean change control −0.38, 95% CI −1.02−0.27 versus mean change intervention 0.73, 95% CI 0.16–1.30; P = 0.017). There was no difference in behaviour scores, as measured by the Nursing Home Behaviour Problem Scale (NHBPS), at follow-up (P = 0.191). Furthermore, there was no difference in the change in NHBPS score across the groups (P = 0.440). The mean monthly on the governamental reimbursement scheme (PBS) total cost for a resident in the study was $AUD100.46 at baseline and $AUD104.94 at follow-up. The highest individual total costs were $359 in the intervention group and $303 in the control group. The mean change in the estimated total monthly cost of medication was $5.72 (SD = 9.47) in the intervention group and $3.37 (SD = 5.79) in the control group. There was no significant difference between the change in PBS total costs in the intervention compared with the control group (P = 0.837).	Multi-disciplinary case conference meetings at residents' nursing homes led to improved medication appropriateness in the intervention group as assessed by the MAI.	2
Dolan, C. et al.	A high prevalence of benzodiazepine and Z-drug use in original audit was found: 54% (38/70) of the group audited. The prevalence fell to 46% (32/70) at the re-audit post intervention. This result was not statistically significant. The percentage of patients commenced on benzodiazepine and Zdrugs prior to admission fell from 36% (25/70) at the initial audit to 23% (16/70) at the re-audit.	Further improvements might be achieved by establishing rolling programmes of education for relevant healthcare workers. The fact that a large percentage of patients were commenced on sedative or hypnotic medication in the inpatient setting may reflect the clinical difficulties of sleep disturbance associated with admission to hospital of the elderly population.	1
Lang, P.O. et al.	Compared with admission, the intervention reduced the total number of medications prescribed at discharge from 1347 to 790 (P < .0001) and incidence rates for potentially inappropriate medications and PO reduced from 77% to 19% (P < .0001) and from 65% to 11% (P < .0001), respectively. Independent predictive factors for PIP at discharge were being a faller (odds ratio [OR] 1.85; 95% confidence interval [CI] 1.43e2.09) and for PO, the increased number of medications (OR 1.54; 95% CI 1.13e1.89) and a Charlson comorbidity index greater than 2 (OR 1.85; 95% CI 1.38 e 2.13). Dementia and/or presence of psychiatric comorbidities were predictive factors for both potentially inappropriate medications and PO at discharge. There was a reduction of BZD in patients prone to falls from (26.6% at admission, 15.7% at discharge). These results don't indicate difference statistically significant between. The difference between Admission and Discharge regarding the prescription of Long-term (ie, >1 month), long-acting BZD was not statistically significant (6,7% at Admission, 3.7% at discharge)	The prescription of medicines in acutely ill hospitalized older patients with mental comorbidities can be substantially improved during the hospital stay by daily and active collaboration between senior geriatricians and psychiatrists and the health care team.	2
Martin, P. et al.	Post-intervention, 45.1% (n = 65) of participants reported increased perceived risk from consumption of benzodiazepines. There were no statistical differences in baseline characteristics between individuals perceiving an increased risk (RISK) and those with no perceptions of increased risk (NO RISK), except for a trend showing a shorter duration of benzodiazepine use among the RISK group (p = 0.08). Knowledge about benzodiazepines was similar between groups at baseline. Eighty percent (52/65) of participants in the RISK group changed an answer from incorrect to correct on at least one knowledge question from pre- to post-intervention compared to only 41% (33/79) in the NO RISK group. The RISK group demonstrated a significantly higher proportion of correct answers post-intervention on the side effects and alternatives questions compared to the safety, NO RISK group (p < 0.001). Only participants in the RISK group who had the potential for knowledge acquisition showed a statistically significant increase on the overall knowledge score (mean change score 1.77 SD (1.3)). The change in overall score was significantly greater among these individuals in the RISK group post-intervention compared to the NO RISK group (mean change score 0.91 95% CI (0.5, 1.3)). Beliefs about benzodiazepines were similar between groups at baseline. Eighty-three percent (54/65) of participants in the RISK group had an improved BMQ-differential score (negative change) from baseline to follow-up, indicating increased risk perception, compared to 27% (31/79) of participants in the NO RISK group. The RISK group showed statistically significant group differences across all three of these BMQ outcomes (p < 0.001) while no significant group changes were detected in the NO RISK group. Post-intervention, the RISK group reported significantly lower scores on the necessity subscale (mean change score -1.31, 95% CI (2.3, 0.4)), significantly higher scores on the concerns subscale (mean change score 3.72, 95% CI (2.9, 4.5)) and a statistically greater necessity-concerns differential (mean change score -5.03, 95% CI (-6.4, -3.6)), compared to the NO RISK group.	In conclusion, a home-based educational program consisting of a document mailed to participants demonstrated significant effects on medication knowledge, beliefs and risk perception in a cohort of older benzodiazepine users. By changing knowledge and increasing perceived risk, consumer-targeted drug information elicited a desire among many older adults to discuss medication safety with their health care providers.	NA
Furbish, Shannon M.L. et al.	Of the 29 patients who attended at least 1 visit, 10 (34.5%) returned for 2 visits, 3 (10.3%) returned for 3 visits, and 2 (6.9%) returned for 4 visits. Selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and nonbenzodiazepine hypnotics were started or optimized in 15 (51.7%) patients at the first visit. Of the 10 patients with 2 visits, there were 8 (80%) interventions made to either start or optimize nonbenzodiazepine medications at the second visit. At the first visit, there were 15 (51.7%) benzodiazepine changes made. These included discontinuing a benzodiazepine completely in 7 (24.1%) patients when down-titration was not necessary, decreasing dose or frequency of benzodiazepine in 6 (20.7%) patients, and switching to a more preferred benzodiazepine in 2 (6.9%) patients. At the second visit, there was only 1 benzodiazepine change made. Table 5 describes the benzodiazepine changes made at visits 1 and 2. For the 9 patients who completed a GAD-7 at visits 1 and 2, the mean decrease in score between visits was −2.0 (95% confidence interval [CI]: −3.57 to −0.43), which was statistically significant (P < 05). For patients who completed the ISI at visits 1 and 2, there was a nonsignificant (P > 05) mean decrease in score between visits of −0.7 (95% CI −3.31 to 1.91). There were too few responses for the Patient Health Questionnaire 9 and PDSS to assess the significance of change. At the first visit, 6 (20.7%) patients were in the precontemplation stage, 6 (20.7%) patients were in the contemplation stage, 8 (27.6%) patients were in the preparation stage, 8 (27.6%) patients were in the action stage, and 1 (3.4%) patient was in the maintenance stage. Of patients with at least 2 visits, 5 (50%) progressed to higher stages, 2 (20%) relapsed stages, and 3 (30%) neither progressed nor relapsed.	This study highlights the benefits of collaborative team-based models of care that include clinical pharmacists in primary care to assist with optimizing high-risk benzodiazepine use. The findings from this study suggest that patients may benefit from improved medication use and symptom improvement, but additional studies with more subjects and a comparison group are needed to validate these preliminary findings. Further studies should also assess provider satisfaction and perceived impact on workload.	1
Mestres Gonzalvo, C. et al.	The clinical rule screened 808 NH patients, 269 (33.3%) of whom were using BZ/Z. Of these, 161 (19.9%) were chronically using BZ/Z to treat insomnia (i.e., longer than 4 weeks). The clinical rule generated 180 alerts, which means that 19 patients were using two BZ/Zs. An advisory per patient was sent to the corresponding NH physician; only 27 out of 161 (16.8%) of the given advisories were followed, meaning that the NH physician had started phasing out the BZ/Z. The other 134 advisories (83.2%) were not followed by the NH physician. The median time a BZ/Z was prescribed before the advisory was given was 19.1 months. This median time-use was slightly longer for the group in which the advisory was not followed (22.3) and was shorter for the groups in which the advisory was followed, i.e., being successfully stopped or restarted (17.2 and 14.8, resp.). Regarding physician performance, five NH physicians did not follow any of the advisories to stop BZ/Z prescribing. The other seven NH physicians adopted the advisory in 9.1 to 65.0% of their patients. The most frequently BZ/Z used was oxazepam, followed by temazepam. In the group in which the advisory was adopted, the use of temazepam was higher than oxazepam.	Even though it is feasible to discontinue chronically used BZ/Z drugs in the nursing home population, the success rate of the CR seems rather low. In the present study, in only 16.8% of the cases was discontinuation initiated, and at 4 months follow-up, 37% were successfully discontinued. Even though the success rate for discontinuance of chronically used BZ/Z described in the present study was rather low, a simple clinical rule, which screens all NH patients within 5 min, can be used to identify which patients qualify for discontinuation.	2
Cabelguenne, D. et al.	A number of 1249 patients were included. Prescribed doses of benzodiazepine decreased in the intervention groups, to a mean of 29-35 mg diazepam equivalent per day, compared to the control group (42 mg/day) (P < .001). The first 4-year period (2000-2004) demonstrated that monthly meetings and systematic pharmaceutical medication review had an impact on prescribed benzodiazepines, limiting consumed doses. The others (2004- 2008, 2008- 2012 and 2012- 2016) confirmed that physicians' adherence to prescription guidelines and the efficacy of pharmacotherapy programme was maintained, particularly in those inmates taking high doses. However, this pharmacotherapy programme had no significant effect in the lower doses' subgroups. In 2009, guidelines were collegially updated on the basis of the conversion table. The maximum daily dose was increased from 40 to 60 mg DE per day, to respect a strict equivalence between molecules in daily dose. In 2012, the increase in prescribed BZD doses raised awareness in pharmacists and psychiatrists, and reminders of prescription rules and the risks of high-dose BZD were given during the monthly meetings. The effectiveness of this teamwork was confirmed by a further significant decrease in prescribed doses in 2016. The <30 mg rate increased, while the >60 mg rate decreased.	There is a positive impact of this pharmacotherapy programme between psychiatrists and pharmacists in reducing prescribed doses of BZDs to prisoner patients and contrib-uting to reduce risk of benzodiazepine-related problems. The results confirmed that physicians' adherence to prescription guidelines and the efficacy of the systematic pharmaceutical medication review were maintained over a period of more 15 years. This encouraging assessment is part of a continuous quality programme for psychiatrists and pharmacists concerning medication management for prisoner patients	2
Stoker, Lennart Jan et al.	The volume of dispensed prescriptions and doses decreased by 12.5% (95% CI 9.0% to 15.9%) and 15.1% (95% CI 11.4% to 17.3%) respectively in January 2009 compared with December 2008. A clear initial effect on the overall incidence (−14.7%; 95% CI −19.8% to 9.6%) and the prevalence of incidental (−17.8%; 95% CI −23.9% to 11.7%), regular (−20.0%; 95% CI −26.1% to 13.9%) and chronic (−16.0%; 95% CI −23.1% to 8.9%) use was observed. A statistically significant reduction in the monthly trend per 1000 medication users was observed for the overall incidence (−0.017; 95% CI −0.031 to 0.003) and the prevalence of incidental (−3.624; 95% CI −4.996 to 2.252) but not for regular (−0.304; 95% CI −1.204 to 0.596) and chronic (0.136; 95% CI −0.858 to 1.130) use. Patients who started treatment before policy had a slightly higher probability of discontinuation (HR=1.013; 95% CI 1.004 to 1.022).	The reimbursement policy had a significant initial effect on the volume, incidence and prevalence of benzodiazepine use. In addition, there is a statistically significant reduction in the monthly trend of overall incidence and of the prevalence of incidental use. No statistically significant reduction in the monthly trend of chronic use, the main purpose of the reimbursement restriction, could be demonstrated.	2

Salonoja, M. et al.	The number of regular users of BZD decreased significantly by 35% (n = 12) in the intervention group and increased by 4% (n = 2) in the controls; the differences in changes being significant in the total population (P = 0.012), in the younger group (P = 0.024) and in women (P = 0.016). The decrease in the intervention group was significant in the total population (OR, 95% CI) (0.61, 0.44–0.86) (P = 0.004), in the younger group (0.55, 0.35–0.87) (P = 0.011) and in women (0.60, 0.42–0.85) (P = 0.004). The number of irregular users of BZD/RD decreased significantly by 28% (n = 22) in the intervention group and by 30% (n = 23) in the control group. The differences in the changes were not significant in the total population or by sex and age. The decrease in the intervention group was significant in the younger group (0.66, 0.45–0.95) (P = 0.027), in the older group (0.61, 0.37–0.99) (P = 0.047) and in women (0.63, 0.46–0.86) (P = 0.004). In controls, respectively, the decrease was significant in women (0.63, 0.45–0.88) (P = 0.007) and in the younger group (0.58, 0.38–0.87) (P = 0.009). In this study, 35% of the participants, a bigger share than at baseline were willing to withdraw them, were free of regular use of BZD/RD after 12 months' intervention by a one-time counselling and a lecture about adverse effects of these high-risk drugs.	A one-time counselling involving careful guidance and information by the geriatrician and proposals with written instructions reduced the numbers of regular longterm users of BZD/RD during a 12-month follow-up. Reduction of the long-term use of BZD/RD can successfully be implemented in primary health care by a one-time counselling.	3
Bachhuber, Marcus A. et al.	Rates of ED visits involving benzodiazepine misuse increased in all metropolitan areas during the study period. PMP implementation was not associated with a change in ED visits (mean difference: 0.9 [95% CI: −0.09 to 1.9] visits per 100,000 population per quarter; p=0.08). When analyzed by number of years after implementation, PMPs were associated with a higher visit rate in year one (0.8 [95% CI: 0.2 to 1.5]; p = 0.01]), but not in year two (0.3 [95% CI: −2.1 to 2.8]; p= 0.78) or year three or later (2.1 [95% CI: −0.4 to 4.7]; p = 0.10).	Did not find evidence that PMP implementation was associated reductions in ED visits involving benzodiazepine misuse. Future work should identify PMP features and capabilities that improve benzodiazepine safety.	0
Jørgensen, V. R. K	The prescription of hypnotics of the benzodiazepine group (N05CD) was reduced in individual practices by between 26,0% and 72,2% with an average reduction of 48,6%. The practioners with the highest prescription rates had rates 9-fold greater than those with the lowes prescription rates. The prescription of anxiolytics of the benzodiazepine group (N05BA) was reduced in the individual practices by between 15,6% and 52,9%, with an average reduction of 40,2%. The practioners with the highest prescription rates had rates 4-fold greater than those with the lowes prescription rates.	Following the intervention, a clear reduction in the prescription of anxiolytics (N05BA) and hypnotics (N05CF and N05CD) was apparent for all practices participating in the project. The overall numerical reduction was significant for anxiolytics, N05BA and the hypnotics group N05CF. The intervention requires a minium of supplementary training, as well as limited (altough focused) effort on the part of practioners. The extra time and effort required is almost minimal, and can be adapted for almost any practice.	3
Chen, Y. C.; Kreling, D. H	The majority of subjects (n=303, 65.0%) continued using benzodiazepines after policy implementation. Of all subjects, 9.2% (n=43), 13.0% (n=60), and 13.0% (n=60) engaged in the fluid movement, switch, and cessation patterns, respectively. The comparison group had significantly higher total drug spending than the intervention group for both before and after policy implementation (917.30 vs. 1206.30 USD, respectively). Both the intervention and comparison groups increased their benzodiazepine spending (49.30 USD in 2005 and 73.45 in 2006 vs. 54.60 in 2005 and 58.43 in 2006, respectively); however, the benzodiazepine spending of the intervention group increased more than that of the comparison group (23.05 vs. 3.83 USD) the primary independent variable, loss of benzodiazepine coverage, was the only significant predictor of whether a senior switched drug use patterns, controlling for age, gender, and comorbidities. Individuals who lost benzodiazepine coverage had nearly two and a half times (2.43) the odds of engaging in the fluid movement pattern and over two times (2.09) the odds of engaging in the switch pattern than individuals receiving continued benzodiazepine coverage. For the cessation pat- tern, losing coverage was not a significant factor, but gender was; women had higher odds (2.27) than men to quit benzodiazepine treatment after the policy. Moreover, individuals who were older or had higher comorbidity scores (RxRisk) were less likely to quit benzodiazepines (odds ratios of 0.95 and 0.92, respectively) than individuals continuing with benzodiazepine use. Economic and pharmaceutical factors generally do not contribute to beneficiaries selecting different courses of action in response to the exclusion beyond the influence of losing coverage. After controlling for expenditures and exposure to benzodiazepines, individuals losing benzodiazepine coverage still had more than two times the odds (2.09) of switching from and back to benzodiazepines, and nearly two times the odds (1.78) of switching to substitute medications relative to individuals with continuous benzodiazepine coverage. For the fluid movement use pattern, when the economic and pharmaceutical factors were included, comorbidity did become a significant factor and individuals with higher comorbidity scores had higher propensity (1.24) to engage in the fluid movement pattern.	Although the exclusion policy did not have a large overall impact on benzodiazepine utilization in this Medicare population, for some individuals, the change in prescription coverage did cause them to switch from benzodiazepines either temporarily or permanently. Concerns about increased cost or decrease in efficacy may have influenced seniors who switched from and back to benzodiazepines.	2
Velert Vila, Josefina et al. (1)	64% of the patients used polytherapy (4 or more medicines). 83.90% of the patients studied used benzodiazepines for more than a month and 66.90% for more than a year for the treatment of insomnia. 83.30% exceed the recommendations of the Spanish Medicines Agency in the treatment of anxiety. In 83 patients 132 interactions were detected (33% with omeprazole, 19% with anxiolytics, 14% with beta-blockers and 8% with other hypnotics followed of antidepressants, ketoconazole, fentanyl and ciprofloxacin, among others. 50% of the study population did not present any adverse drug reaction (ADR), 26% presented a and the rest two or more (one patient referred 6 ADRs simultaneously). In total they manifested 278 ADR. 32% loss of memory, 21% drowsiness, 12% lack of motor coordination, followed by dizziness and confusion (8.30%) and disorientation (8.3%). Of the patients with ADR, 61% (95% CI: 50.97-71.92%) were taking medications with potential interactions, versus 46% (95% CI: 39.46-52.31%) who had no interactions. The differences between the patient ratio with ADR and the presence or absence of possible interactions pharmacological in their treatment were statistically significant ($p < 0.05$). Taking into account only patients in polytherapy, 61% presented ADR at the same time reported by the patient and interactions ($p > 0.05$). 426 pharmaceutical interventions were carried out, of which that 30 were accepted by the doctor and 136 directly by the patient. Of these, 78 were resolved at the end of the year. Given the consultation made to all patients about of the time in which they had to continue with the treatment, only the 5% of insomnia cases knew it should be lower at one month. 73% of the patients stated that the treatment was going well and only 5% admitted not noticing improvement or even go wrong.	In this study, pharmacists performed a significant number of pharmaceutical interventions directly with the patient or through the physician in order to improve medication use. 39% were accepted and 47% of the accepted interventions were resolved.	1
Velert Vila, Josefina et al. (2)	Most of the patients did not know the time of use of the treatment with BZD (36.3%) or considered that the duration was indefinite (31.3%). 85% of the patients in the study used BZDs longer than recommended by Spanish Medicines Agency. Pharmacist interventions to adapt the use of BZD are resolved in a greater proportion (84%) when they are referred and accepted by the doctor than the interventions performed directly by the pharmacist (41%). In this study, it is observed that the mediation of the pharmacist improves the use of BZD in 29% of patients in the intervention group compared to 10.8% of patients in the control group; this improvement means a decrease in the patient's cognitive impairment, assessed using the Pfeiffer questionnaire, and a decrease in the number of adverse reactions. No differences were observed in the Siu-Reuben questionnaire.	The pharmacist's interventions to adapt the use of BZD are resolved in a greater proportion (84%) when are referred and accepted by the doctor than interventions performed directly by the pharmacist (41%), hence the importance of good doctor-pharmacist collaboration. At the end of the study, the intervention group has improved the use of BZD (decrease in dose, transition to a sporadic use of BZD, elimination of this or, if the use is chronic, change to lorazepam) in a higher percentage (29%) than the control group (10.8%). All patients in the study who improve their use of BZDs show less cognitive impairment and a greater decrease in the number of adverse reactions than patients who do not improve their use of BZDs.	2
Clay, Emilie et al.	Countries where the sales of BZD and Z-drugs decreased since 2007: Greece, Finland and Denmark. In Greece there was no anti-BZD campaign before the launch of PR-melatonin, and the consumption of the BZD and Z-drugs was stable. BZD and Z-drug consumption decreased by 14.5 % over 3 years after the introduction of PR-melatonin in the market. The decrease in BZD/Z drug consumption since 2008 can thus be attributed to the launch of PR-melatonin and its considerable market penetration. On average, an increase in 1 SU of PR-melatonin was associated with a decrease of about 4 SUs of BZD/Z-drugs. The combined launch of PR-melatonin and anti-BZD campaigns in Finland and Denmark seems to be associated with a reduction ofBZD/Z-drugs usage. This decrease is concomitant with the penetration of PR-melatonin on the market and the campaign implementation. Again, uptake of 1 SU PR-melatonin in Finland was associated with a decrease of 3 SUs of BZD/Z drugs consumption in this country. Countries where the sales of BZD decrease while Z-drugs increase: Norway, the Netherlands and the UK. In these countries the anti-BZD campaigns seem effective for BZDs, but essentially resulted in a shift in prescription patterns towards Z-drugs. In Norway, there was an overall increase in BZD/Z drugs consumption since 2005 but the BZD sales decreased in favor of Z-drugs. Since PR-melatonin was launched, the increase in Z-drug sales stopped and the consumption was stabilized, as if the switch from BZDs gradually shifted from Z-drugs to PR-melatonin. The same evolution of BZD and Z-drug sales was observed in the Netherlands, but the decrease in BZD sales was mostly related to the change in the reimbursement status, suggesting that BZD/Z drug consumption in this country is price sensitive and reimbursement itself has some encouraging effect on hypnotic drug consumption. Nevertheless, Z-drug sales remained stable between 2009 and 2011. PR-melatonin sales did not rise considerably in the Netherlands perhaps because it is more expensive than the other drugs and is not actively promoted in this country. In the UK, a decrease was seen only in BZD. There was a steady increase in Z-drug use of up to 7.3 % in 2011, although NICE has issued the following recommendation: "It is recommended that, because of the lack of compelling evidence to distinguish between zaleplon, zolpidem, zopiclone or the shorter-acting benzodiazepine hypnotics, the drug with the lowest purchase cost (taking into account daily required dose and product price per dose) should be prescribed". Possibly, higher market acceptance of PR-melatonin might gradually change this situation as seen in Norway. Countries where the sales of BZD were stable and Z-drug use increased, resulting in overall increases in BZD and Z-drug sales despite anti-BZD campaigns: France, Sweden and Spain. In these countries the anti-BZD/Z-drug campaigns that were sometimes quite intense and long lasting (like in France) had no or very limited impact on prescription levels. As BZDs and Z-drugs are reimbursed while PR-melatonin is not, and these markets are reimbursement-sensitive, PR-melatonin was not commercially launched in France and was not put on the market in Spain.	Campaigns aimed to reduce the prescription of BZD/Z-drugs and achieve discontinuation of long-term treatment fail when they were not associated with the availability and uptake of sales of PR-melatonin. The reimbursement of PR-melatonin may support a better market penetration and a higher reduction of sales of BZD/Z-drugs. The non-reimbursement of BZD/Z-drugs appeared to have no effect on Z-drug prescription, and even showed an increase in prescription during 2011. When considering campaigns aiming to limit the usage of BZD/Z-drugs, policymakers should carefully consider the availability of reimbursed effective and safe pharmacological alternatives.	2

Hoebert, Joëlle M. et al.	The proportion of patients being prescribed a benzodiazepine following a diagnosis was slightly lower in 2009 than in 2008 for both anxiety (33,7% vs 30,1%, P<..05) and sleeping disorder (67.0% vs 59,1%, P<.05). The proportion of patients being prescribed more than 1 benzodiazepine was lower in 2009 than in 2008 for both anxiety (36.4% vs 42,6%, P<.05) and sleeping disorders (35.0% vs 42.6%, P<.05). Patients wit newly diagnosed anxiety, no difference in discontinuation rates was observed (HR = 0.87; 95% CI, 068-1.11). Patients sleeping disorder in 2009 had a lower risk of discontinuation than did patients with newly diagnosed sleeping disorder in 2008 (HR 0.63; 95% IC, 0.52-0.76). Adjustment for age and sex had no effect The number of patients actually starting SSRI treatment after a diagnosis of anxiety was low. In 2008 and 2009 only 6.2% and 5.3% (2008 and 2009) of patients with new diagnosis started SSRI treatment (P>.05). The reimbursement restriction had no effect on switching to SSRI treatment among patients discontinuing benzodiazepines treatment when anxiety was diagnosed).	The number of reimbursed prescriptions for benzodiazepines in the Netherlands increased in 2009 by 4.1%. Even so, benzodiazepines disappeared from the top 10 most-prescribed medicines and were among the top 10 medications with the steepest decrease in number of prescriptions. This change in ranking suggests that the policy measure has influenced the total use of benzodiazepines in the Netherlands. Reimbursement restriction has led to a moderately positive effect on the decrease in the number of incident diagnoses and initiation of benzodiazepine use in patients with newly diagnosed anxiety or sleeping disorder. At the same time, the proportion of patients receiving prescriptions for benzodiazepines decreased moderately. These findings indicate that in healthcare settings where no such reimbursement settings exist, physicians have room to reduce benzodiazepine prescribing.	2
Reeves, Rusty	For the benzodiazepine study, 36 psychiatrists were with the providers at all 3 intervals (baseline, 7 months later, and 20 months later). The average caseload for each full-time equivalent (FTE) psychiatrist was 125 patients. Clonazepam was the benzodiazepine overwhelmingly prescribed. The mean and median numbers of patients for whom each FTE psychiatrist prescribed a benzodiazepine were as follows: at baseline, 5.6 and 4; at 7 months, 3.3 and 2; and at 20 months, 3.4 and 2. These numbers highlight the fact that a few psychiatrists prescribed considerably more benzodiazepines than their peers. Using a signed rank-order test, the difference between the means at baseline and at 7 months is statistically significant (p < .0005; Table 1). The difference between the means at baseline and at 20 months is also statistically significant (p < .003). The difference between the means at 7 months and at 20 months is not statistically significant. Relative to baseline, the differences between these means reflect 39% and 38% absolute reductions (i.e., without adjustment to FTE status of physicians) in the numbers of inmates prescribed a benzodiazepine at 7 months and 20 months, respectively.	The ease with which a guideline, education, and peer comparison effected change in physicians' prescribing patterns, and the magnitude and duration of these changes, suggest that these techniques should be used together more often	3
Tannenbaum, Cara et al.	A total of 261 participants (86%) completed the 6-month follow-up. Of the recipients in the intervention group, 62% initiated conversation about benzodiazepine therapy cessation with a physician and/or pharmacist. At 6 months, 27%of the intervention group had discontinued benzodiazepine use compared with 5%of the control group (risk difference, 23%[95% CI, 14%-32%]; intracluster correlation, 0.008; number needed to treat, 4). Dose reduction occurred in an additional 11% (95% CI, 6%-16%). In multivariate subanalyses, age greater than 80 years, sex, duration of use, indication for use, dose, previous attempt to taper, and concomitant polypharmacy (10 drugs or more per day) did not have a significant interaction effect with benzodiazepine therapy discontinuation.	Direct-to-consumer education effectively elicits shared decision making around the overuse of medications that increase the risk of harm in older adults.	3
Rat, C. et al.	In the overall population, 18.18% and 18.97% of patients continued the treatment for more than 12 weeks in 2011 and in 2012, respectively (p = 0.030), whereas 27.43% and 28.66% of patients older than 65 years, respectively, continued treatment beyond the 12-week period (p = 0.30). The percentage of patients older than 65 who were prescribed a long half-life benzodiazepine decreased from 53.5% to 48.8% (p < 0.005) between 2011 and 2012.	The implementation of the pay-for-performance strategy did not affect the prescription of long half-life benzodiazepines, while the number of prescriptions of short half-life drugs increased between 2011 and 2012. An adverse effect of this evolution was the continuation of benzodiazepine treatments for more than 12 weeks, in so far as short half-life drugs have been associated with a higher rate of withdrawal than long half-life drugs.	0
Azermai, M. et al.	In the intervention group (INH, n = 118), where a shift towards person-centered approach in addition to educational courses took place, some changes in the medication use were noticed. Moreover, there was a significant decrease in mean number of medication use (p = 0.033). Predominantly prescribed medication classes were alimentary (85%) and cardiovascular (82%) medications. There was a 6% decline in central nervous system drugs, although not significant (p = 0.148). In the prevalence of psychotropic medication use, a 10% decrease from 73 to 63% was noticed, although not significant (p = 0.095). The concomitant use of psycho-tropic agents decreased as well (from 42 to 32%). The prevalence of hypno-sedative use decreased significantly by 13% (from 49 to 36%, p = 0.048). The prevalence of antidepressant and antipsychotic users did not change significantly. In the control group (CNH), no statistically significant changes in medication use were recorded. A total of 91 residents were still residing in the intervention nursing home at the moment of the follow-up measurement. The overall prevalence of psychotropic medication intake in this surviving group at the start was 75%. At the end of the follow-up, this prevalence decreased significantly to 55% (p = 0.005). A further significant decrease was noticed in the prevalence of hypno-sedative (from 51 to 31%, p = 0.007) and antidepressant users (from 42 to 25%, p = 0.019). The antipsychotic use decreased significantly as well (p = 0.019). In the control nursing home, a total of 209 residents were still residing there at the time of follow-up. The overall prevalence of psychotropic medication users increased over time (from 64 to 68%), predominantly due to an increase in the prevalence of benzodiazepine (from 41 to 46%) and antipsychotic (from 19 to 22%) users. However, all prevalence in psychotropic drug use did not change significantly.	The results of this study indicate that the sole introduction of a knowledge-based training may not be sufficient in the long term in order to reduce psychotropic drug use. Management of common behavioural and psychological problems in older adults (e.g. sleeping problems, depression, agitation) requires a multidisciplinary approach. In this quality improvement project, a transition towards a person-centred care in a nursing home in Belgium led to a significant decrease in the use of psychotropic drugs, even after 1-year follow-up.	0
Geka, M. et al.	The ratios of the subjects who could discontinue BZRA use on each floor in 2013, 2014, and 2015 were as follows: Floor A: 2/30 (6.7%), 21/44 (48%), and 17/36 (47%); Floor B: 4/47 (8.5%), 2/57(3.5%) and 16/59(27%), respectively. The average numbers of BZRA doses administered according to the individualized recommendations were as follows: Floor A in 2013: 1.6±0.75; in 2014: 1.0±1.0; in 2015: 0.85±0.59; Floor B in 2013: 1.7±0.72; in 2014: 1.6 ±0.79; in 2015: 1.2±0.78. The average numbers of BZRA administered on Floor A in 2013, 2014, and 2015 were subjected to analysis of variance. The results showed a statistically significant difference between 2013 when there was no intervention and 2014 when there was an intervention. No statistically significant difference was noted between 2014 and 2015, both of which involved interventions. Factoring in their time dependence, the average numbers of BZRA administered on Floor B in 2013, 2014, and 2015 were also subjected to analysis of variance. The results showed no statistically significant difference between 2013 and 2014, neither of which involved an intervention. However, statistically significant difference was noted between each of these years and 2015, during which an intervention occurred. The average equivalent diazepam doses (mg) were as follows: Floor A in 2013: 12±10; in 2014: 6.6±10; in 2015: 6.0±5.5; Floor B in 2013: 14±12; in 2014: 16 ±11; in 2015: 9.2±11.	Multidisciplinary clinical team meetings where pharmacists can effectively share information on the current status of BZRA use and their prescription recommendations with other clinical team members can lead to reduced BZRA dosages.	3
Badr, A.F. et al.	For the primary out-comes, 25% of a total of 97 orders were discontinued within 24h after pharmacist intervention during the prospective phase. The number of patients receiving more than one sedative/hypnotic agents was significantly lower in the intervention group compared to the control group (15 Vs. 34, P = 0.003). For the secondary outcomes, reported complications of over-sedation, falls, and delirium did not differ significantly between the two groups (p = 0.835, p = 0.369, p = 0.745, respectively).	The study findings suggest that the use of sedative/hypnotics in the inpatient units (excluding the critical care unit), is somewhat prevalent and that many patients may be on more than one sedative-hypnotic agents. Active monitoring by a pharmacist can have a major impact on the safe use of sedative/hypnotics in this setting, thus circumventing potential deleterious effects. Twenty-five percent of the total in-hospital orders for sedative/hypnotic agents were discontinued following pharmacist interventions with significant reductions in multiple orders, though complication rates did not differ. Further efforts should be implemented to optimize the use of sedative/ hypnotics in hospitalized patients especially when they are being introduced for the first time, including active monitoring of these medications by pharmacists.	3

Davidson, S.; Thomson, C.; Prescott, G.;	1. Pre-intervention Ninety-two patients had a repeat prescription for diazepam. Sixty-one percent were male. Age of the patients ranged from 28 to 83 years. The average time on diazepam was 81 months (range, 2 months to 23 years). Forty-five percent of the patients had been on diazepam for more than 5 years. The total daily dose was between 2 mg and 25 mg. Fifty-seven (62%) of the repeat prescriptions of diazepam were initially prescribed for a psychiatric indication. Fifty two patients (56.5%) had undergone a medication review past 4 months. Initially, 27 patients (29.3%) were under psychiatric evaluation. Their diazepam dose was reviewed and reduced, if appropriate, by their psychiatrist. Eight patients (8.7%) were occasionally using extremely low doses of diazepam and were given a suitable titration plan. Fifty-seven patients (62.0%) were eligible for the standard intervention. 2. Post-Intervention Initial follow-up took place 12 months after the intervention. Attendance was very high, with 87 patients (94.6%) attending the review appointment to discuss the intervention. At 12 months, 51 patients (55.4%) had successfully titrated down and stopped diazepam. Two patients were continued on a slower titration plan, 11 (12.0%) were using diazepam intermittently, and 28 (30.4%) were unable to stop using diazepam. Due to a boundary change, seven patients had moved GP practice. Eighty patients remained at the practice. Five patients had died. In total, 28 patients (30.4%) were unable to participate in a reducing regime. At 24 months since the beginning of the intervention, 58 patients (63.0% of the 92 and 75.3% of the 77 still at the practice) had successfully titrated down and stopped diazepam. Nine of these patients had been given a one-off acute prescription for a specific purpose. Two patients continued with a slower titration plan, one under practice care, and the other by psychiatry. During 2016, 3 more patients moved practice. Sixty-three patients (81.8% of the 77 still at the practice) had stopped or were in the process of stopping regular use of diazepam. Out of 14 patients (18.2% of the 77 patients still at the practice) unable to stop regular use of diazepam, three patients were under care for learning disabilities and five were under care of psychiatry. For diazepam, the estimated prescribing rate was 1.7 DDD per 1,000 patients per day per month (ppdpm), increasing by 0.015 per month (95% confidence interval [CI], 0.008 to 0.022), to approximately 2.2 DDD per 1,000 ppdpm in October 2014 (month 34). There were two substantial, but non-significant step decreases of around 0.3 DDD per 1,000 ppdpm, at the start of the intervention (month 34), and at full implementation (month 37). There was a non-significant rate of decline of 0.032 DDD per 1,000 ppdpm (95% CI, -0.210 to 0.273) during implementation. Following full implementation at month 37 (January 2015), the prescribing rate was 1.5 DDD per 1,000 ppdpm with a statistically significant linear rate of decline of 0.032 per month (95% CI, 0.022 to 0.042). By the end of the study, the prescribing rate was approximately 0.7 DDD per 1,000 ppdpm. For benzodiazepines, the estimated initial prescribing rate was 2.6 DDD per 1,000 ppdpm, increasing by 0.010 per month (95% CI, 0.002 to 0.017) before the intervention, to approximately 2.8 DDD per 1,000 ppdpm at month 34. At this point, there was a large, non-significant step decrease of 0.390 (95% CI, -0.026 to 0.806) and a steep decline by 0.126 DDD per 1,000 ppdpm (95% CI, -0.180 to 0.432). Following full implementation at month 37, the prescribing rate was around 2.0 DDD per 1,000 ppdpm with a shallower decline of 0.032 DDD per 1,000 ppdpm (95% CI, 0.021 to 0.043) to a rate of 1.3 DDD per 1,000 ppdpm by the end of the study. The monthly linear declines in diazepam and benzodiazepines prescribing rates were almost identical after full implementation at month 37.	This study has been able to produce a statistically significant, durable reduction in overall diazepam prescribing by using a minimal intervention strategy and maintaining a collaborative, proactive relationship between primary and secondary care providers. New patients to this practice, who are on repeat prescriptions of diazepam, are immediately scheduled for an appointment with a GP to review their diazepam prescription. For patients authorized to use diazepam on an as required basis, the medical files are clearly annotated with the amount and frequency of the authorized dose. It is practice policy for diazepam to be dispensed weekly for all patients. These are important long-term safeguards to ensure that a patient's use of the drug does not change without good reason or review. This should be considered a gold standard for General Practice in prescribing diazepam and other drugs with a propensity for causing iatrogenic dependence.	3
Gemelli, Maria Grazia; Yockel, Katherine; Hohmeier, Kenneth C.;	A total of 36 patients were enrolled in the study based on inclusion/exclusion criteria. Overall, 39 interventions were performed. Gradual dose reductions/discontinuation of select sedative/hypnotics were accepted for 19 residents (48.7%). Of the other recommendations, 8 (20.5%) were denied and 12 (30.8%) were left unanswered. Primary reasons for denial included family refusal, satisfactory response to current dose, and requirement of increased dose as a result of worsening insomnia. Among the recommendations that were accepted, gradual dose reductions (GDRs) were the slightly more favorable option for physicians. Overall, 9 sedative/hypnotics were discontinued, and 10 were gradually reduced (with 1 subsequently discontinued shortly thereafter).	While some physicians were hesitant to discontinue residents' long-term sedative/hypnotic use, pharmacist intervention resulted in the successful decrease/discontinuation of sedative/hypnotics in approximately 50% of all participants. Establishing relationships with providers, attempting GDRs, providing evidence-based recommendations, and offering education to providers, family members, and patients, are all successful methods toward increasing acceptance rates in this population. A multidisciplinary effort, including pharmacists, general practitioners, and nurses, is a key to optimizing medication utilization and achieving improved patient outcomes.	1
Mondielllo, T. B.; Stutzman, L. A.	Sixty-three recommendations were made by pharmacists, and 48% of these recommendations were accepted by providers. There was a 27% reduction of the use of high-risk medications, a 44% reduction of omissions of care, and a 74% reduction of incomplete medication monitoring after pharmacists' recommendations. The most commonly prescribed psychotropic medications were zolpidem (31%), lorazepam (23%), and clonazepam and temazepam (each 15%). The most common indications for these medications were anxiety and insomnia (each 46%), with 8% of patients having an indication for both.	Although some patients may not have been agreeable to change, this study did increase the discussion of high-risk medications between the provider and patient. Even if the recommendation was not implemented, we found documented discussions between the provider and patient about the potential hazard of high-risk psychotropic medications. Pharmacists' recommendations improved geriatric pharmacotherapy by decreasing the overall instances of suboptimal prescribing.	2
Rowntree, R. et al.	There were increases in total benzodiazepine and z-hypnotic prescribing despite intervention. A reduction of 2mg occurred in the mean regular dose of benzodiazepine prescribed. Lorazepam was the most prescribed benzodiazepine throughout. In both data sets, at least 50% of regular z-hypnotics and benzodiazepines were initiated before admission. There was an increase of 14% in regular benzodiazepines initiated in hospital exceeding 4 weeks in duration. In neither data collection did regular z-hypnotics initiated in hospital exceed this cut off. A greater number of individuals were in the process of being withdrawn from regular benzodiazepine or z-hypnotic prescriptions in the re-audit. There were minimal improvements in 'as required' prescribing as regards documentation of an indication, time limit and maximum dose.	The increase in overall prescribing, despite intervention, maybe because these medications continued to be indicated in the acute presentations needing inpatient treatment. The small improvements in 'as required' prescribing patterns suggest that the intervention was limited in effecting change in this area	0
Navy, H.J. et al.	Of the 153 patients sent a letter, 30 (19.6%, 95% CI 13.6%-26.8%) called the study clinical pharmacist within 14 days of the letter being mailed. One patient called the study clinical pharmacist after 14 days and was included in the did not call group. Twelve (40.0%) patients declined study participation and, thus, were not included in the assessment of alprazolam discontinuation, dose reduction, or interchange to alternate medication. The percentages of patients who discontinued alprazolam, reduced their alprazolam dose, or interchanged to an alternative therapy were equivalent between the intervention (34.0%) and control (35.3%) groups (P =0.822). There were no differences between the groups on the individual outcomes (all P > 0.05). In the sub analyses of patients in the intervention group, a higher percentage of intervention patients who called There were 346 patients who met inclusion criteria and the study clinical pharmacist (77.8%) discontinued alprazolam, reduced were randomized. After prescriber review, 20 patients their alprazolam dose, or switched to alternative therapy were excluded from the intervention group. A total of compared with intervention patients who did not call 153 and 173 patients were and were not, respectively, the study clinical pharmacist (27.6%) (P < 0.001) (Table 3). There were sent a letter. Patients who were mailed a letter equivalent percentages of patients who had an alprazolam (intervention group) were well-matched with patients dispensing during follow-up (P > 0.05); however, patients who were not mailed a letter (control group) in regard who called the study clinical pharmacist were more likely to have had an alternate medication dispensing (72.2% vs. 13.0%; P < 0.001) and/or ≥ 50% decrease in alprazolam dose (38.9% vs. 4.9%; P < 0.001).	This study identified that a low-cost patient educational outreach coupled with CP care efficiently can engage a subset of older adults in the benzodiazepine use-reduction process. Nevertheless, this study highlights that benzodiazepines continue to be a challenging medication for patients to discontinue. While the decision on whether or not to continue a PIM often ends up being the patient's, a letter intervention is a low-cost strategy requiring minimal time and effort to identify older patients who can be engaged in the use-reduction decision-making process	0
Cadogan, C.A.; Bradley, C.P.; Bennet, K.	Prior to the legislation (January 2016 to April 2017), there was a significant monthly decline in the prevalence rate of benzodiazepine prescribing (β = -1.18; 95% CI -1.84, -0.51; p < 0.001) but no significant change in prevalence rate of Z-drug prescribing (β = 0.07; 95%CI − 0.53, 0.66; p = 0.82). Over the period following introduction of the legislation (May 2017 to September 2019), increases were observed in prevalence rates of benzodiazepine (β =1.04; 95%CI0.17, 1.92; p = 0.021) and Z-drug prescribing (β = 1.04; 95% CI 0.26, 1.83; p =0.010). There were no differences in monthly prevalence trends when benzodiazepines were grouped as short-acting or long-acting. Prior to the legislation (January 2016 to April 2017), there was a significant decline in monthly DDDs per benzodiazepine prescription but no significant change in monthly DDDs per Z-drug prescription. Over the period following introduction of the legislation (May 2017 to September 2019), no changes in the trends were observed in monthly DDDs per prescription for benzodiazepines or Z-drugs. Significant increases in monthly DDDs per benzodiazepine prescription were observed post-legislation for the younger age group across both genders, whereas no change in the trend was observed in the middle-aged and older age groups. Similar trends in monthly DDDs per Z-drug prescription were observed post-legislation when stratified according to gender and age group. The analysis involving DME-DDD showed similar trends.	The findings indicate that the new legislation did not have the anticipated impact on the prescribing of these medications at a population level whereby overall prescribing of both benzodiazepines and Z-drugs increased marginally during the post-introduction period.	0

NA - Not applicable. Martin, P. et al. measured the participants perceived risk from consumption of benzodiazepines.
Drug use improvements were qualitatively evaluated accordingly to each study results and key findings: 0 – None or worsening; 1 – Minor; 2 – Moderate improvements; 3 – Large improvements.

Appendix F

Summary of the appraisal of evidence using the MMAT tool (version 2018)

	SCREENING QUESTIONS		2. RANDOMIZED CONTROLLED TRIALS					3. NON-RANDOMIZED STUDIES				
Autor(s)	**S1. Are there clear research questions?**	**S2. Do the collected data allow to address the research questions?**	**2.1. Is randomization appropriately performed?**	**2.2. Are the groups comparable at baseline?**	**2.3. Are there complete outcome data?**	**2.4. Are outcome assessors blinded to the intervention provided?**	**2.5 Did the participants adhere to the assigned intervention?**	**3.1. Are the participants representative of the target population?**	**3.2. Are measurements appropriate regarding both the outcome and intervention (or exposure)?**	**3.3. Are there complete outcome data?**	**3.4. Are the confounders accounted for in the design and analysis?**	**3.5. During the study period, is the intervention administered (or exposure occurred) as intended?**
Crotty, M. et al.	Yes	Yes	Yes	Yes	Yes	No	Yes					
Salonoja, M. et al.	Yes	Yes	Yes	Yes	Yes	No	Yes					
Velert Vila, J et al. (1)	Yes	Yes	Yes	Yes	Yes	No	Yes					
Velert Vila, J et al.(2)	Yes	Yes	Yes	Yes	Yes	No	Yes					
Tannenbaum , Cara et al.	Yes	Yes	Yes	Yes	Yes	No	Yes					
Navy, H. J. et al.	Yes	Yes	Can't tell	Yes	Yes	No	No					
Jørgensen, V. R. K.	No	Yes						Yes	Yes	Yes	Can't tell	Can't tell
Dolan, C. et al.	Yes	Yes						Yes	Yes	Yes	Can't tell	Can't tell
Höebert, J. M.	Yes	Yes						Yes	Yes	Yes	Yes	Yes
Lang, P.O.	Yes	Yes						Yes	Yes	Yes	No	Yes
Reeves, Rusty	Yes	Yes						Can't tell	Yes	Yes	No	Can't tell
Clay, Emilie et al.	Yes	Yes						Yes	Yes	Yes	Can't tell	Can't tell
Martin, P. et. al.	Yes	Yes						Yes	Yes	Yes	Can't tell	Yes
Chen, Y. C.; Kreling, D. H	Yes	Yes						Yes	Yes	Yes	No	Yes
Rat, C. et al.	No	Yes						Yes	Yes	Yes	No	Yes
Rowntree, R. et al.	No	Yes						Can't tell	Yes	Yes	No	Yes
Bachhuber, Marcus A. et al.	Yes	Yes						Can't tell	Yes	Yes	No	Can't tell
Gemelli, Maria Grazia; Yockel, Katherine; Hohmeier, Kennetch C.	Yes	Yes						Yes	Yes	Yes	No	Yes
Mondiello, T.B.; Stutzman, L.A.	Yes	Yes						Yes	Yes	Yes	No	Can't tell
Furbish, Shannon M. L. et al.	No	Yes						Yes	Yes	Yes	No	No
Azermai, M. et al.	No	Yes						Yes	Yes	Yes	Can't tell	Yes
Badr, A.F. et al.	No	Yes						Yes	Yes	Yes	No	Yes
Cabelguenne, D. et al.	Yes	Yes						Yes	Yes	Yes	No	Can't tell
Mestres Gonzalvo, C. et. al.	Yes	Yes						Yes	Yes	Yes	No	Yes
Geka, M. et al.	Yes	Yes						Yes	Yes	Yes	Can't tell	Can't tell
Stoker, Lennart Jan et al.	Yes	Yes						Yes	Yes	Yes	Yes	Yes
Davidson, S; Thomson, C; Prescott, G.;	Yes	Yes						Yes	Yes	Yes	Can't tell	Yes
Cadogan, C.A.; Bradley, C.P.; Bennet, K.	Yes	Yes						Yes	Yes	Yes	Can't tell	Yes

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