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Use of hypnotics, sedatives and anxiolytics in relation to multimorbidity in 2009-2012

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UNIVERSITY OF ICELAND
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Notkun svefn- og kvíðastillandi lyfja í tengslum við fjölsjúkleika á árunum 2009-2012

Margrét Sif Sigurðardóttir

Lokaverkefni til meistaraprófs í lyfjafræði

Leiðbeinandi: Lárus Steinþór Guðmundsson

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ABSTRACT

Use of hypnotics, sedatives and anxiolytics in relation to multimorbidity in 2009-2012

Background: Hypnotics, sedatives and anxiolytics, used in treating insomnia, are more prescribed in Iceland than in any other Nordic country. Comparing them, the difference in the use of benzodiazepine related, Z-drugs is the most pronounced. Insomnia is often associated with chronic conditions like chronic pain and mental disorders and increases with age.

Objective: The objective of this study was to analyse the use of hypnotics, sedatives and anxiolytics in multimorbid patients with different mental and chronic pain diagnoses.

Methods: Data from Primary Healthcare of the Capital Area in Iceland and the Icelandic Medicine Registry was used in the analysis. The data covered patients seeking medical attention in the primary healthcare centres in the Capital area in the years 2009-2012. From the study population (n = 114,130) eight disease groups were created with different combination of mental and chronic pain diagnoses. The prevalence of Z-drug use and change in DDDs between years was examined.

Results: The highest prevalence of three-year Z-drug use was among multimorbid patients (13.3-41.1%). The prevalence increased with each additional chronic condition and was highest among patients with at least three chronic diseases. Being comorbid with mental disorders seemed to have more effect on increased Z-drug use than being comorbid with chronic pain condition. Defined daily doses (DDDs) of Z-drugs did not increase between years for patients filling a prescription for three consecutive years.

Conclusion: The prevalence of Z-drug use in multimorbid patients in Iceland is high. Even though the doses of Z-drugs did not increase between years, the majority of three-year Z-drug users in all disease groups were exceeding the recommended duration of treatment. Other treatment options for insomnia should be considered before using Z-drugs or benzodiazepine derivates long term and there should be more focus on treating underlying diseases in multimorbid patients.

ÁGRIP

Notkun svefn- og kvíðastillandi lyfja í tengslum við fjölsjúkleika á árunum 2009 til 2012

Bakgrunnur: Notkun svefn- og kvíðastillandi lyfja er meiri á Íslandi en á hinum Norðurlöndunum. Sér í lagi er notkun benzodiazepine-skyldra lyfja (Z-lyf) afgerandi meiri hér en í hinum löndunum. Margir glíma við svefnleysi samhliða öðrum krónískum sjúkdómum svo sem geðsjúkdómum og verkjum og ágerist það með hækkandi aldri.

Markmið: Að skoða notkun svefn- og kvíðastillandi lyfja meðal fjölveikra sjúklinga með áherslu á geð- og verkjagreiningar.

Aðferðir: Gögn frá Heilsugæslu höfuðborgarsvæðisins og lyfjagagnagrunni Embættis landlæknis voru notuð við vinnslu verkefnisins og náðu þau til allra þeirra sem leituðu til heilsugæslunnar á árunum 2009-2012. Úr þýðinu (n = 114.130) voru myndaðir átta sjúkdómaflokkar með tilliti til mismunandi samsetninga af geð- og verkjagreiningum. Algengi Z-lyfjanotenda og breytingar á skilgreindum dagskömmtum (DDDs) milli ára var skoðað.

Niðurstöður: Algengi sjúklinga með sögu um þriggja ára Z-lyfjanotkun var hæst meðal sjúklinga með fjölsjúkleika (13.3-41.1%). Algengið jókst með hverri viðbótargreiningu og var hæst meðal sjúklinga með þrjá króníska sjúkdóma eða fleiri. Algengi Z-lyfjanotkunar jókst meira þegar geðgreining bættist við fyrri greiningar en þegar verkjagreiningar bættust þar við. Skilgreindir dagskammtar af Z-lyfjum jukust ekki milli ára meðal sjúklinga sem leystu út lyf samfellt á þriggja ára tímabili og gilti það um rannsóknarþýðið í heild og alla undirhópa sem rannsakaðir voru.

Umræður: Algengi Z-lyfjanotkunar meðal fjölveikra sjúklinga er hátt á Íslandi. Jafnvel þótt skammtar hafi ekki aukist milli ára, var meðferðarlengd lengri en ráðleggingar segja til um hjá meirihluta þeirra sjúklinga sem höfðu sögu um þriggja ára Z-lyfjanotkun. Aðrir meðferðarmöguleikar við svefnleysi ættu að vera skoðaðir áður en langtíma meðferð er hafin á Z-lyfjum og benzodiazepine afleiðum og leitast við því að meðhöndla undirliggjandi sjúkdóma meðal fjölveikra.

LIST OF ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
ATC	Anatomical Therapeutic Chemical
CBT	Cognitive-behavioural Therapy
CNS	Central Nervous System
DDD	Defined Daily Dose
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
GAD	Generalized anxiety disorder
ICD-10	International Statistical Classification of Diseases, 10th revision
MDD	Major depressive disorder
PTSD	Post-traumatic stress disease
SD	Standard deviation
SmPC	Summary of Product Characteristics
SSRI	Selective Serotonin Reuptake Inhibitors
WHO	World Health Organization

Table of Contents

List of Figures

List of Tables

1 Introduction

1.1 Hypnotics, sedatives and anxiolytics

Hypnotics, sedatives and anxiolytics are widely used classes of drugs that cause depression of the CNS function. Many drugs can be used as CNS depressants but most recognized are the barbiturates and benzodiazepines, along with other chemicals like alcohol. Agents that depress the CNS cause drowsiness and a calming effect and are most commonly used as a sleeping aid (Brunton, Chabner, & Knollmann, 2011). In addition to pharmaceutical drugs, herbal preparations have been used for a long time as sedatives (Charles M Morin & Benca, 2012).

Hypnotics, sedatives and anxiolytics are often used as a sleeping aid and all have a similar function but are used in slightly different ways (Brunton et al., 2011). WHO classifies active substances by anatomical, therapeutic, pharmacological and chemical subgroups. Hypnotics and sedatives are classified together and include many different drug classes such as benzodiazepine derivatives, benzodiazepine related drugs, melatonin receptor agonist, barbiturates and many more (WHO Collaborating Centre for Drug Statistics and Methodology, 2018). In addition to being used as a sleeping aid, anxiolytics are a class of drugs used in the treatment of anxiety. Anxiety is a normal emotion but when it has debilitating impact on daily life, medication is often essential (Brunton et al., 2011). A variety of drug classes are helpful in the treatment of anxiety. Derivatives of benzodiazepine, diphenylmethane and azaspirodecanedione are among drugs classified as anxiolytics according to WHO (WHO Collaborating Centre for Drug Statistics and Methodology, 2018).

Hypnotics, sedatives and anxiolytics have been around for a long time. In the beginning of the 20th century a new drug was released on the market, barbital. Barbital belongs to a subclass of drugs called barbiturates, which have a sedative effect. About 50 drugs followed and were released to the market throughout the next six decades. Around 1940 phenytoin and trimethadione were discovered. They had more CNS selectivity and were less sedative than the barbiturates and

are now used in the treatment of epilepsy. A little later chlorpromazine and meprobamate were developed in the search for more selectivity. These drugs laid the foundation for the development of the first benzodiazepine, chlordiazepoxide. Many benzodiazepines, benzodiazepine derivatives and benzodiazepine-related drugs have reached the market since then (Brunton et al., 2011). Benzodiazepines became the most prescribed drug all over the world in the late 1970s and have since then somewhat maintained their popularity (Ashton, 2005). The benzodiazepine related drugs weren't introduced into clinical practice until the late 1980s (Hajak, Müller, Wittchen, Pittrow, & Kirch, 2003).

1.1.1 Benzodiazepine derivatives and related drugs

Benzodiazepines have various effects on the body. They are sedative, hypnotic, anticonvulsant, decrease anxiety, relax muscles and cause anterograde amnesia. The mechanism of action of benzodiazepines is through a $GABA_A$ receptor. Benzodiazepines work as positive allosteric modulators on $GABA_A$ receptors. These receptors consist of five subunits and when activated they cause an influx of chloride and inactivation of neurons (Brunton et al., 2011).

Whether benzodiazepine derivatives and benzodiazepine related drugs are used as a sedative, hypnotic or anxiolytic depends on the selectivity for the receptor and the half-life of the drug. Benzodiazepines with a shorter half-life are used in higher doses as a sleeping aid, while the ones with a longer half-life are used in smaller doses for anxiety or as an anticonvulsant (Brunton et al., 2011). Use of benzodiazepine derivatives and related drugs is often associated with education, age and gender. Females and less educated individuals are more likely to use benzodiazepines and the prevalence of use increases with age (Demyttenaere et al., 2008; Linnet et al., 2016).

For the majority of benzodiazepine derivatives and benzodiazepine-related drugs, the intended use is for a maximum 2-4 weeks and often a shorter period for the first prescription. To make the treatment better, patients should be informed about the short duration of the treatment before initiation. To prevent tolerance, intermittent dosing can be feasible (Medicines Management Team, Ipswich and East Suffolk CCG, 2016).

1.1.2 Benozodiazepines and related drugs dependence

It was not until the early 1980s that doctors noticed loss of efficacy over time among long-term benzodiazepine users and their subsequent need for higher doses. It was then that doctors were advised to prescribe benzodiazepines for short-term use and in the lowest therapeutic dose possible. Benzodiazepines meet all criteria for substance dependence that include an increase in dosage, tolerance, continued use despite of being aware of adverse effects and effort to stop, and withdrawal syndrome. Tolerance varies greatly between individuals and action. Tolerance is developed more quickly, for example, for a hypnotic effect than for anxiolytic effects (Ashton, 2005).

Most benzodiazepine-dependent patients are long-term users that are prescribed the same or similar dose repeatedly over the course of months or even years. A minority of benzodiazepine-dependent patients start on prescribed benzodiazepine and increase their doses excessively and may visit several doctors to get more of the medicine prescribed. Then there is a minority of people that use benzodiazepine as a recreational drug in combination with other drugs. The reason benzodiazepine is used as a recreational drug is to enhance the “high” and ease the withdrawal effects of stimulant drugs (Ashton, 2005).

When the hypnotics and more short-acting benzodiazepine-related drugs zopiclone and zolpidem were released to the market they were thought to be safer. The belief was that patients were less likely to suffer from dependence, development of tolerance and daytime sleepiness (Lader, Tylee, & Donoghue, 2009). There is not full consensus among researchers about the safety of benzodiazepine related drugs. A systematic review including a total of 58 case reports found that reported dependence was remarkably lower than for benzodiazepines used for insomnia (Hajak et al., 2003).

1.1.3 Benzodiazepines and related drugs withdrawal

Withdrawal syndrome follows long-term use of benzodiazepine. Symptoms of withdrawal can be mild or severe depending on duration of use and the dose, along with other factors. Some withdrawal symptoms are common to anxiety

states such as anxiety, insomnia, depression, poor concentration and memory, muscle pain, dizziness and tremor. Other symptoms are more specific to the withdrawal of benzodiazepines, including hallucinations, depersonalization, tinnitus, psychotic symptoms and numbness (Ashton, 2005).

According to protocols and studies, switching to equivalent doses of diazepam or other long-acting benzodiazepine with slow elimination can be beneficial when withdrawing from benzodiazepines (Zitman & Couvée, 2001; Ashton, 2002). In a 2001 study carried out in the Netherlands depressed patients and long-term benzodiazepine users were switched to equivalent doses of diazepam and half of the patients were given SSRI antidepressants and the other half were given a placebo. A total of 63% of the patients reported withdrawal symptoms and 68% of the patients successfully tapered off benzodiazepine use. The use of SSRIs had little effect on the success rates of tapering off but decreased anxiety symptoms in the withdrawal phase rather than the depression symptoms. Furthermore, this study showed that not all long-term benzodiazepine users are willing to try to discontinue use of the drug (Zitman & Couvée, 2001).

1.1.3.1 Benzodiazepines related, Z-drugs (N05CF)

Benzodiazepine related drugs are also known as Z-drugs and include zopiclone, zolpidem and zaleplone. Zaleplon is not sold in Iceland. Z-drugs are the most commonly used benzodiazepine drugs in Iceland (Nomesco, 2017). Z-drugs are relatively short acting with a half-life ranging from 1-6 hours. Zolpidem has the longest half-life of the Z-drugs and is less likely to cause wakening in the middle of the night but instead can lead to more daytime impairment (Charles M Morin & Benca, 2012).

The National Institute for Health and Care Excellence (NICE) guideline for use of zaleplone, zolpidem and zopiclone advises that Z-drugs are only to be prescribed short-term for the management of severe insomnia interfering daily life (NICE, 2004). According to SmPC the duration of treatment with zopiclone and zolpidem is not supposed to exceed 4 weeks. Table 1.1 includes the drugs sold in Iceland that belong to the ATC class N05CF (Sérlyfjaskrá, 2018d, 2018e).

Table 1.1: Drugs (P.O.) in the ATC class N05CF available in Iceland

ATC – class	Drug
N05CF01	Zopiclone
N05CF03	Zolpidem

1.1.3.2 Benzodiazepine derivatives (N05CD)

Drugs in the class N05CD are benzodiazepine derivatives and are used as hypnotics and sedatives in sleeping disorders. The half-life of the drugs in this class varies widely. Some are short acting while others have a long onset of action and elimination. Drugs in this class are intended for short-term use and should not exceed 2-4 weeks according to SmPC. Recommended duration of treatment depends on which drug is being used. All drugs available in Iceland that belong to the ATC class N05CD can be seen in table 1.2 (Sérlyfjaskrá, 2018a, 2018b, 2018c).

Table 1.2: Drugs (P.O.) in the ATC class N05CD available in Iceland

ATC – class	Drug
N05CD02	Nitrazepam
N05CD03	Flunitrazepam
N05CD05	Triazolam

1.1.3.3 Benzodiazepine derivatives (N05BA)

Drugs in this class are benzodiazepine derivatives and are classified as anxiolytics. Their intended use is for the treatment of anxiety disorder, situational anxiety and panic disorders. Because of their sedative and hypnotic effects, like other benzodiazepine derivatives, they are often used in the treatment of sleeping disorders. They are more long acting and are given in lower strength than other benzodiazepines. The half-life of the drugs ranges from 8 hours for oxazepam to

43 hours for diazepam. Drugs in this class can have a rapid onset and are therefore desirable in cases of abuse. Benzodiazepines are useful and often preferred over other anxiolytics in anxiety treatment because they are effective for acute treatment as well as chronic treatment (Brunton et al., 2011). Benzodiazepine derivatives can be especially useful in treating insomnia that is associated with anxiety (Medicines Management Team, Ipswich and East Suffolk CCG, 2016). Duration of treatment varies between drugs but the recommended duration is usually longer for drugs in this class as they are not only intended for insomnia but also to assuage anxiety. Duration of treatment for all drugs in this class should not exceed 8-12 weeks according to SmPC and the dose should be reduced in this period. Oxazepam should not be used for a longer time than 4 weeks if being used to treat insomnia. Table 1.3 lists all the orally administered drugs in the ATC class N05BA available in Iceland (Sérlyfjaskrá, 2017a, 2018f, 2017b, 2017c, 2016).

Table 1.3: Drugs (P.O.) in the ATC class N05BA available in Iceland

ATC – class	Drug
N05BA01	Diazepam
N05BA02	Chlordiazepoxide
N05BA04	Oxazepam
N05BA08	Bromazepam
N05BA12	Alprazolam

1.1.3.4 Side effects

Even though benzodiazepines are considered relatively safe and safer than their predecessors there are still some serious side effects. Benzodiazepines cause little effect on respiration in a normal patient but can cause serious respiration depression in higher doses and when taken with another CNS depressant like alcohol or other drugs. Misuse of benzodiazepines is lower than of most other sedatives and hypnotic agents and is more often misused with another drugs (Brunton et al., 2011). When taken with opioids, the risk for drug interaction and adverse events increases. These adverse events include increased sedation, falls

and respiratory depression (Nielsen et al., 2015). Another problem that benzodiazepines can cause is the increased risk of falls in patients and especially in the elderly. Side effects appear most commonly after prolonged use. Longer than recommended duration of treatment with benzodiazepines result in tolerance and dependence. The need for larger doses and loss of effect becomes apparent. Discontinuation after prolonged use can result in some serious withdrawal symptoms. Other known side effects include confusion, memory loss and even insomnia (Medicines Management Team, Ipswich and East Suffolk CCG, 2016).

1.1.4 Use in Iceland

More is sold of drugs in the three above-mentioned classes (ATC: N05CD, N05CF and N05BA) combined in Iceland than in any other Nordic country. The amount of drugs sold is measured in DDD/1000 inhabitants per day. From 2005 to 2016 Iceland had the highest selling rates by far in the Z-drug group (ATC: N05CF) but had more similar selling rates to the Nordic countries for the benzodiazepine derivatives (Nomesco, 2017).

From the beginning of 2009 until the end of 2012, 13.9% of the Icelandic population was prescribed hypnotics/anxiolytics, of whom 10.1% were men and 17.5% women. The number of prescriptions increased with older age with a small drop for the oldest age group. In 2011, 56% of patients receiving their first prescription for hypnotic/anxiolytic had one prescription only, whereas 11% received 5 prescriptions or more (Linnet et al., 2016).

The sale of benzodiazepine derivatives (N05CD) and benzodiazepine-related drugs (N05CF) in Iceland and other Nordic countries from 2005 to 2016 is shown in figure 1.1. As can be seen in the figure, drugs in ATC class N05CF are much more often prescribed than drugs in ATC class N05CD and are also much more often prescribed in Iceland than in any other Nordic country (Nomesco, 2017).

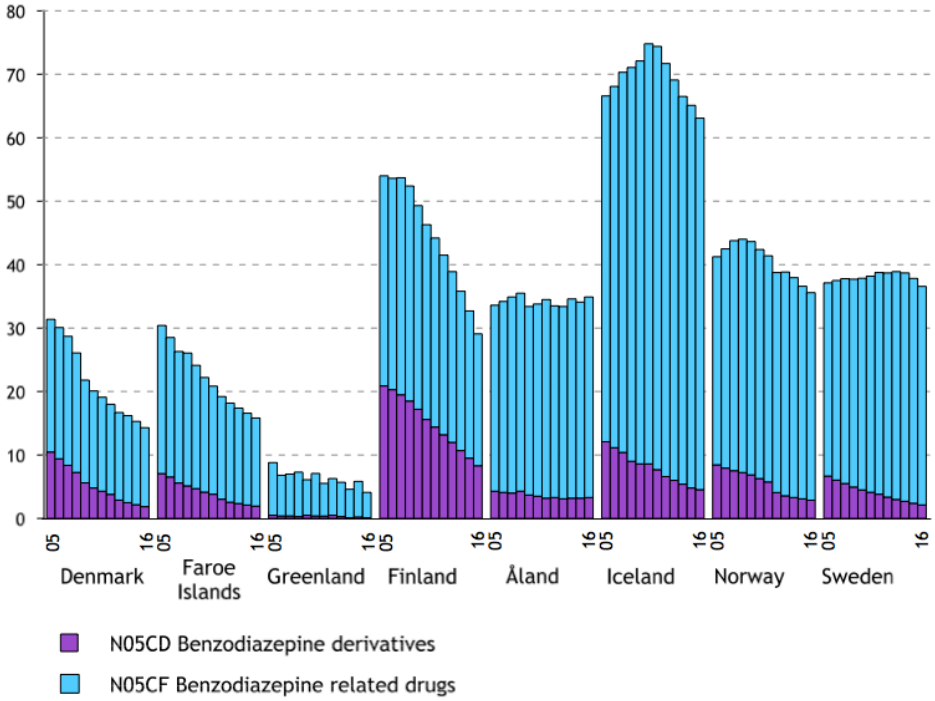

Figure 1.1: The sale of benzodiazepine derivatives (ATC-N05CD) and benzodiazepine related drugs (ATC-N05CF) DDD/1000 inhabitants/ per day in the Nordic countries from 2005-2016 (Nomesco, 2017)

1.2 Insomnia

Insomnia is the inability to sleep properly and the symptoms are often described as either lack of quality of sleep or sleep of short duration. Difficulty falling asleep, waking up too early or in the middle of the night, daytime fatigue and mood disturbances are all signs of insomnia (Charles M Morin & Benca, 2012). Insomnia is not always a chronic problem as it can also be situational or acute (C. M. Morin, LeBlanc, Daley, Gregoire, & Mérette, 2006). Many classification criteria for insomnia exist but are not always used by doctors when diagnosing insomnia and prescribing hypnotics (Leger, Guilleminault, Dreyfus, Delahaye, & Paillard, 2000). Insomnia can be classified as primary and secondary insomnia where primary insomnia is not a direct result of a medical disorder or substance use, whereas secondary insomnia is. A minority of those suffering from any form of insomnia have primary insomnia, but it is more frequent in young adults (Edinger & Means, 2005). Sleep disorders in various forms are classified as a mental illness by the ICD-10 classification but most often goes undiagnosed (World Health Organization, 2016).

The prevalence of insomnia may vary between countries and by how insomnia is measured. DSM-IV stands for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, and provides the criteria sometimes used to diagnose insomnia. Studies carried out to estimate the prevalence of insomnia use different methods to measure the presence of insomnia in participants. Some studies use the DSM-IV criteria which result in a lower prevalence while others use a self-reporting questionnaire where the prevalence is often much higher (Sivertsen, Krokstad, Øverland, & Mykletun, 2009).

A Norwegian study measured the prevalence of insomnia in a county in Norway. Of the total sample 13.5% of the participants reported insomnia symptoms. Those with occasional symptoms of insomnia were not considered to suffer from insomnia. The prevalence increased with older age and more prominently in women. Insomnia was also much more common among less educated individuals or twice as prevalent (Sivertsen et al., 2009). Multimethod research was carried out to shed light on the prevalence and disability burden of mental disorders in Europe. Information from eight studies was used to estimate the prevalence of insomnia that turned out to range from 6-12% (Wittchen et al., 2011).

In a Canadian study with a randomly selected sample from Quebec, about one-tenth of the population suffered from insomnia while 25% of the population were dissatisfied with their sleep. The information was obtained through a telephone survey (Charles M. Morin et al., 2006). Two studies from the UK and Canada showed that 69% and 74%, respectively, of patients with insomnia had persisting insomnia 1 year later, and 46% three years later in the Canadian study (Charles M. Morin, Bélanger, et al., 2009; Morphy, Dunn, Lewis, Boardman, & Croft, 2007)

Multiple studies have shown that women are more likely to develop insomnia than men (Buysse et al., 2008; Sivertsen et al., 2009). A French study from 2000 used questionnaires to gain information about the prevalence of insomnia in the French population. Women were much more likely to suffer from either mild or severe insomnia in all age groups. As the criteria for insomnia were narrowed, the

greater was the relative difference between the prevalence for men and women (Leger et al., 2000). According to the multimethod research mentioned above, twice as many women as men suffered from insomnia (Wittchen et al., 2011).

1.2.1 Prevalence in Iceland

A questionnaire was sent out in 2015 in Iceland for a study about sleep habits. A total of 8,220 people received the questionnaire with 1,219 people responding. This study presented similar results to other studies and showed that women are more likely to suffer from insomnia, 8.7% of the women against 4.8% of the men. More women than men answered the questionnaire and the overall prevalence of insomnia turned out to be 7.1% (Thorarinsson, 2016).

1.2.2 Treatment

There is no single magic cure for insomnia and the same treatment is not suitable for everyone. Pharmacotherapy with benzodiazepine and cognitive-behavioural therapy (CBT) are two of the best-known therapies for insomnia patients.

1.2.2.1 Drug therapy

When using drug therapy, the duration and frequency of dose can vary widely between patients. Follow-up for effectiveness and control of side effects is important and should be done regularly by the doctor. Patients should be prescribed the lowest effective dose to avoid side effects. It is recommended for most patients to have intermittent dosing or use the drug irregularly to avoid risk of tolerance or daytime sedation. Some patients, however, will need long-term treatment or nightly dosing (Charles M. Morin & Benca, 2012).

1.2.2.2 Cognitive behavioral therapy (CBT)

The “mechanism” of insomnia is not fully understood but it is known that the condition is maintained by cognitive and behavioural factors. Because of this, behaviour therapies are important (Edinger & Means, 2005). CBT uses psychological and behavioural procedures and education on sleep hygiene to treat insomnia. These procedures involve, for example, sleep restriction, relaxation and cognitive strategies (Charles M. Morin & Benca, 2012).

Treatment with benzodiazepines is sometimes preferred in short-term management while CBT might be more helpful in long-term management. Because of these different features of pharmacotherapy and CBT, these therapies in combination could be desirable (Charles M. Morin & Benca, 2012). Not everyone agrees on the benefits of combination therapy. One study from 2005 looking at CBT for primary insomnia showed better sleep improvements at the end of a 2-year follow-up period with only CBT than combined pharmacotherapy and CBT (Edinger & Means, 2005). A study from Quebec, Canada, showed that in extended treatments, discontinuation of pharmacotherapy while still receiving CBT might be more beneficial than continuation of combination therapy (Charles M. Morin, Vallières, et al., 2009).

CBT has been shown to improve sleep and decrease pain in osteoarthritis patients with co-morbid insomnia (Vitiello, 2009). In a randomized, controlled pilot study, a higher rate of remission of depression and insomnia was seen with combination therapy of antidepressants and CBT in patients with major depressive disorder (MDD) and co-morbid insomnia (Manber et al., 2008).

1.2.2.3 Implementing CBT

Individual sessions of CBT for primary insomnia patients are the most common and known form of CBT and require trained sleep specialists. CBT is therefore time consuming and costly to begin with but could be cost-effective in the long term as CBT is more likely to show long-term benefits than pharmacotherapy. Since there is a lack of trained sleep specialists, healthcare professionals could be trained to administer CBT to patients. Group sessions, self-help interventions via the Internet and shorter individual sessions are also some alternative delivery methods of CBT that could be considered (Edinger & Means, 2005).

1.3 Multimorbidity

Many patients suffer from two or more chronic diseases and the term that describes this is multimorbidity (van den Akker, Buntinx, Metsemakers, Roos, & Knottnerus, 1998). Another term, comorbidity, is used to describe a disease

additionally developed beyond the index disorder, with the main focus on the index disorder (Marengoni et al., 2011).

Infectious diseases were the leading health care issue and cause of death until the twentieth century when life expectancy increased and people started to live longer. Because of this longevity people now develop more diseases in old age. Chronic conditions have replaced the previous high incidence of infectious diseases and are now the modern dominant health care burden (Marengoni et al., 2011).

Increasing age, a history of multiple previous diseases and less education are risk factors for multimorbidity and it has been shown to have an effect on disability, health care cost and quality of life (Marengoni et al., 2011).

1.3.1 Multimorbidity in Iceland

A 2016 study of medical records from Primary Health Care of the Capital Area in Iceland showed the prevalence of multimorbidity. The prevalence of multimorbidity in Iceland was found to be lowest in the youngest population (1-19 years old) with 10% suffering from more than one disease. The prevalence increased steadily with age and peaked in the age group 70-79 with 68% prevalence, and then began to fall again after that. In total, 35% of the population was considered to have multiple diseases, whereas 18% of the total population only had one chronic disease. As can be expected, the number of patients suffering from only two diseases was most prevalent among the multimorbid and the number of patients decreased steadily with each extra chronic disease (Linnet et al., 2016).

1.3.1.1 Multimorbidity and the use of hypnotics in Iceland

From the same Icelandic prevalence study mentioned above, the following information was obtained. A total of 85% of patients prescriped hypnotics/anxiolytics in Iceland were multimorbid and 15% suffered from one or no chronic disease. Approximately one third of those multimorbid were prescribed a hypnotic/anxiolytic while only 3% of those not multimorbid were prescribed the same drugs. From this information it can be concluded that multimorbid patients are much more likely to be prescribed anxiolytics/hypnotics. As the number of

chronic diseases within the same patient increases they are given a proportionately increased number of prescriptions. A total of 93% of the anxiolytic drugs reported in the study were benzodiazepines. For the hypnotic drugs, 11% were benzodiazepines and 88% Z-drugs (Linnet et al., 2016).

Figure 1.2 shows the number of patients described hypnotics, sedatives or anxiolytics in relation to age and how many chronic conditions the patients were suffering from. As mentioned earlier and can be seen from the figure, those suffering from multimorbidity are much more likely to be prescribed hypnotics, sedatives or anxiolytics (Linnet et al., 2016).

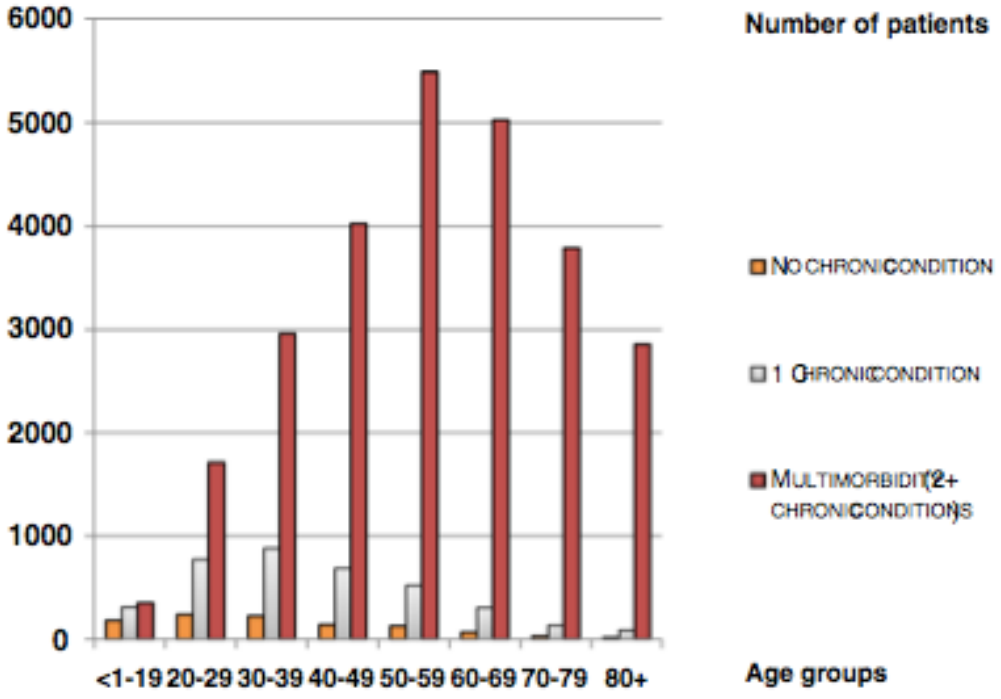

Figure 1.2: Number of patients prescribed hypnotics, sedatives or anxiolytics stratified by age and number of chronic conditions (Linnet et al., 2016)

1.4 Chronic pain

Chronic pain is a broad term used to describe various symptoms caused by varous diseases or conditions. Chronic pain has been defined in many ways but it can be explained as a constant pain that lasts for a long time or longer than expected (Manchikanti et al., 2009). Sometimes it is defined as a pain lasting for at least 6 months and regular experiences of moderate to severe pain (Breivik,

Eisenberg, & O'Brien, 2013). Causes of chronic pain can be, for example, lower back pain, arthritis, trauma, spinal fractures, migraine headaches, nerve damage or other unknown cause. In a study with data from several countries in Europe, not including Iceland, the prevalence of chronic pain in the population ranged from 12-30% for various countries (Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006).

An Icelandic study from 2007 measured the prevalence of chronic musculoskeletal pain from a random sample in the Icelandic population. The prevalence was measured with a questionnaire and turned out to be 19.9%, or 15.2% among the men and 24.7% among the women. Chronic back pain was the most prevalent chronic musculoskeletal pain measured with a prevalence of 16.2% (Guðmundsson & Magnúsdóttir, 2011).

1.4.1 Chronic back pain

Chronic back pain includes lower back pain, neck pain, lumbago, pain in the thoracic spine, unspecified back pain, and other disorders relaited to the back (World Health Organization, 2016).

Back pain is a very common condition among adults. In a large WHO study from 1998, patients from 15 general health care centres in 14 countries all across the world participated. Primary care patients were surveyed, and 22% reported chronic pain of which 48% suffered from back pain (Gureje, Korff, Simon, & Gater, 1998). Another study showed that back pain was more common in people over 45 years old and in women (Manchikanti et al., 2009). A 1992 study was carried out to develop and evalutate pain severity. Patients with back pain were more likely to grade their pain as severe (high disability) than patients with temporomandibular disorders (TMD) pain or headache (Von Korff, Ormel, Keefe, & Dworkin, 1992). From the Australian study mentioned above, past use of benzodiazepine and chronic neck and back pain had a higher association (OR (95% CI) = 1.56 (1.14–2.13)) than other chronic pain conditions observed (arthritis, headache, visceral pain, fibromyalgia) (Nielsen et al., 2015).

1.4.2 Musculoskeletal problems other than chronic back pain

Many disorders are included in musculoskeletal problems other than chronic back pain such as polyarthritis, arthropathies, acquired deformation of limbs, disorder of ligament, joint pain, scoliosis, spondylopathies, myositis, disorders of muscles and tendon, soft tissue disorders, shoulder lesions and osteomalacia (disorders related to bones) (World Health Organization, 2016).

A Korean study from 2015 analysed almost 500 patients in a university hospital in Korea. The goal was to examine insomnia in chronic lower back pain patients. Insomnia was reported by 43% of the patients, and 20% of the patients with chonic lower back pain also reported additional musculoskeletal pain such as pain in the shoulders, neck, arms and joints. Of the patient data collected, comorbidity with musculoskeletal pain other than low back pain was found to be by far the strongest risk factor for insomnia in patients with chronic lower back pain with an odds ratio of 8.074 (95% CI 4.250 - 15.339) (Kim et al., 2015).

1.4.3 Treatment of chronic pain

It has preveously been stated that chronic pain conditions are relatively common in the modern world. Despite being a big burden on the society it is often inappropriately or undertreated. Better pain management and pain education to doctors is important and could lead to better public health and less indirect socioeconomic costs (Breivik et al., 2013). Meta-analysis from 2013 suggests that there is a positive association between pain related fear and disability. Focusing on treatment of pain related fear could be valuable in treating disability related to pain (Zale, Lange, Fields, & Ditre, 2013).

A treatment option summary for chronic pain from the Swedish Council on Health Technology Assessment can be seen in table 1.4 (Swedish Council on Health Technology, 2006).

Table 1.4: Treatment options for chronic pain (Swedish Council on Health Technology, 2006)

Treatment	Example
Drugs	Paracetamol, COX-2 inhibitors, other NSAIDs, amitriptyline, tricyclic antidepressants, opioids, carbamazepine, capsaicin
Cognitive Behavioural Therapy	Results in better social and physical functioning
Multimodal Rehabilitation	Combination of psychological interventions and physical activity, physical exercise or physical therapy
Medical Intervention	Spinal cord stimulation, radiofrequency denervation, physical activity, relaxation, biofeedback, massage, manipulation, physical therapy and orthosis active, specific and professionally supervised exercise
Acupuncture	Western acupuncture
Other	Occlusal splints, balneotherapy

1.4.4 Chronic pain and insomnia

Symptoms of insomnia are common in patients with chronic pain conditions from various causes. Self-reporting studies show that from 50% to as high as 88% of patients with chronic pain reported some dissatisfaction with their sleep quality (Pilowsky, Crettenden, & Townley, 1985; Atkinson, Ancoli-Israel, Slater, Garfin, & Gillin, 1988).

Prevalence of sleep disturbances can vary by type of pain condition and are more common is some types (Michael T. Smith & Haythornthwaite, 2004). Pain not only affects sleep but can negatively affect quality of life, both mental and physical. Chronic pain can affect social interactions and family life (Dueñas, Ojeda, Salazar, Mico, & Failde, 2016).

Chronic pain can affect quality of sleep which can in turn delay healing of the pain. Figure 1.3 shows the relationship between chronic pain and insomnia and the vicious cycle it can lead to (Meskill, 2015).

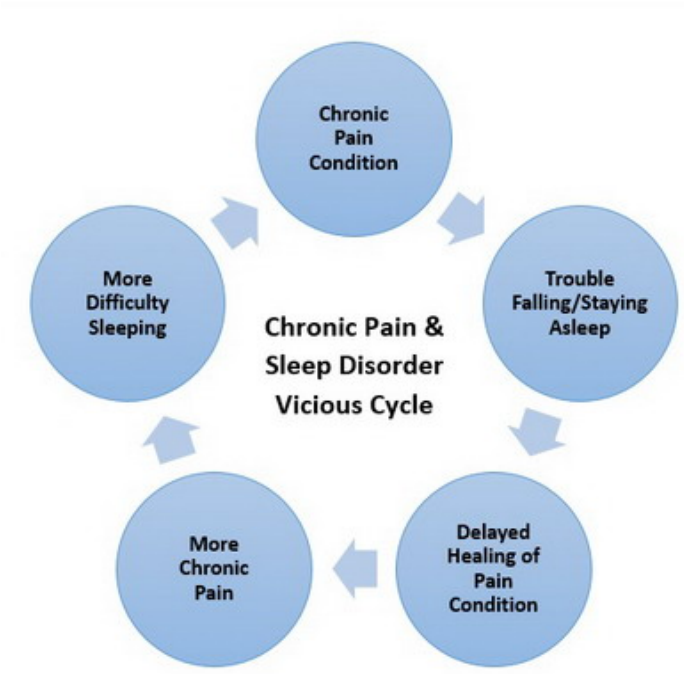

Figure 1.3: Vicious cycle of chronic pain and insomnia (Meskill, 2015)

1.4.5 Chronic pain and benzodiazepines and related drugs treatment

Hypnotics are often used in treatment of patients with chronic pain who also suffer from sleeping disorders. The drug treatment decreases symtoms of insomnia but doesn't reduce the pain itself. Some drugs that are not prescriped for primary insomnia are used in patients also suffering from chronic pain (Charles M. Morin & Benca, 2012). Australian study used information derived from local pharmacies to describe patterns of benzodiazepine use in chronic noncancer patients using opiods. 33% of the participants reported use of benzodiazepine in the last month while daily intake was reported by 17%. Patients taking benzodiazepines on a daily basis appeared to experience more severe pain that interfered with daily life. There was an association between benzodiazepine use and less confidence and participation in social life and work. These patients also had higher frequency of mental health problems, substance use disorders and use of antidepressant and antipsychotic medications (Nielsen et al., 2015).

1.5 Mental health problems

Mental health problems represent wide group of diseases. Examples of diseases that fall under the category are anxiety, addictions, schizophrenia, bipolar, depression and anorexia nervosa (World Health Organization, 2016).

A study was made in 2009 in Iceland to estimate the prevalence of mental disorders. Participants from three age groups answered a questionnaire and a diagnostic interview. Only 52% of those asked to take part participated and the lifetime prevalence turned out to be 49.8% of any ICD-10 disorder (Stefánsson & Líndal, 2009). Statistics from the USA from 1994 showed that around 50% of participants from the age 15-54 reported at least one lifetime mental disorder (Kessler et al., 1994).

A 2005 study carried out in the United States used DSM-IV criteria to estimate the 12-month prevalence of anxiety, mood, impulse control, and substance disorders. Anxiety disorders turned out to be the most prevalent DSM-IV disorder affecting 18.1% of the population. Then came mood disorders and impulse disorders with a prevalence of 9.5% and 8.9%, respectively. Major depression and bipolar disorders were included in the definition of mood disorders and conduct disorders and ADHD in impulse disorders. Only 3.8% suffered from substance disorders and 26.2% from other diseases. Even though anxiety disorders were the most common mental disorders, mood disorders had the highest rate of serious cases. Severity was also related to comorbidity with two or more mental disorders (Kessler, Chiu, Demler, & Walters, 2005).

A WHO study from 1995 was designed to research psychological problems across the world. Patients from many health care centres around the world participated and the results showed that the prevalence of psychological problems between counties and cultures varied greatly. The prevalence of diagnosis of mental disorder was lowest in Asia and highest in Europe and South America with an average prevalence of 23.2%. The variation was due to many different factors. However, what the countries had in common was the common form and burden of the syndromes (Sartorius, Ustün & World Health Organization, 1995).

1.5.1 Mental health and insomnia

Figure 1.4 shows the effect insomnia can have on the body. Stress, mental disorders and pain can be related to insomnia and can all affect each other. Polypharmacy is a possible consequence of these symptoms (Badre, 2014).

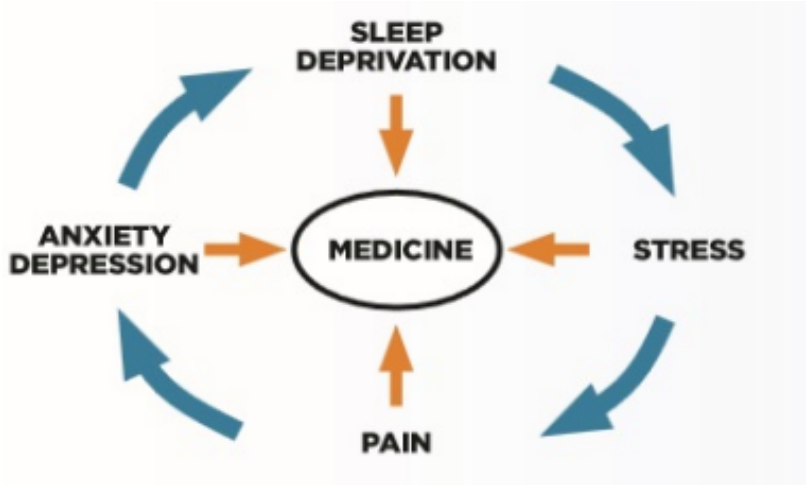

Figure 1.4: Vicious cycle of insomnia (Badre, 2014)

In a study examining insomnia and mental disorder around 25% of those suffering from insomnia had a history of mental disorder and around 50% were currently suffering from a mental disorder. Of those who did not have insomnia, only 8% had a history of mental disorder. The study also showed that having a diagnosis of two mental disorders was associatied with having more severe insomnia than having only one mental disorder. When looking at the relationship between insomnia and anxiety and those suffering from both, the two criteria most frequently developed simultaneously or the anxiety developed first (Ohayon & Roth, 2003).

Boundaries between insomnia and psychiatric disorders can sometimes be unclear so it is not always obvious what is causing certain symptoms. In recent studies the relationship between psychiatric and sleeping disorders is considered to be bi-directional, rather than sleeping disorders being a symptom of psychiatric disorders (Krystal, 2012).

Psychiatric disorders are a wide group of diseases and the effect they have on sleep varies by disease. A sleep problem is one of the diagnostic criteria for most psychiatric disorders. Major depressive disorder (MDD), bipolar disorder, post-traumatic stress disease (PTSD) and generalized anxiety disorder (GAD) all share a common core feature which is a change in sleep patterns. Schizophrenia does not share this core feature, but a sleep problem is still prevalent in schizophrenia patients. Half of the patients with generalized anxiety disorder have difficulty staying or falling asleep and patients with PTSD sleep less than the general population. Sleep disturbance among alcoholics, both abuse and dependence alcohol use, is extremely common and not only limited to the perioids of alcohol consumption. On the other hand, it has also been shown that sleep disturbance can increase the risk of psychiatric disorder. Those suffering from insomnia are more likely to develop depression (MDD) or anxiety (GAD) than those not suffering from any sleep problems (Krystal, 2012).

1.5.2 Mental health and benzodiazepines and related drugs treatment

According to a study from five Europe countries, a majority of those using benzodiazepines had been suffering from depression or anxiety in the preceding 12 months. Antidepressants and benzodiazepine derivatives or related drugs were commonly prescribed together. Around 40% of those using an antidepressant were also using benzodiazepine (Demyttenaere et al., 2008).

1.6 Insomnia, mental health and chronic pain

Insomnia is associated with many different diseases and conditions. However, it can be difficult to estimate association such as of chronic pain and insomnia because depression is common among insomnia patients and it could be explained by the depression and not by the insomnia. According to the Norwegian study also mentioned above, insomnia had the strongest association with pain conditions of uncertain etiology and mental conditions. This was followed by association with chronic pain. The association was still significant when adjusting for confounders, mainly comorbidities (Sivertsen et al., 2009).

From the Australian 2015 study mentioned earlier, past use of benzodiazepine among patients with chronic pain was associated (OR (95% CI) = 2.98 (2.16–4.12)) with a history of a mental health condition (Nielsen et al., 2015). One study showed that those suffering from chronic widespread pain were more likely to develop mental disorders, with an odds ratio of 3.18 (95% CI 1.97–5.11) (Benjamin, Morris, McBeth, Macfarlane, & Silman, 2000).

A 2008 study focused on chronic pain conditions in developed and developing countries. When looking at the countries resembling Iceland the mean prevalence of depression/anxiety patients was 19.5%, and 12.8% were comorbid with chronic pain. The countries selected to calculate the average prevalence were the Netherlands, Germany, Belgium and France (Tsang et al., 2008).

Figure 1.5 shows the number of patients prescribed hypnotics, anxiolytics or sedatives in Iceland by the most common diagnosis and either one time use, 2-4 times use or regular use (5 prescriptions or more). From the graph it can be seen that most of the patients prescribed hypnotics, anxiolytics or sedatives were multimorbid with pain-related and a mental diagnosis. The combined number of patients prescribed hypnotics, anxiolytics or sedatives who only had one diagnosis, mental or pain related, was still much lower than with those multimorbid with pain related and a mental diagnosis (Linnet et al., 2016).

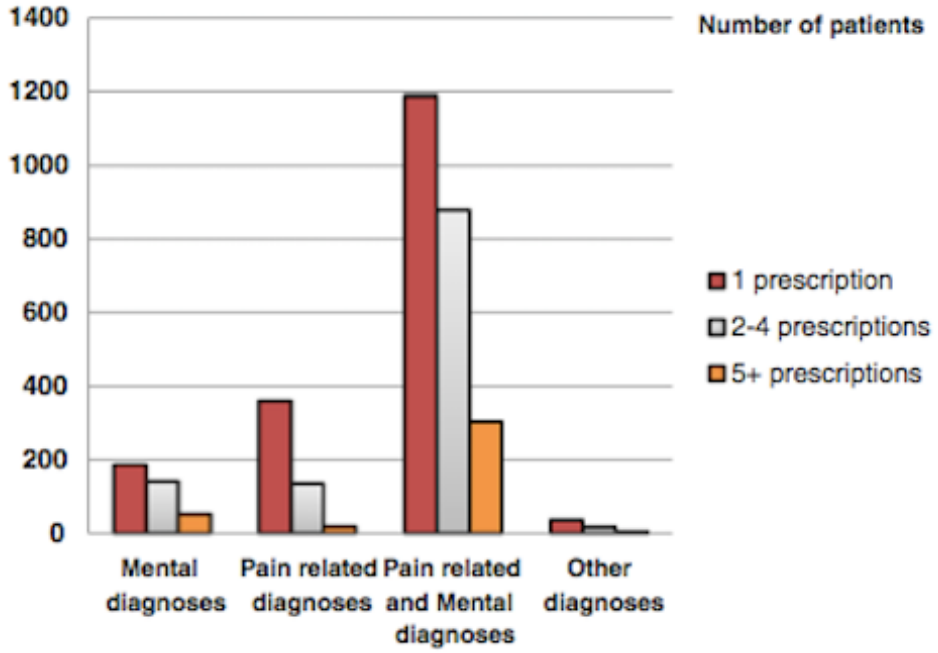

Figure 1.5: Number of patients prescribed hypnotics, anxiolytics or sedatives in Iceland by the most common diagnosis (Linnet et al., 2016)

2 Objectives

The objective of this study was to analyse the use of hypnotics, sedatives and anxiolytics in multimorbid patients with different mental and chronic pain diagnoses. Prevalence and change in defined daily doses (DDDs) of three-year Z-drug use was examined using data collected from Primary Healthcare of the Capital Area in Iceland and the Icelandic Medicine Registry. Distribution of Z-drug use was also observed in regard to gender and age.

Research questions:

What is the prevalence of three-year consistent use of hypnotics, sedatives and anxiolytics in multimorbid patients with different mental and chronic pain diagnoses?

Do defined daily doses (DDDs) of Z-drugs increase over the three years under study?

3 Methods

3.1 Study population

Data was collected from Primary Healthcare of the Capital Area in Iceland, which includes Reykjavík and its bordering towns, and the Icelandic Medicine Registry and used in the analyses carried out in this study. The data covered patients seeking medical attention in the primary healthcare centres in the capital area in 2009-2012. Subjects not registered in Iceland, those under 10 and over 79 years old were excluded from the study. Subjects that died during the first 3 years, subjects with intermittent use and subjects that entered after 2009 were also excluded from the study. Intermittent users were defined as patients filling a prescription for only one or two years. The remaining number of subjects (n = 114,130) made up the study population. The inclusion and exclusion critera for the study population are explained in a flow chart (figure 3.1). The personal identity for subjects was not revealed in the data. After the data was collected the unique personal identifier (ID) for each subject was encrypted.

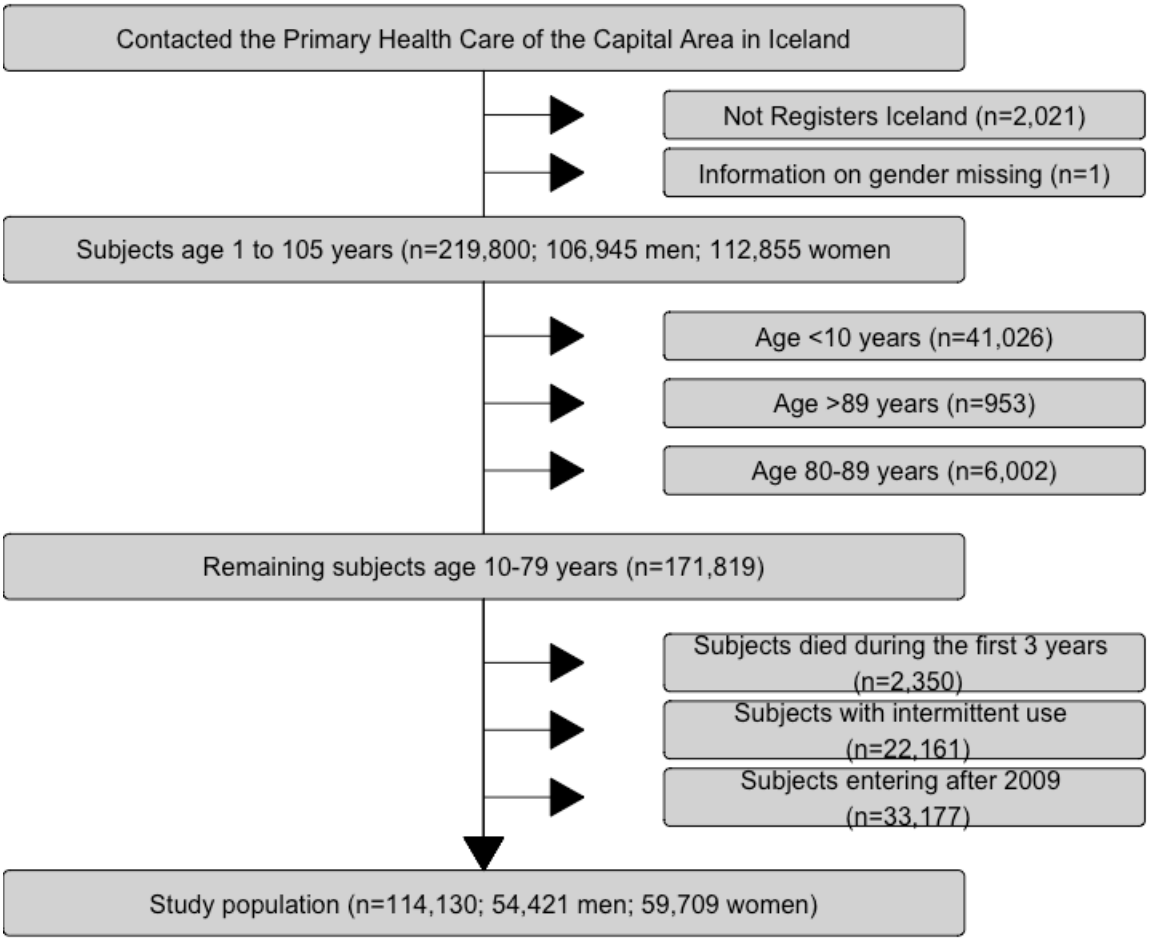

Figure 3.1: Flow chart of participants included in analysis

3.2 Data analysis

The data contained information about benzodiazepine derivative and Z-drug (benzodiazepine related) use, both the defined daily doses (DDDs) for each year and duration of use in years for each drug class. Furthermore it contained information about patient's diagnoses covering the 25 chronic disease variables present in the data. Patients could be diagnosed as having no, one or more diseases. The prescriptions of hypnotics, anxiolytics and sedatives were linked to the diagnoses in the data for each patient. Those with more than two diagnoses were also marked as multimorbid in the data. Variables for age and gender are present in the data, along with date of first prescription. The study population was summarized with descriptive statistics.

3.2.1 Drug use

The data contained information about the total DDDs for every patient in each year, during a three year period in 2009-2012, where patient had used Z-drugs and/or benzodiazepines (ATC- N05CD, ATC-N05CF, ATC-N05BA). The focus of the present study was on patients filling at least one prescription every year during three consecutive years. The DDDs in the data are based on prescription filled in pharmacies and the full dose is assumed to be used. Benzodiazepine use among Z-drug users was also analysed. An overview of all drugs included in the two drug classes is shown in table 3.1 for Z-drugs and table 3.2 for benzodiazepine derivatives. Two of these drugs have been withdrawn from the market since the data was recorded in 2009-2012.

Table 3.1: Z-drugs

ATC class	ATC code	Active ingredient
N05CF	N05CF01	Zopiclone
	N05CF02	Zolpidem

Table 3.2: Benzodiazepine derivatives

ATC class	ATC code	Active ingredient
N05BA	N05BA01	Diazepam
	N05BA02	Chlordiazepoxide
	N05BA04	Oxazepam
	N05BA06	Lorazepam*
	N05BA08	Bromazepam
	N05BA09	Clobazam*
	N05BA12	Alprazolam
N05CD	N05CD01	Flurazepam
	N05CD02	Nitrazepam
	N05CD03	Flunitrazepam
	N05CD05	Triazolium
	N05CD08	Midazolam

*Withdrawn in Iceland

3.2.2 Chronic diseases

In the study the focus was on patients diagnosed with one, two or all out of the three disease groups mentioned in the introduction section, mental health problems, chronic back pain and other chronic musculoskeletal problems. The three diseases were selected because they have been shown to be associated with Z-drug and benzodiazepine use (Linnet et al., 2016). No distinction was made between individual diseases within these three disease groups when analysing the data. ICD-10 codes for every disease group are listed in table 4.1. In comparison to the disease groups a group consisting of patients with no diagnosis and another group including everyone in the data were also examined. Table 4.1 shows how the patients were grouped and every ICD-10 code belonging to the groups.

3.2.2.1 Chronic back pain

In the data, chronic back pain was defined as diseases with ICD-10 codes M53-M54. This includes lower back pain, neck pain, lumbago, pain in the thoracic spine, unspecified back pain and other disorders related to the back (World Health Organization, 2016).

3.2.2.2 Other chronic musculoskeletal problems

Other chronic musculoskeletal problems are defined as diseases or conditions with ICD-10 codes M00–M03, M20–M43, M46–M51, M60–M77, M83–M99. Many disorders are included in this definition such as polyarthritis, arthropathies, acquired deformation of limbs, disorder of ligament, joint pain, scoliosis, spondylopathies, myositis, disorders of muscles and tendon, soft tissue disorders, shoulder lesions and osteomalacia (disorders related to bones) (World Health Organization, 2016).

3.2.2.3 Mental health problems

Mental disorders are defined as diseases with ICD-10 codes F00-F99 in the data. Examples of diseases that fall under the category are depression, anxiety, addictions, schizophrenia, mood disorders, eating disorders, dementia and mental and behavioural disorders due to psychoactive substance use (World Health Organization, 2016).

3.2.2.4 Combination of the three diseases

Eight disease groups were created from the three diseases, and became the focus of the study. Three of the eight disease groups consisted of patients only suffering from each of the three diseases. The rest of the disease groups consisted of multimorbid patients. Three groups consisted of patients suffering from only two out of the three diseases and no other disease. One group consisted of patients diagnosed only with all three diseases and yet another group consisted of patients with at least the three diseases. In the last mentioned group the number of conditions was not limited and could include patients with up to 25 chronic diseases. In comparison a group consisting of patients with no diagnosis of disease was observed, and yet another group including everyone covered by the data. Table 3.3 shows how the patients were grouped.

Table 3.3: Disease groups created

Disease groups	ICD-10
Everyone	A15–A19, B02, B20–B24, C00–C97, E00–E07, E10–E14, E65-E68, E78, F00–F99, G40, I00–I09, I16–I99, I10–I15, J44, J45–J46, J47, K21, L40, M05–M14, M15–M19, M45, M53–M54, M79, M80–M82, M00–M03, M20–M43, M46–M51, M60–M77, M83–M99, N18–N19 or no diagnosis
No diagnosis	No ICD-10 code
Only chronic back pain	M53-M54
Only mental health problems	F00-F99
Only other chronic musculoskeletal problem	M00–M03, M20–M43, M46–M51, M60–M77, M83–M99
Only chronic back pain and other chronic musculoskeletal problem	M53-M54, M00–M03, M20–M43, M46–M51, M60–M77, M83–M99
Only chronic back pain and mental health problems	M53-M54, F00-F99
Only other chronic musculoskeletal problem and mental health problems	F00-F99, M00–M03, M20–M43, M46–M51, M60–M77, M83–M99
Only chronic back pain, mental health problems and other chronic musculoskeletal problem	F00-F99, M53-M54, M00–M03, M20–M43, M46–M51, M60–M77, M83–M99
Chronic back pain, mental health problems and other chronic musculoskeletal problem and any other disease	F00-F99, M53-M54, M00–M03, M20–M43, M46–M51, M60–M77, M83–M99 and any of the following ICD-10 codes: A15–A19, B02, B20–B24, C00–C97, E00–E07, E10–E14, E65-E68, E78, F00–F99, G40, I00–I09, I16–I99, I10–I15, J44, J45–J46, J47, K21, L40, M05–M14, M15–M19, M45, M53–M54, M79, M80–M82, M00–M03, M20–M43, M46–M51, M60–M77, M83–M99, N18–N19 or no diagnosis

Abbreviations: ICD-10, International Classification of Diseases 10th Revision

3.2.3 Age groups

Two new age variables were created to categorize patients into age groups. One variable sorted patients into seven 10-years age groups and the other variable sorted patients into three 20-years age groups. For analysis where the 20-years age group was used patients under 20 years of age were excluded. The 20-years

age groups were used in the analysis because when the criteria got more specific, there were more subgroups and fewer subjects in each group.

3.3 Software

Most of the statistic work and graphs were made in Rstudio (Version 1.1.463) and the tables were made in Microsoft Excel for Mac 2011 (Version 14.1.0).

3.4 Approvals

The National Bioethics Committee in Iceland approved the study (VSN 16-151) and I was granted access to the data used in this study by The National Bioethics Committee in Iceland in November 2018.

4 Results

4.1 Distribution of the study population

A total of 114,130 patients were included in this study, which was almost one-third of the total population of Iceland in 2009-2012. Seven of the disease groups with a combination of mental health problems, chronic back pain and other chronic musculoskeletal problems and the number of patients in each group is demonstrated in a venn diagram (figure 4.1).

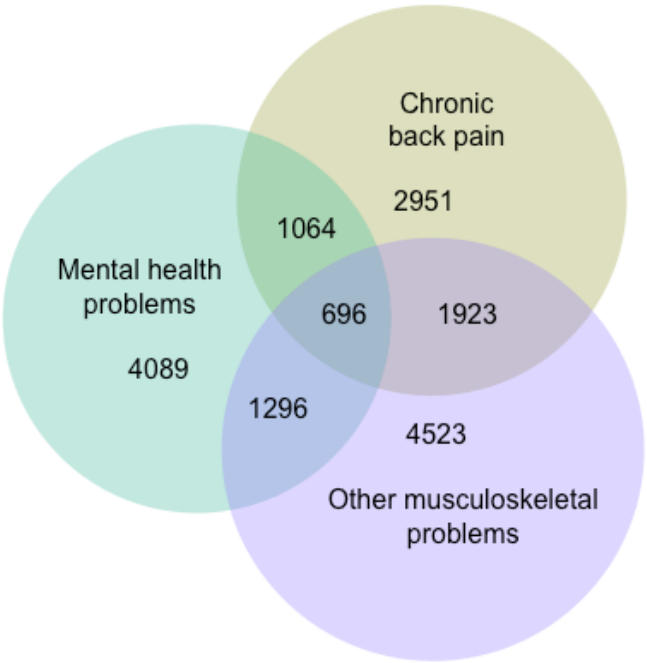

Figure 4.1: Number of patients in 7 disease groups

The number of all patients included in the study and the number of patients with no diagnosis, as well as the selected disease groups by different age groups are shown in more detail in table 4.1. The prevalence in different disease groups by gender can also be seen in the table. Tables with prevalence of patients stratified for gender and age can be found in the appendix (tables B.1-B.2 in appendix B)

The percentage of patients in the observed disease groups ranged from 0.6% for patients diagnosed only with chronic back pain, mental disorders and

other chronic musculoskeletal problems to 5.5% for patients diagnosed with at least mental disorders, chronic back pain and other chronic musculoskeletal problem. A total of 36.2% of all patients were not diagnosed with any disease.

The seven disease groups that restricted the criteria to one to three diseases had the lowest percentage of patients in the age group 70-79 and the proportion was highest in the under 50 age groups. For patients with at least chronic back pain, mental disorders and other chronic musculoskeletal problem, the proportion of patients increased with age from 1.1% for the age group 10-19 to 12.8% for those 70-79.

The gender distribution was equal, with 54,421 (47.7%) males and 59,709 (52.3%) females. When it came to difference by gender in the disease groups, males were more prevalent in most of the groups. Females were more prevalent than males in patients diagnosed with at least chronic back pain, mental disorders,, other chronic musculoskeletal problem and any other disease.

Table 4.1: Number of all patients, patients with no diagnosis and 8 disease groups by different age groups and percentage of the whole population

		All patients	No diagnosis	Only chronic back pain	Only mental health problem	Only other chronic musculoskeletal problem	Only chronic back pain and other chronic musculoskeletal problem	Only chronic back pain and mental health problem	Only other chronic musculoskeletal problem and mental health problem	Only chronic back pain, mental health problems and other chronic musculoskeletal problem	At least chronic back pain, mental health problems and other chronic musculoskeletal problem
Age Range	**10-19**	21161 (100%)	10901 (51.5%)	652 (3.1%)	1331 (6.3%)	1382 (6.5%)	357 (1.7%)	177 (0.8%)	312 (1.5%)	81 (0.4%)	238 (1.1%)
	20-29	21734 (100%)	10710 (49.3%)	849 (3.9%)	1115 (5.1%)	898 (4.1%)	380 (1.7%)	313 (1.4%)	243 (1.1%)	125 (0.6%)	507 (2.3%)
	30-39	19646 (100%)	7911 (40.3%)	753 (3.8%)	714 (3.6%)	850 (4.3%)	456 (2.3%)	250 (1.3%)	255 (1.3%)	157 (0.8%)	766 (3.9%)
	40-49	17342 (100%)	4934 (28.5%)	423 (2.4%)	433 (2.5%)	718 (4.1%)	439 (2.5%)	183 (1.1%)	241 (1.4%)	177 (1%)	1230 (7.1%)
	50-59	15999 (100%)	3419 (21.4%)	197 (1.2%)	303 (1.9%)	475 (3%)	219 (1.4%)	85 (0.5%)	180 (1.1%)	94 (0.6%)	1437 (9%)
	60-69	11279 (100%)	2194 (19.5%)	59 (0.5%)	125 (1.1%)	157 (1.4%)	65 (0.6%)	42 (0.4%)	44 (0.4%)	46 (0.4%)	1251 (11.1%)
	70-79	6969 (100%)	1195 (17.1%)	18 (0.3%)	68 (1.0%)	43 (0.6%)	7 (0.1%)	14 (0.2%)	21 (0.3%)	16 (0.2%)	894 (12.8%)
Gender	**Female**	59709 (52.3%)	20065 (33.6%)	1480 (2.5%)	1936 (3.2%)	1979 (3.3%)	823 (1.4%)	548 (0.9%)	614 (1%)	325 (0.5%)	4037 (6.8%)
	Male	54421 (47.7%)	21199 (39%)	1471 (2.7%)	2153 (4%)	2544 (4.7%)	1100 (2%)	516 (0.9%)	682 (1.3%)	371 (0.7%)	2286 (4.2%)
	Total	**114,130 (100%)**	**41264 (36.2%)**	**2951 (2.6%)**	**4089 (3.6%)**	**4523 (4%)**	**1923 (1.7%)**	**1064 (0.9%)**	**1296 (1.1%)**	**696 (0.6%)**	**6323 (5.5%)**

4.2 Prevalence of Z-drug use in multimorbid disease groups

Table 4.2 shows the prevalence of patients prescribed Z-drugs for three consecutive years in 2009 – 2012 in disease groups by different ages. The number of patients with history of three-year Z-drug use in the whole data was 11,725 (10.3%) and the percentages show the proportion of three-year users within each disease group included in the analysis. Tables with prevalence of prescription stratified by genders and age can be found in the appendix (tables B.3-B.4 in appendix B).

The Z-drug use within disease groups differed greatly as the smallest group consisted of only 20 patients with Z-drug use, whereas patients diagnosed with at least chronic back pain, mental disorders and other chronic musculoskeletal problems had the highest number of Z-drug users (n= 2,598).

The results show that 41.1% of patients diagnosed with at least chronic back pain, mental health problems and other chronic musculoskeletal problems had history of three-year Z-drug use. Proportion of Z-drug users in some of the disease groups was very low. Only 1.4% of patients with chronic back pain were three-year Z-drug users and the percentage was even lower when chronic back pain was in combination with other chronic musculoskeletal problems. The prevalence of three-year Z-drug use was higher in females as compared to males in all groups and the ratio between females and males was similar for every group.

Table 4.2: Number of all patients, patients with no diagnosis and 8 disease groups with three-year history of Z-drug use in different age groups and percentage of patients in each subgroup

		All patients	No diagnosis	Only chronic back pain	Only mental health problem	Only other chronic musculoskeletal problem	Only chronic back pain and other chronic musculoskeletal problem	Only chronic back pain and mental health problem	Only other chronic musculoskeletal problem and mental health problem	Only chronic back pain, mental health problems and other chronic musculoskeletal problem	At least chronic back pain, mental health problems and other chronic musculoskeletal problem
Age groups	**10-19**	19 (0.1%)*	1 (0%)	0	4 (0.3%)	0	0	0	1 (0.3%)	0	4 (1.7%)
	20-29	320 (1.5%)	37 (0.3%)	0	56 (5%)	1 (0.1%)	1 (0.3%)	12 (3.8%)	17 (7%)	9 (7.2%)	51 (10.1%)
	30-39	791 (4%)	74 (0.9%)	11 (1.5%)	95 (13.3%)	2 (0.2%)	5 (1.1%)	30 (12%)	24 (9.4%)	14 (8.9%)	154 (20.1%)
	40-49	1688 (9.7%)	183 (3.7%)	7 (1.7%)	95 (21.9%)	6 (0.8%)	3 (0.7%)	44 (24%)	61 (25.3%)	40 (22.6%)	419 (34.1%)
	50-59	3080 (19.3%)	376 (11%)	13 (6.6%)	123 (40.6%)	22 (4.6%)	4 (1.8%)	31 (36.5%)	58 (32.2%)	30 (31.9%)	693 (48.2%)
	60-69	3190 (28.3%)	435 (19.8%)	6 (10.2%)	55 (44%)	8 (5.1%)	6 (9.2%)	16 (38.1%)	17 (38.6%)	21 (45.7%)	710 (56.8%)
	70-79	2633 (37.8%)	382 (32%)	3 (16.7%)	31 (45.6%)	5 (11.6%)	1 (14.3%)	8 (57.1%)	7 (33.3%)	4 (25%)	567 (63.4%)
Gender	**Female**	7848 (13.1%)	925 (4.6%)	22 (1.5%)	261 (13.5%)	27 (1.4%)	9 (1.1%)	82 (15%)	114 (18.6%)	59 (18.2%)	1842 (45.6%)
	Male	3877 (7.1%)	563 (2.7%)	18 (1.2%)	198 (9.2%)	17 (0.7%)	11 (1%)	59 (11.4%)	71 (10.4%)	59 (15.9%)	756 (33.1%)
	Total	**11,725 (10.3%)**	**1488 (3.6%)**	**40 (1.4%)**	**459 (11.2%)**	**44 (1%)**	**20 (1%)**	**141 (13.3%)**	**185 (14.3%)**	**118 (17%)**	**2598 (41.1%)**

**Percentages calculated from numbers in table 4.1*

Figure 4.2 shows the ratio of patients with history of three-year Z-drug use to non-users within groups for all patients, individuals with no diagnosis and the eight disease groups.

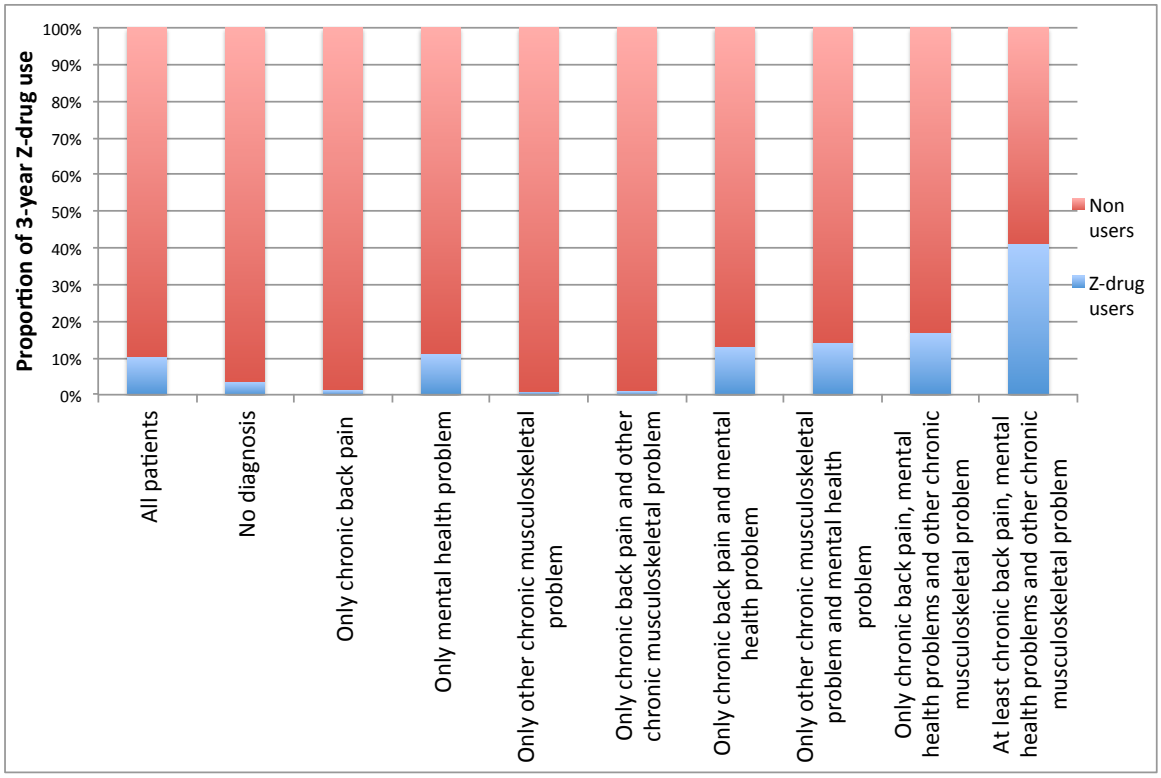

Figure 4.2: Ratio between patients with three-year history of Z-drug use and non-users in each disease group

4.2.1 Prevalence of Z-drug and benzodiazepine derivatives use

The number of all patients with history of three-year Z-drug and benzodiazepine derivatives use was 3053 (2.7%). Table 4.3 shows the prevalence of combination use of Z-drugs and benzodiazepine derivatives by different subgroups, ages and genders. Tables with prevalence of patients prescribed both benzodiazepine derivatives and Z-drugs stratified by gender and age can be found in the appendix (tables B.5-B.6 in appendix B)

The proportion of three-year Z-drug and benzodiazepine derivatives users in each group ranged from 0-12.8%. Disease groups excluding diagnosis of mental health problems had the lowest percentage of three-year Z-drug and benzodiazepine derivatives users. One subgroup, patients with chronic back pain and other chronic musculoskeletal problem, had no users with three-year history of

the two drugs combined. Female users were more prevalent in all groups. The distribution of Z-drug and benzodiazepine derivative use in age groups was similar to that of Z-drug use only.

Table 4.3: Number of all patients, patients with no diagnosis and 8 disease groups with three-year history of z-drug and benzodiazepine derivatative use in different age groups and percentage of all patients in each subgroup

		All patients	No diagnosis	Only chronic back pain	Only mental health problem	Only other chronic musculoskeletal problem	Only chronic back pain and other chronic musculoskeletal problem	Only chronic back pain and mental health problem	Only other chronic musculoskeletal problem and mental health problem	Only chronic back pain, mental health problems and other chronic musculoskeletal problem	At least chronic back pain, mental health problems and other chronic musculoskeletal problem
Age group	**10-19**	6 (0.0%)*	0	0	0	0	0	0	0	0	2 (0.8%)
	20-29	80 (0.4%)	10 (0.1%)	0	12 (1.1%)	0	0	1 (0.3%)	4 (1.6%)	1 (0.8%)	12 (2.4%)
	30-39	221 (1.1%)	17 (0.2%)	2 (0.3%)	23 (3.2%)	1 (0.1%)	0	6 (2.4%)	6 (2.4%)	5 (3.2%)	50 (6.5%)
	40-49	421 (2.4%)	38 (0.8%)	1 (0.2%)	15 (3.5%)	2 (0.3%)	0	6 (3.3%)	13 (5.4%)	9 (5.1%)	115 (9.3%)
	50-59	767 (4.8%)	100 (2.9%)	2 (1.0%)	43 (14.2%)	0	0	8 (9.4%)	13 (7.2%)	7 (7.4%)	200 (13.9%)
	60-69	856 (7.6%)	116 (5.3%)	0	14 (11.2%)	3 (1.9%)	0	4 (9.5%)	5 (11.4%)	4 (8.7%)	244 (19.5%)
	70-79	702 (10.1%)	99 (8.3%)	1 (5.6%)	9 (13.2%)	1 (2.3%)	0	1 (7.1%)	1 (4.8%)	0	184 (20.6%)
Gender	**Female**	2179 (3.6%)	256 (1.3%)	5 (0.3%)	71 (3.7%)	5 (0.3%)	0	15 (2.7%)	35 (5.7%)	13 (4%)	606 (15%)
	Male	874 (1.6%)	124 (0.6%)	1 (0.1%)	45 (2.1%)	2 (0.1%)	0	11 (2.1%)	7 (1%)	13 (3.5%)	201 (8.8%)
	Total	**3053 (2.7%)**	**380 (0.9%)**	**6 (0.2%)**	**116 (2.8%)**	**7 (0.2%)**	**0 (0%)**	**26 (2.4%)**	**42 (3.2%)**	**26 (3.7%)**	**807 (12.8%)**

**Percentages calculated from numbers in table 4.1*

Figure 4.3 shows the ratio of patients with three-year history of combination use of Z-drug and benzodiazepine derivatives to three-year Z-drug users and non-users within each group. It can be seen from the column chart that the ratio of three-year use of both drugs in combination to three-year Z-drug use only is similar in all groups.

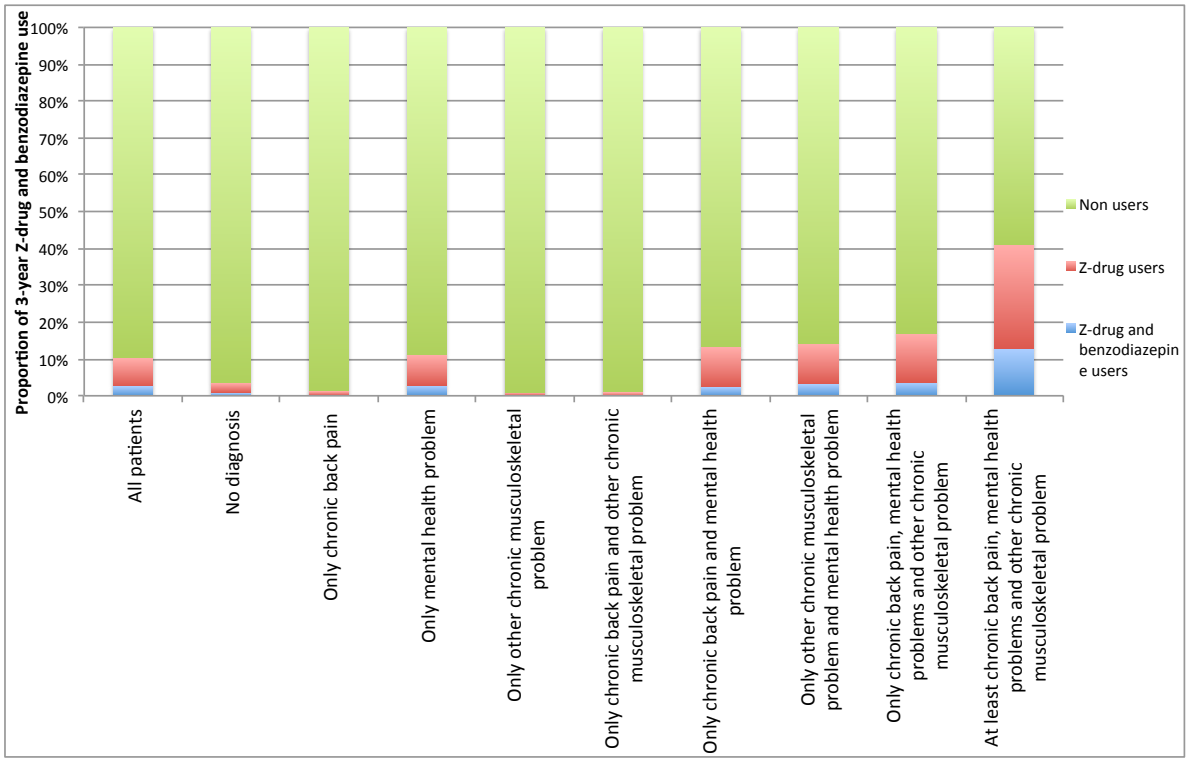

Figure 4.3: Ratio between patients with three-year history of Z-drug and benzodiazepine use and three-year Z-drug use only and non-users in each disease group

4.3 Defined daily doses (DDDs)

Defined daily doses (DDDs) of Z-drugs were collected for patients with three-year history of Z-drug use. DDDs in the first year were compared by different genders and 20-years age groups. Boxplots showing DDDs of Z-drugs in the first year for all patients and patients in the two largest disease groups with a three-year history of Z-drug use can be found in figures 4.4-4.8. Percentiles (5%, 25%, 50%, 75%, 95%), mean and standard deviation (SD) for DDDs is shown in tables 4.4-4.8 below each boxplot. Results for the six smallest disease groups and patients with no diagnosis were not included in this section but can be found in appendix (figures B.1-B.7 and tables B.7-B.12 in appendix B).

The results for all patients with three-year Z-drug use in the first year can be seen in figure 4.4 and table 4.4. For males the mean DDDs increased by 67.1 DDDs/year (29.9%) between the first two age groups but only by 12 DDDs (4.1%) from the second to third age group. For females the increase with older age in mean DDDs was not as pronounced. Difference in mean DDDs between genders was most in the youngest age group. The mean DDDs was 20% (44.9 DDDs/year) higher for females than the mean DDDs for males. The median DDDs increased with each age group for both genders. The distribution of DDDs was wide but the range from first quartile to third quartile was small.

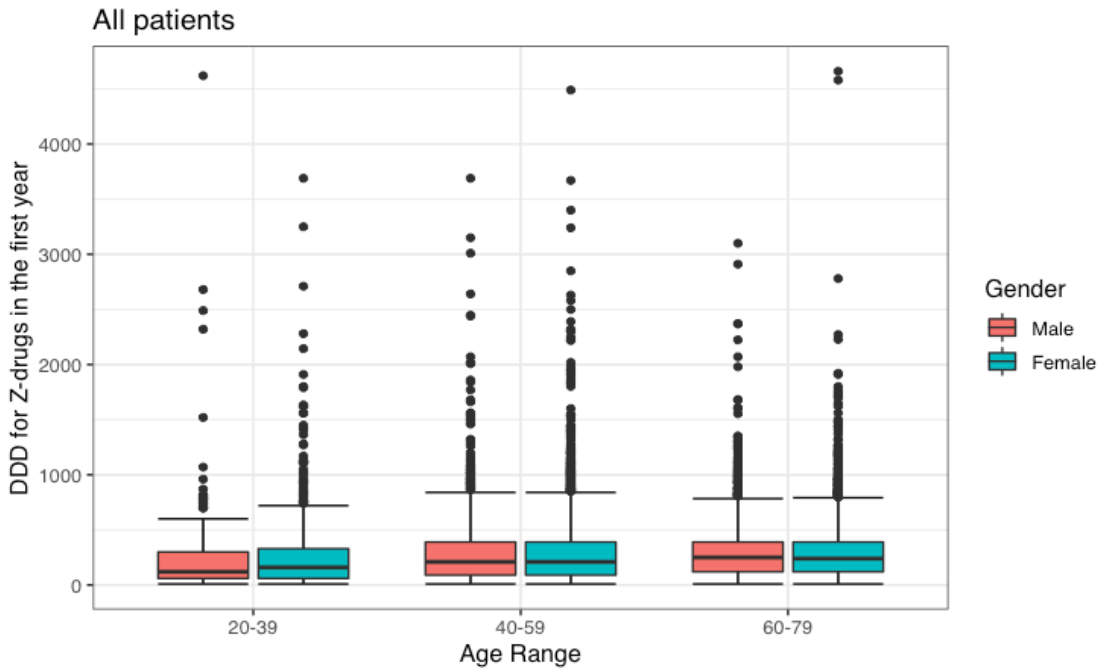

Figure 4.4: Boxplot for DDDs of Z-drugs in the first year for all patients using Z-drugs for 3 years

Table 4.4: DDDs in the first year by different age groups and genders

	20-39		40-59		60-79	
	Male (n = 412)	**Female (n = 699)**	**Male (n = 1516)**	**Female (n = 3256)**	**Male (n = 1940)**	**Female (n = 3883)**
95%	645	930	794	787	750	690
75%	300	330	390	390	390	390
50%	**120**	**160**	**210**	**210**	**250**	**240**
25%	60	60	90	90	120	120
5%	20	20	30	30	30	40
Mean (SD)	224.2 (353.9)	269.1 (365.5)	291.3 (318.4)	284.7 (307.7)	303.3 (261.4)	296.6 (248)

For patients diagnosed only with mental disorders, the increase of mean and median DDDs with older age in the first year was more prominent among males than females (figure 4.5 and table 4.5). Mean DDDs of Z-drugs increased by 46.1% (87.4 DDDs/year) from first to second age group and then by another 38,1% (105.6 DDDs/year) from the second to the third age group. For females the mean DDDs did not differ as much between age groups.

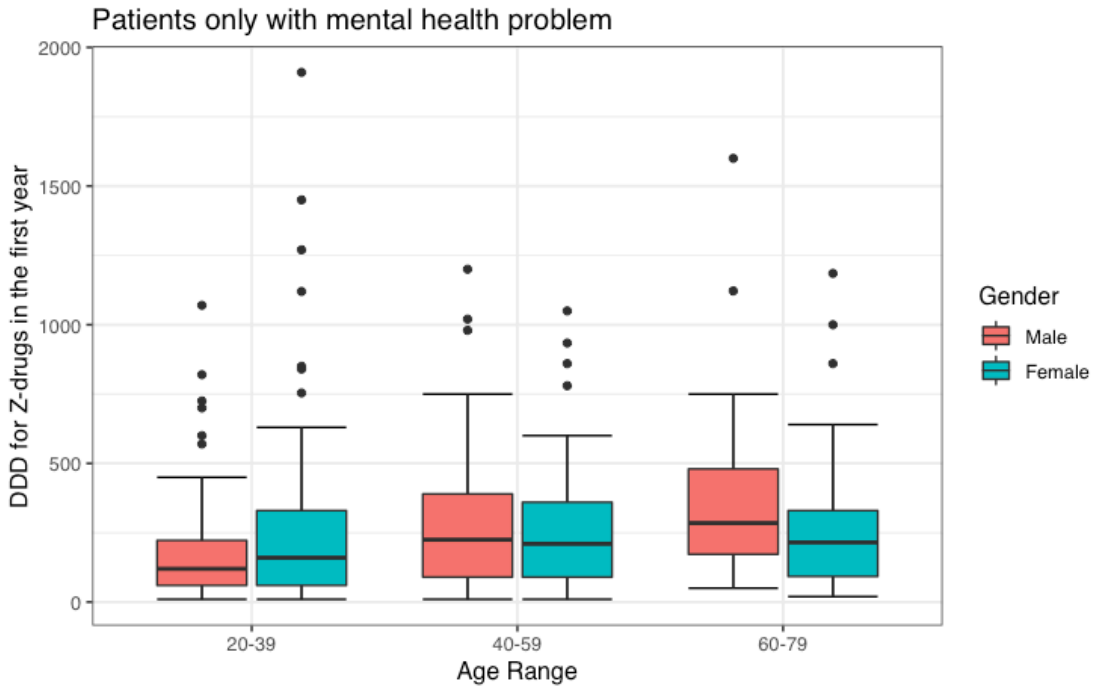

Figure 4.5: Boxplot for DDDs of Z-drugs in the first year for patients only with mental health problems using Z-drugs for 3 years

Table 4.5: DDDs in the first year by different age groups and genders

	20-39		40-59		60-79	
	Male (n = 70)	**Female (n = 81)**	**Male (n = 90)**	**Female (n = 128)**	**Male (n = 36)**	**Female (n = 50)**
95%	655	850	726.6	516.5	843	761
75%	222.5	330	390	360	480	330
50%	**120**	**160**	**225**	**210**	**285**	**215**
25%	60	60	90	90	172.5	92.5
5%	20	20	30	30	60	24.5
Mean (SD)	189.5 (209.5)	261.1 (334.3)	276.9 (229.8)	247.7 (189.6)	382.5 (321.8)	267 (240.9)

Figure 4.6 and table 4.6 show DDDs for patients with at least mental disorders, chronic back pain and other chronic musculoskeletal problems in the first year. Among both genders the mean DDDs were highest among 40-59 years old and lowest among those 20-39. The difference between the highest and lowest mean DDDs was not much regardless of gender.

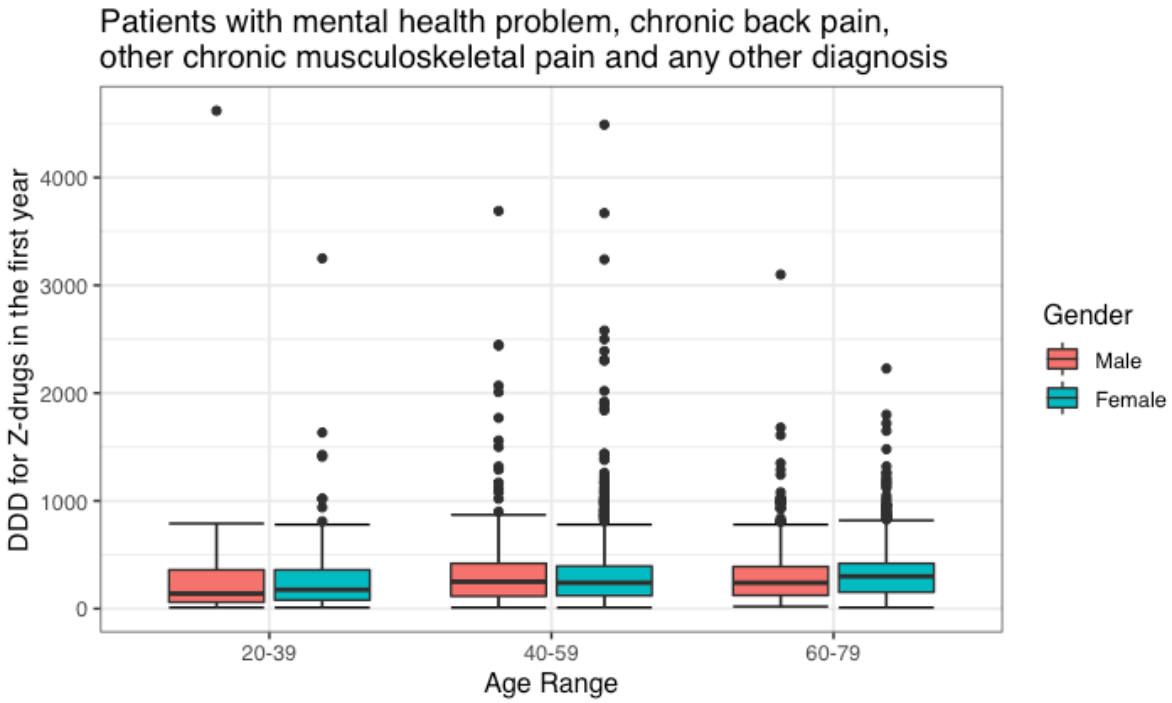

Figure 4.6: Boxplot for DDDs of Z-drugs in the first year for patients with at least mental health problems, chronic back pain and other chronic musculoskeletal problem using Z-drugs for 3 years

Table 4.6: DDDs in the first year by different age groups and genders

	20-39		40-59		60-79	
	Male (n = 65)	**Female (n = 140)**	**Male (n = 315)**	**Female (n = 797)**	**Male (n = 375)**	**Female (n = 902)**
95%	756	816.5	849	930	819	779
75%	360	360	420	395	390	420
50%	**140**	**175**	**250**	**240**	**240**	**300**
25%	60	80	115	120	123.5	152.5
5%	20	20	30	30	37	40
Mean (SD)	293.1 (582.2)	289.7 (380.6)	341.1 (396.6)	330.2 (390.8)	313.7 (291.2)	329.6 (245.6)

4.4 Change in DDDs between years

Comparison of yearly DDDs between the three years for three-year Z-drug users in selected disease groups was carried out with boxplots and tables showing percentiles, mean and SD of DDDs (figures 4.7-10 and tables 4.7-4.10).

Focusing on the largest disease groups, results for the two largest disease groups along with results for patients with mental disorders and chronic back pain were observed. For comparison, results for all three-year Z-drug users were also observed. Boxplots and tables for the age group 40-59 are shown in this section. This was done because results were similar for all age groups. Boxplots and tables with percentiles for age groups 20-39 and 60-79 can be found in the appendix (figures B.8-B.15 and tables B.14-B.21 in appendix B).

Not much change in DDDs was present between the three years under study and the mean and median DDDs did not show much variation between years within each subgroup. The subgroups with the fewest Z-drug users showed the most variation in mean and median DDDs between years.

For all patients with three-year history of Z-drug use the mean DDDs in the age groups 20-39 and 40-59 showed a slight top in the second year (figure 4.7 and table 4.7, figure B.8 and table B.14 in appendix B), that is the DDD values in the second year tended to be higher than for the first and the third year. The median DDDs for all patients in the age group 40-59 remained exactly the same for both genders in all three years and the mean DDDs also remained consistent. For all patients in the age group 60-79 the median DDD was the same in year two and three of Z-drug use but 7.4% and 11.1% less in year one for males and females, respectively (figure B.9 and table B.15 in appendix B).

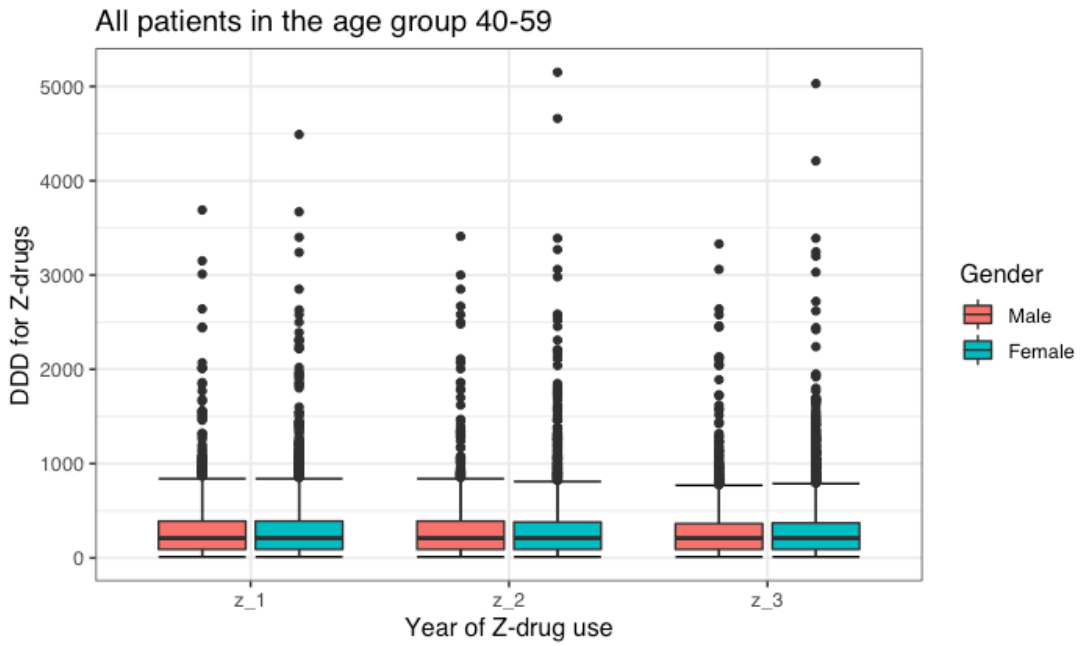

Figure 4.7: Boxplot showing DDDs between years for all patients in the age group 40-59 using Z-drugs for 3 years

Table 4.7: DDDs of Z-drugs between years (40-59) for all patients

	All patients 40-59					
	First year		Second year		Third year	
	Male (n = 1516)	**Female (n = 3256)**	**Male (n = 1516)**	**Female (n = 3256)**	**Male (n = 1516)**	**Female (n = 3256)**
95%	794	787	812.5	810	780	780
75%	390	390	390	380	364.3	370
50%	210	210	210	210	210	210
25%	90	90	90	90	90	90
5%	30	30	30	30	30	30
Mean (%)	291.3 (318.4)	284.7 (307.7)	294.1 (322.8)	289.8 (321.8)	285.2 (313.9)	282.9 (312.9)

The mean and median DDDs of Z-drugs for patients only diagnosed with mental disorders did not change much in the three years (figure 4.8 and table 4.8, figures B.10-B.11 and tables B.16-B.17 in appendix B). The most significant change in mean DDDs between years was seen between first and second year for males in the age group 20-39 or 15.4% increase.

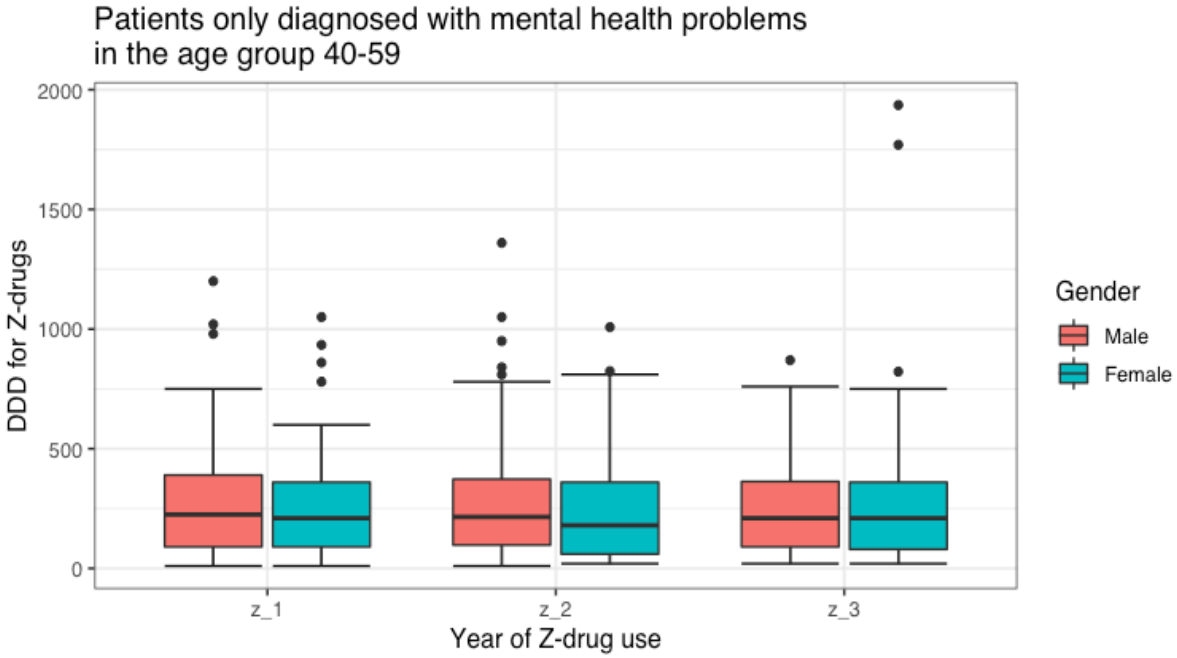

Figure 4.8: Boxplot showing DDDs between years for patients only diagnosed with mental health problems in the age groups 40-59 using Z-drugs for 3 years

Table 4.8: DDDs of Z-drugs between years (40-59) for patients diagnosed with mental health problems

Only mental health problems 40-59						
	First year		Second year		Third year	
	Male (n = 90)	**Female (n = 128)**	**Male (n = 90)**	**Female (n = 128)**	**Male (n = 90)**	**Female (n = 128)**
95%	726.6	516.5	796.5	636.5	731	648
75%	390	360	373	360	363	360
50%	225	210	215	180	210	210
25%	90	90	97.5	60	90	80
5%	30	30	30	30	30	30
Mean (SD)	276.9 (229.8)	247.7 (189.6)	279.4 (244.3)	238.4 (204.2)	269.1 (208.5)	252.1 (271.9)

Table 4.9 and figure 4.9 show change in DDDs between years for patients with mental disorders and chronic back pain in the age group 40-49. An increase by 14.2% (40 DDDs/year) in mean DDDs was found between first and second year for females but the mean DDDs dropped again in the third year. Among males the mean DDDs decreased only slighly in each year. Mean and median DDDs for both females and males in the age group 20-39 increased slighly in the second year but dropped again in the third year (table B.12 and figure B.18 in appendix B).

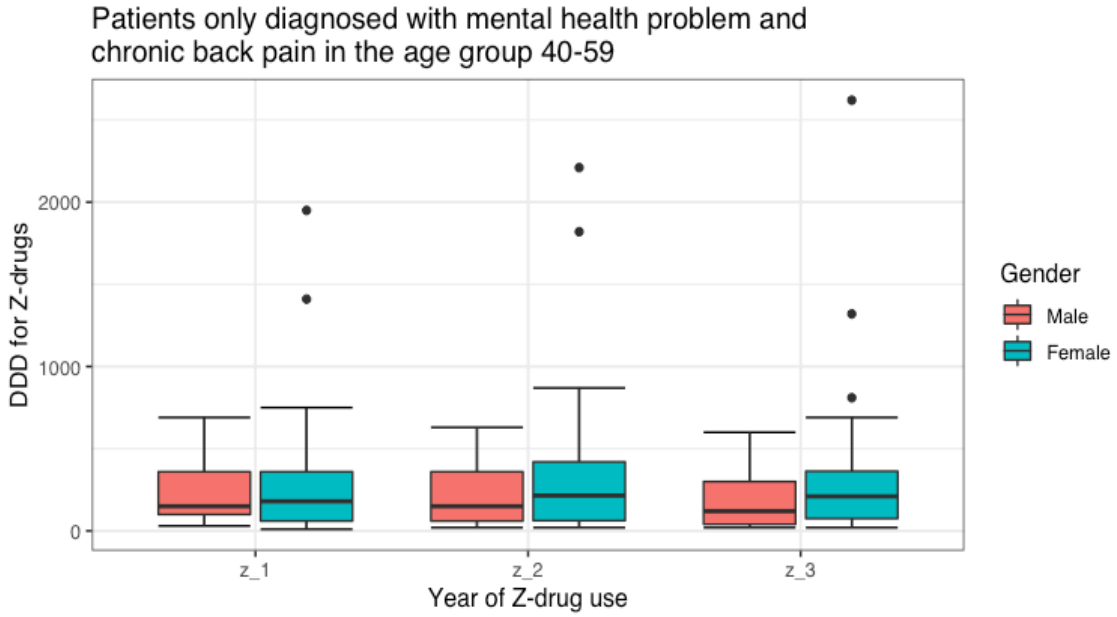

Figure 4.9: Boxplot showing DDDs between years for patients diagnosed with mental health problems and chronic back pain in the age group 40-59 using Z-drugs for 3 years

Table 4.9: DDDs of Z-drugs between years (40-59) for patients diagnosed with mental health problems and chronic back pain

Only mental health problems and chronic back pain 40-59						
	First year		Second year		Third year	
	Male (n = 29)	**Female (n = 46)**	**Male (n = 29)**	**Female (n = 46)**	**Male (n = 29)**	**Female (n = 46)**
95%	534	742.5	558	832.5	514	780
75%	360	360	360	420	300	363
50%	150	180	150	215	120	210
25%	100	60	60	62.5	40	75
5%	34	20	30	20	20	30
Mean (SD)	221.7 (174.9)	281.7 (357.9)	210.3 (187.4)	321.7 (420.2)	182.8 (167.9)	301 (427.4)

For the biggest disease group, patients diagnosed with at least mental health problem, chronic back pain and other chronic musculoskeletal problem, the change of mean and median DDDs between the three years was not much (figure 4.10 and table 4.10, figures B.14-B.15 and tables B.20-B.21 in appendix). The most difference in mean DDDs between years was seen among males in the age group 20-39 where the mean DDDs decreases by 10.4% from the second to the third year.

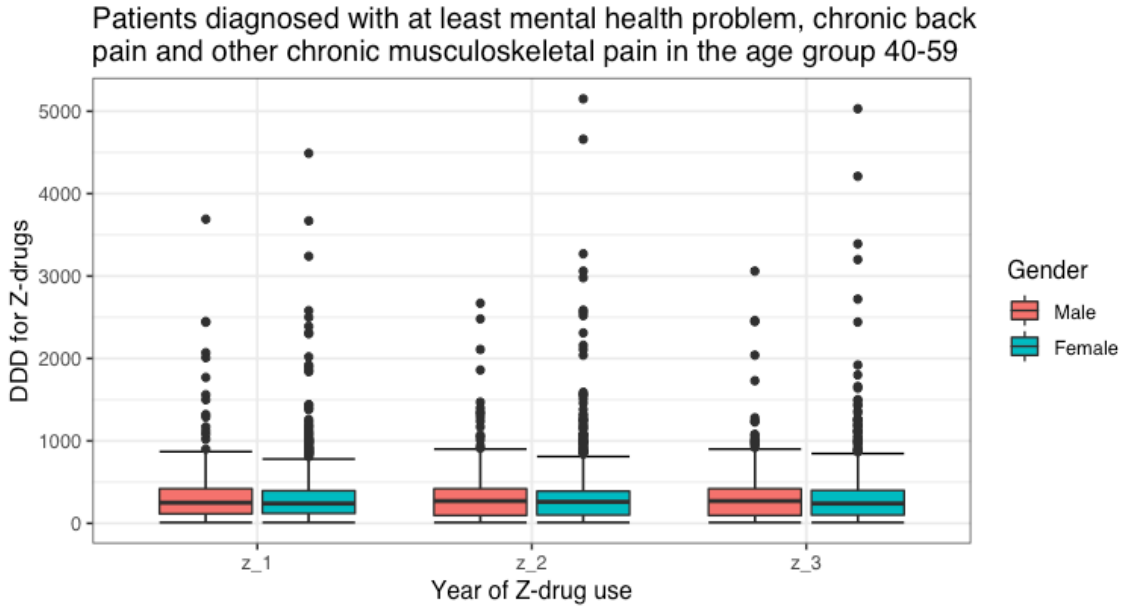

Figure 4.10: Boxplot showing DDDs between years for patients diagnosed with at least mental health problems, chronic back pain and other chronic musculoskeletal problems in the age group 40-59 using Z-drugs for 3 years

Table 4.10: DDDs of Z-drugs between years (40-59) for patients diagnosed with at least mental health problems, chronic back pain and other chronic musculoskeletal problems

Mental health problem, chronic back pain and other musculoskeletal pain 40-59						
	First year		Second year		Third year	
	Male (n = 315)	**Female (n = 797)**	**Male (n = 315)**	**Female (n = 797)**	**Male (n = 315)**	**Female (n = 797)**
95%	849	930	903	982	932	884
75%	420	395	420	390	420	400
50%	250	240	270	260	270	240
25%	115	120	95	100	95	100
5%	30	30	30	30	30	30
Mean (SD)	341.1 (396.6)	330.2 (390.8)	338.8 (352.5)	345.7 (433.3)	338 (367.7)	332.3 (400.8)

5 Discussion

5.1 Main outcomes

5.1.1 Prevalence of three-year Z-drug use

The prevalence of three-year Z-drug use was in most cases highest among patients with multiple diseases. Disease groups with patients diagnosed with three or more chronic conditions had the highest prevalence of three-year Z-drug use. When both pain related conditions coexisted with mental health diagnoses the prevalence increased to 17%. The group not restricted to any number of chronic diseases (At least mental disorders, chronic back pain and other chronic musculoskeletal problem) had not only by far the highest number of three-year Z-drug users (n=2,598) but also the highest prevalence (41.1%) out of all the groups observed. Prevalence of three-year Z-drug use among patients with mental disorders was 11.3% and the prevalence increased slightly in disease groups with either additional diagnosis of chronic back pain or diagnosis of other chronic musculoskeletal problem to 13.3% and 14.3%, respectively. The two groups with patients only diagnosed with either one of the pain related chronic diseases had the lowest prevalence, 1.4% and 1%, of three-year Z-drug use. When chronic back pain diagnosis was added to preexisting diagnosis of other chronic musculoskeletal problems and vice versa, the prevalence (1%) of three-year Z-drug use did not seem to increase. Individuals with no diagnosis had higher prevalence of three-year Z-drug use (3.6%) than the three chronic pain related disease groups.

Of the whole study population (n=114,130), 10.3% had history of three-year Z-drug use (n=11,725). In comparison, 2.9% of the Icelandic population used Z-drugs every year in a ten year period from 2003-2013 (Guðmundsson et al., 2011). Patients with history of combined three-year use of benzodiazepine derivatives and Z-drugs was 2.7% of the study population.

Three-year history of combination use of benzodiazepine derivatives and Z-drugs was more prevalent in the multimorbid groups. This could be seen in every group with multimorbid patients except for patients with only chronic back pain and

other chronic musculoskeletal problems. There were no three-year Z-drug and benzodiazepine derivative users in that group. Higher proportion of patients with diagnosis of mental health problems using Z-drugs were also three-year benzodiazepine users compared to patients with no mental diagnosis. This could be expected as benzodiazepine derivatives are also used in treatment of anxiety which is classified as mental health problems.

This increased prevalence of Z-drug and benzodiazepine derivative users among multiorbid patients is in line with a recent study. Linnet et al. demonstrated that multimorbid patients in general were more likely to be prescribed hypnotics and anxiolytics (Linnet et al., 2016). The only exception in our results was with patients multimorbid with two pain related diagnoses, chronic back pain and other chronic musculoskeletal problems. Being comorbid with mental disorder seemed to have more effect on increased Z-drug use than being comorbid with chronic pain condition.

Prevalence of Z-drug user increased with age in all disease groups observed. Females were more prevalent three-year Z-drug users compared to males in all disease groups. These results are in agreement with previous findings (Mokhar et al., 2018, Linnet et al., 2016, Demyttenaere et al., 2008k).

5.1.2 Change in DDDs

According to the results, there was no dose increase of Z-drugs between years. We found that there was no significant difference in DDDs between the three years for three-year Z-drug users in any of the groups observed. Wide distribution of DDDs was evident and especially in the larger groups. The range from the minimum to third quartile was relatively small for most of the subgroups which indicates that DDDs for majority of the patients was in similar range. The distribution of DDDs indicates that some of the three-year Z-drug users were using Z-drugs intermittently over the three years but others were using Z-drugs continuously. Minority of patients used more than 365 DDDs of Z-drugs in one year which indicates that the majority of three-year Z-drug users did not use Z-drugs daily. The highest doses did not increase over the three years. The lowest 5% of Z-drug users in most of the disease groups used below 30 DDDs which corresponds to one prescription of zopiclone or zolpidem.

DDDs increased with older age in the first year in most groups observed. For patients with at least mental health problem, chronic back pain and other chronic musculoskeletal problem the mean DDDs was slightly higher among the age group 40-59 than among those 60-79. Interestingly, mean DDDs did not increase with age among female patients with mental disorders while the increase in mean DDDs for corresponding group of males increased significantly. The most significant difference in mean DDDs between genders was present among 60-79 years old patients with mental health problems where the males had 43.2% higher DDDs than women.

5.2 Clinical significance

The prevalence of three-year Z-drug users was very low within some of the disease groups observed. This was particularly noticable for pain related diseases. A total of 1.4% (n = 40) of chronic back pain patients and 1% (n = 44) of patients with other chronic musculoskeletal problems had three-year history of Z-drug use. The same applied to patients diagnosed with both conditions but only 20 patients in this disease group were three-year Z-drug users. These findings were unexpected as chronic pain is known to cause insomnia or affect sleep quality like stated in the introduction chapter (Atkinson et al., 1988; Pilowsky et al., 1985). Our study indicates that patients only diagnosed with chronic back pain suffering from undiagnosed insomnia are not being treated with Z-drugs. There are numerous treatment options available for both insomnia and chronic pain which these patients are possibly rather receiving.

Number of patients using Z-drugs for three consecutive years in the whole population is high considering the fact that Z-drugs are only intended for short-term use in patients with severe insomnia according to guidelines (NICE, 2004). The prevalence is even higher among multimorbid patients. Treatments other than long-term pharmacotherapies are available for insomnia which are according to some studies more efficient in the long run (Atkinson et al., 1988, Charles M. Morin, Vallières, et al., 2009). Edinger & Means stated that cognitive behavioural therapy (CBT) for primary insomnia showed better sleep improvements at the end of a 2-year follow-up period than combined pharmacotherapy and CBT. Exploring other treatment options for patients with insomnia is therefore desirable.

Although Z-drugs are known to cause dependence and tolerance, doctors in the general practice do not seem to be increasing patient's doses of Z-drugs from one year to another. These results differ slightly from one previous study (Tvete, Bjørner, Andreas Aursnes, & Skomedal, 2013), but they are in consistent with another study where no changes in doses of benzodiazepines were observed over time (Soumerai et al., 2003). Soumerai et al. found that there was no escalation in median dose among long-term benzodiazepine users over time. However, one subgroup, benzodiazepine users also filling prescriptions for antidepressants had elevated odds of dose escalation. Our results do not support this as no escalation was seen in DDDs in any subgroup related to mental health disease. The fact that our data did not include information about other medication and that we were only analysing DDDs of Z-drugs has to be taken into account.

There were no information as to whether the patients in present study had previously used Z-drugs before the timeframe under study. It can be estimated that at least part of the patients had been using Z-drugs for some time before. It would be interesting to see if the DDDs would increase between years among incidence users.

5.3 Strengths and limitations

The sample size was large and very representative of the population as a whole which strengthens the generalisability of the study. All data used in the study was from the same database with electronic medical records.

Some disease variables in the data included many diagnoses, e.g. mental health problems etc., possibly leading to underestimation of multimorbidity in the study. This partly explains why Z-drug use increased more in groups where patients were comorbid with mental health problems than in groups with patients comorbid with chronic back pain or other chronic musculoskeletal problem.

The disease group criteria created for the study was often limited and left us with a small population of patients in some groups because many patients were comorbid with other diseases. On the other hand, this could be considered an advantage because it presents well defined disease groups.

Patients filling prescription for Z-drugs and benzodiazepines were assumed to complete the whole dose prescribed but it is difficult to know with certainty the actual use. The use of Z-drugs and benzodiazepines is therefore rather overestimated than underestimated. Also, we have no knowledge of actual daily dose and duration of treatment.

The focus in this study was on patients filling at least one prescription for three consecutive years so the number of prescriptions each year varies greatly. Prevalence studies have various definitions of long-term users which made it difficult to compare to other studies.

There are very few studies that give insight into use of Z-drugs and benzediazepine derivatives within common multimorbid disease groups. This is of particular interest because of the excessive use of benzodiazepines and especially Z-drugs in Iceland.

6 Conclusions

In conclusion, the highest prevalence of three-year Z-drug use was among multimorbid patients. The prevalence increased even more with each additional chronic condition and was highest among patients with at least three diseases and among patients comorbid with mental disorders. Surprisingly, the results indicated that doctors were not increasing their patient's doses of Z-drugs over the three years. Nevertheless, the majority of three-year Z-drug users in all disease groups were still exceeding the recommended duration of treatment according to guidelines. Other treatment options should be considered before using Z-drugs or benzodiazepine derivates long term and there should be more focus on treating underlying diseases in multimorbid patients.

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APPENDICES

Appendix A – Approval

Appendix B – Results

Appendix A - approval

VÍSINDASIÐANEFND
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Reykjavík 6. nóvember 2018
Tilv.: VSNb2016100010/03.03

Efni: 16-151-V1 - Dánartíðni sjúklinga í tengslum við sjúkdómaklasa og ávísun svefnlyfja og/eða kvíðastillandi lyfja.

Á fundi sínum 06.11.2018 fjallaði Vísindasiðanefnd um umsókn þína er barst, 30.10.2018 og viðbótarupplýsingar 31.10.2018, vegna viðbótar nr. 1 við ofangreinda rannsóknaráætlun. Í erindi þínu segir:

„Óska eftir því að heimilað verði að bæta Margréti Sif Sigurðardóttur, lyfjafræðinema, kt. 030294-2469, við hóp rannsakenda vegna rannsóknar sem ber heitið „Dánartíðni sjúklinga í tengslum við sjúkdómaklasa og ávísun svefnlyfja og/eða kvíðastillandi lyfja", VSN-16-151. Ætlunin er að hún vinni nemaverkefni til meistaraprófs sem byggir á gögnum sem safnað hefur verið fyrir þessa rannsókn. Leiðbeinendur hennar, Lárus S. Guðmundsson, lektor við HÍ, og undirritaður ábyrgðarmaður rannsóknarinnar munu bera ábyrgða á vinnu hennar með gögnin. Jafnframt verður óskað eftir heimild Heilsugæslu höfuðborgarsvæðisins.
Meðfylgjandi viðhengi: a) Undirrituð umsókn b) Þagnarheit vegna rannsóknar á heilbrigðissviði sem neminn hefur undirritað."

Í viðbótarupplýsingum til nefndarinnar koma fram eftirfarandi upplýsingar: *„Verkefni Margrétar Sifjar felst í því að kanna notkun svefnlyfja (N05CD og N05CF) og kvíðastillandi lyfja (N05BA) í skilgreindum dagskömmtum á tímabilinu 2009 til 2012 í tengslum við fjölsjúkleika og lifun á eftirfylgnitíma. Sérstaklega verður athyglinni beint að ICD-10 greiningum sem tengjast þrálátum verkjum (ICD-10: M00-M03, M05-M43, M45-M51, M53-M54, M60-M77, M79-M99 og N18-N19) ásamt geðgreiningum (ICD-10: F00-F99)."*

Vísindasiðanefnd hefur farið yfir bréf þitt og gerir ekki athugasemdir við tilgreindar breytingar. Viðbót nr. 1 við ofangreinda rannsókn, er endanlega samþykkt af Vísindasiðanefnd.

Vísindasiðanefnd bendir á að ábyrgðarmaður rannsóknarinnar ber ábyrgð á að sótt sé um viðeigandi leyfi vegna viðbóta/breytinga hjá þeim stofnunum sem við á. Óheimilt er að hefja framkvæmd rannsóknarinnar fyrr en slík leyfi liggja fyrir. Afrit leyfa/samstarfsyfirlýsinga þurfa að berast nefndinni. Jafnframt ber ábyrgðarmanni að tilkynna þeim stofnunum, sem veitt hafa leyfi vegna framkvæmdar rannsóknarinnar eða öflunar gagna, um framangreint, ef við á. Óheimilt er að breyta framkvæmd rannsóknarinnar fyrr en slík leyfi liggja fyrir.

Með kveðju, f.h. Vísindasiðanefndar,
Kristján Erlendsson, læknir, formaður

Appendix B – Results

Tables with number of patients in all groups by genders:

Table B.1: Number of all patients, individuals with no diagnosis and 8 disease groups for females by different age groups.

Age Range	Everyone	No diagnosis	Only chronic back pain	Only mental health problems	Only other chronic musculoskeletal problem	Only chronic back pain and other chronic musculoskeletal problem	Only chronic back pain and mental health problem	Only other chronic musculoskeletal problem and mental health problem	Only chronic back pain, mental health problems and other chronic musculoskeletal problem	Chronic back pain, mental health problems and other chronic musculoskeletal problem
10-19	10718 (50.6%)	5299 (48.6%)	358 (54.9%)	548 (41.2%)	653 (47.3%)	179 (50.1%)	102 (57.6%)	151 (48.4%)	42 (51.9%)	144 (60.5%)
20-29	11970 (55.1%)	5575 (52.1%)	481 (56.7%)	569 (51%)	396 (44.1%)	178 (46.8%)	174 (55.6%)	112 (46.1%)	64 (51.2%)	327 (64.5%)
30-39	10279 (52.3%)	3769 (47.6%)	366 (48.6%)	361 (50.6%)	337 (39.6%)	182 (39.9%)	128 (51.2%)	116 (45.5%)	64 (40.8%)	478 (62.4%)
40-49	8883 (51.2%)	2197 (44.5%)	170 (40.2%)	219 (50.6%)	319 (44.4%)	168 (38.3%)	82 (44.8%)	110 (45.6%)	85 (48%)	773 (62.8%)
50-59	8167 (51%)	1549 (45.3%)	73 (37.1%)	135 (44.6%)	190 (40%)	87 (39.7%)	38 (44.7%)	90 (50%)	41 (43.6%)	923 (64.2%)
60-69	5890 (52.2%)	1059 (48.3%)	26 (44.1%)	71 (56.8%)	61 (38.9%)	26 (40%)	16 (38.1%)	22 (50%)	20 (43.5%)	788 (63%)
70-79	3802 (54.6)	617 (51.6%)	6 (33.3%)	33 (48.5%)	23 (53.5%)	3 (42.9%)	8 (57.1%)	13 (61.9%)	9 (56.3%)	604 (67.6%)
Total	**59709 (52.3%)**	**20065 (48.6%)**	**1480 (50.2%)**	**1936 (47.3%)**	**1979 (43.8%)**	**823 (42.8%)**	**548 (51.5%)**	**614 (47.4%)**	**325 (46.7%)**	**4037 (63.8%)**

Table B.2: Number of all patients, individuals with no diagnosis and 8 disease groups for males by different age groups.

Age Range	Everyone	No diagnosis	Only chronic back pain	Only mental health problems	Only other chronic musculoskeletal problem	Only chronic back pain and other chronic musculoskeletal problem	Only chronic back pain and mental health problem	Only other chronic musculoskeletal problem and mental health problem	Only chronic back pain, mental health problems and other chronic musculoskeletal problem	Chronic back pain, mental health problems and other chronic musculoskeletal problem
10-19	10443 (49.4%)	5602 (51.4%)	294 (45.1%)	783 (58.8%)	729 (52.7%)	178 (49.9%)	75 (42.4%)	161 (51.6%)	39 (48.1%)	94 (39.5%)
20-29	9764 (44.9%)	5135 (47.9%)	368 (43.3%)	546 (49%)	502 (55.9%)	202 (53.2%)	139 (44.4%)	131 (53.9%)	61 (48.8%)	180 (35.5%)
30-39	9367 (47.7%)	4142 (52.4%)	387 (51.4%)	353 (49.4%)	513 (60.4%)	274 (60.1%)	122 (48.8%)	139 (54.5%)	93 (59.2%)	288 (37.6%)
40-49	8459 (48.8%)	2737 (55.5%)	253 (59.8%)	214 (49.4%)	399 (55.6%)	271 (61.7%)	101 (55.2%)	131 (54.4%)	92 (52%)	457 (37.2%)
50-59	7832 (49%)	1870 (54.7%)	124 (62.9%)	168 (55.4%)	285 (60%)	132 (60.3%)	47 (55.3%)	90 (50%)	53 (56.4%)	514 (35.8%)
60-69	5389 (47.8%)	1135 (51.7%)	33 (55.9%)	54 (43.2%)	96 (61.1%)	39 (60%)	26 (61.9%)	22 (50%)	26 (56.5%)	463 (37%)
70-79	3167 (45.4%)	578 (48.4%)	12 (66.7%)	35 (51.5%)	20 (46.5%)	4 (57.1%)	6 (42.9%)	8 (38.1%)	7 (43.8%)	290 (32.4%)
Total	**54421 (47.7%)**	**21199 (51.4%)**	**1471 (49.8%)**	**2153 (52.7%)**	**2544 (56.2%)**	**1100 (57.2%)**	**516 (48.5%)**	**682 (52.6%)**	**371 (53.3%)**	**2286 (36.2%)**

Table B.3: Number of all patients, individuals with no diagnosis and 8 disease groups using Z-drugs for 3 years for females by different age groups.

Age Range	Everyone	No diagnosis	Only chronic back pain	Only mental health problems	Only other chronic musculoskeletal problem	Only chronic back pain and other chronic musculoskeletal problem	Only chronic back pain and mental health problem	Only other chronic musculoskeletal problem and mental health problem	Only chronic back pain, mental health problems and other chronic musculoskeletal problem	Chronic back pain, mental health problems and other chronic musculoskeletal problem
10-19	10 (0.1%)	0	0	2 (0.4%)	0	0	0	1 (0.7%)	0	3 (2.1%)
20-29	203 (1.7%)	19 (0.3%)	0	29 (5.1%)	0	1 (0.6%)	10 (5.7%)	10 (8.9%)	4 (6.3%)	36 (11%)
30-39	496 (4.8%)	44 (1.2%)	5 (1.4%)	52 (14.4%)	0	1 (0.5%)	16 (12.5%)	11 (9.5%)	5 (7.8%)	104 (21.8%)
40-49	1142 (12.9%)	105 (4.8%)	2 (1.2%)	56 (25.6%)	4 (1.3%)	2 (1.2%)	26 (31.7%)	37 (33.6%)	19 (22.4%)	294 (38%)
50-59	2114 (25.9%)	231 (14.9%)	8 (11%)	72 (53.3%)	14 (7.4%)	2 (2.3%)	20 (52.6%)	38 (42.2%)	17 (41.5%)	503 (54.5%)
60-69	2133 (36.2%)	282 (26.6%)	5 (19.2%)	33 (46.5%)	5 (8.2%)	2 (7.7%)	5 (31.3%)	11 (50%)	12 (60%)	495 (62.8%)
70-79	1750 (46%)	244 (39.5%)	2 (33.3%)	17 (51.5%)	4 (17.4%)	1 (33.3%)	5 (62.5%)	6 (46.2%)	2 (22.2%)	407 (67.4%)
Total	**7848** (13.1%)	**925** (4.6%)	**22** (1.5%)	**261** (13.5%)	**27** (1.4%)	**9** (1.1%)	**82** (15%)	**114** (18.6%)	**59** (18.2%)	**1842** (45.6%)

Table B.4: Number of all patients, individuals with no diagnosis and 8 disease groups using Z-drugs for 3 years for males by different age groups.

Age Range	Everyone	No diagnosis	Only chronic back pain	Only mental health problems	Only other chronic musculoskeletal problem	Only chronic back pain and other chronic musculoskeletal problem	Only chronic back pain and mental health problem	Only other chronic musculoskeletal problem and mental health problem	Only chronic back pain, mental health problems and other chronic musculoskeletal problem	Chronic back pain, mental health problems and other chronic musculoskeletal problem
10-19	9 (0.1%)	1 (0%)	0	2 (0.3%)	0	0	0	0	0	1 (1.1%)
20-29	117 (1.2%)	18 (0.4%)	0	27 (4.9%)	1 (0.2%)	0	2 (1.4%)	7 (5.3%)	5 (8.2%)	15 (8.3%)
30-39	295 (3.1%)	30 (0.7%)	6 (1.6%)	43 (12.2%)	2 (0.4%)	4 (1.5%)	14 (11.5%)	13 (9.4%)	9 (9.7%)	50 (17.4%)
40-49	546 (6.5%)	78 (2.8%)	5 (2%)	39 (18.2%)	2 (0.5%)	1 (0.4%)	18 (17.8%)	24 (18.3%)	21 (22.8%)	125 (27.4%)
50-59	970 (12.4%)	145 (7.8%)	5 (4%)	51 (30.4%)	8 (2.8%)	2 (1.5%)	11 (23.4%)	20 (22.2%)	13 (24.5%)	190 (37%)
60-69	1057 (19.6%)	153 (13.5%)	1 (3%)	22 (40.7%)	3 (3.1%)	4 (10.3%)	11 (42.3%)	6 (27.3%)	9 (34.6%)	215 (46.4%)
70-79	883 (27.9%)	138 (23.9%)	1 (8.3%)	14 (40%)	1 (5%)	0	3 (50%)	1 (12.5%)	2 (28.6%)	160 (55.2%)
Total	**3877 (7.1%)**	**563 (2.7%)**	**18 (1.2%)**	**198 (9.2%)**	**17 (0.7%)**	**11 (1%)**	**59 (11.4%)**	**71 (10.4%)**	**59 (15.9%)**	**756 (33.1%)**

Table B.5: : Number of all patients, individuals with no diagnosis and 8 disease groups using Z-drugs and benzodiazepine derivatives for 3 years for females by different age groups.

Age Range	Everyone	No diagnosis	Only chronic back pain	Only mental health problems	Only other chronic musculoskeletal problem	Only chronic back pain and other chronic musculoskeletal problem	Only chronic back pain and mental health problem	Only other chronic musculoskeletal problem and mental health problem	Only chronic back pain, mental health problems and other chronic musculoskeletal problem	Chronic back pain, mental health problems and other chronic musculoskeletal problem
10-19	3	0	0	0	0	0	0	0	0	1
20-29	56	5	0	8	0	0	1	3	0	10
30-39	150	12	1	14	0	0	2	6	2	36
40-49	306	18	1	8	2	0	4	10	6	88
50-59	554	66	2	27	0	0	7	11	3	149
60-69	608	81	0	9	2	0	1	4	2	178
70-79	502	74	1	5	1	0	0	1	0	144
Total	**2179**	**256**	**5**	**71**	**5**	**0**	**15**	**35**	**13**	**606**

Table B.6: Number of all patients, individuals with no diagnosis and 8 disease groups using Z-drugs and benzodiazepine derivatives for 3 years for males by different age groups.

Age Range	Everyone	No diagnosis	Only chronic back pain	Only mental health problems	Only other chronic musculoskeletal problem	Only chronic back pain and other chronic musculoskeletal problem	Only chronic back pain and mental health problem	Only other chronic musculoskeletal problem and mental health problem	Only chronic back pain, mental health problems and other chronic musculoskeletal problem	Chronic back pain, mental health problems and other chronic musculoskeletal problem
10-19	3	0	0	0	0	0	0	0	0	1
20-29	24	5	0	4	0	0	0	1	1	2
30-39	71	5	1	9	1	0	4	0	3	14
40-49	115	20	0	7	0	0	2	3	3	27
50-59	213	34	0	16	0	0	1	2	4	51
60-69	248	35	0	5	1	0	3	1	2	66
70-79	200	25	0	4	0	0	1	0	0	40
Total	874	124	1	45	2	0	11	7	13	201

Boxplots with DDDs for patients with no diagnosis and five disease groups between age groups and genders in the first year:

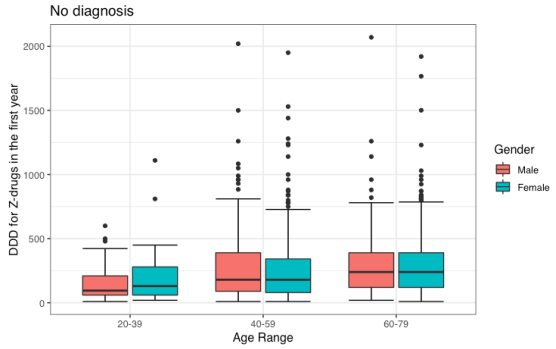

Figure B.1: Boxplot for DDD of Z-drugs in the first year for patients with no diagnosis using Z-drugs for 3 years

Table B.7: DDDs of Z-drugs in the first year by different age groups and genders

	20-39		40-59		60-79	
	Male (n = 48)	**Female (n = 63)**	**Male (n = 223)**	**Female (n = 336)**	**Male (n = 291)**	**Female (n = 526)**
95%	460	417	759.4	780	700	701.5
75%	210	280	390	342	390	390
50%	**95**	**130**	**180**	**180**	**240**	**240**
25%	60	60	90	80	120	120
5%	20	21	31	30	30	40
Mean (SD)	165.7 (153.5)	192.7 (186)*	278.4 (274)	258.1 (264)	290.8 (228)	284.3 (224.7)

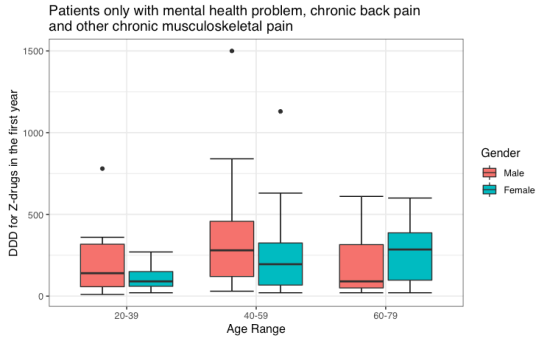

Figure B.2: Boxplot for DDD of Z-drugs in the first year for patients only with mental health problem, chronic back pain and other chronic musculoskeletal problem using Z-drugs for 3 years

Table B.8: DDDs of Z-drugs in the first year by different age groups and genders

	20-39		40-59		60-79	
	Male (n = 14)	**Female (n = 9)**	**Male (n = 34)**	**Female (n = 36)**	**Male (n = 11)**	**Female (n = 14)**
95%	507	234	820.5	562.5	500	522
75%	317.5	150	457.5	325	315	387
50%	140	90	280	195	90	285
25%	57.5	60	120	67.5	50	97.5
5%	16.5	36	40	20	25	33
Mean (SD)	**210 (207.5)**	**112.2 (76.8)**	**348.5 (311.3)**	**239.2 (230.8)**	**183.6 (194.5)**	**266.9 (185.3)**

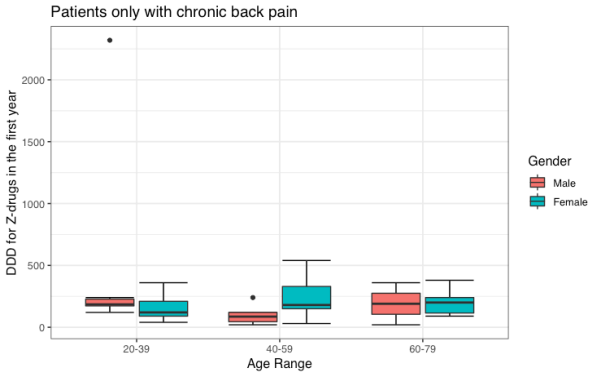

Figure B.3: Boxplot for DDD of Z-drugs in the first year for patients only with chronic back pain using Z-drugs for 3 years

Table B.9: DDDs of Z-drugs in the first year by different age groups and genders

	20-39		40-59		60-79	
	Male (n = 6)	**Female (n = 5)**	**Male (n = 10)**	**Female (n = 10)**	**Male (n = 2)**	**Female (n = 7)**
95%	1800	330	186	472.5	343	347
75%	227.5	210	120	330	275	240
50%	185	120	86	180	190	200
25%	172.5	90	45	150	105	115
5%	132.5	50	20	57	37	90

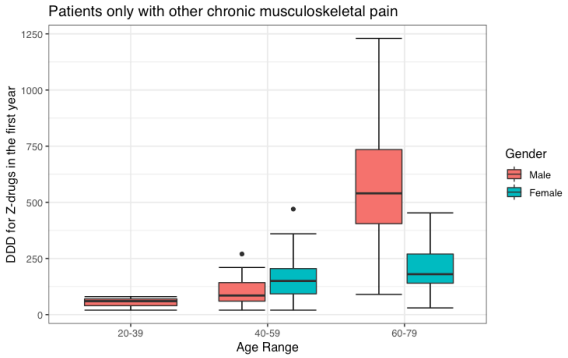

Figure B.4: Boxplot for DDD of Z-drugs in the first year for patients only with other chronic musculoskeletal problem using Z-drugs for 3 years

Table B.10: DDDs of Z-drugs in the first year by different age groups and genders

	20-39		40-59		60-79	
	Male (n = 3)	**Female (n = 0)**	**Male (n = 10)**	**Female (n = 18)**	**Male (n = 4)**	**Female (n = 9)**
95%	78	NA	243	376.5	1131	415.8
75%	70	NA	142.5	205	735	270
50%	60	NA	85	150	540	180
25%	40	NA	60	92.5	405	140
5%	24	NA	29	20	153	42

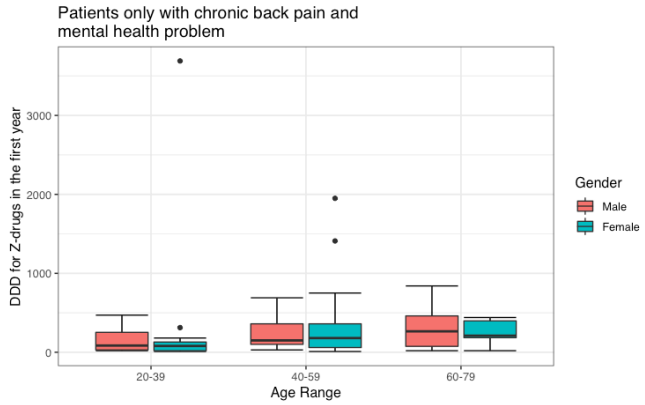

Figure B.5: Boxplot for DDD of Z-drugs in the first year for patients only with chronic back pain and mental health problems using Z-drugs for 3 years

Table B.11: DDDs of Z-drugs in the first year by different age groups and genders

	20-39		40-59		60-79	
	Male (n = 16)	**Female (n = 26)**	**Male (n = 29)**	**Female (n = 46)**	**Male (n = 14)**	**Female (n = 10)**
95%	455	279	534	742.5	781.5	431
75%	252.5	130	360	360	460.5	398
50%	85	80	150	180	265	210
25%	30	20	100	60	75	185
5%	20	12.5	34	20	33	51.5

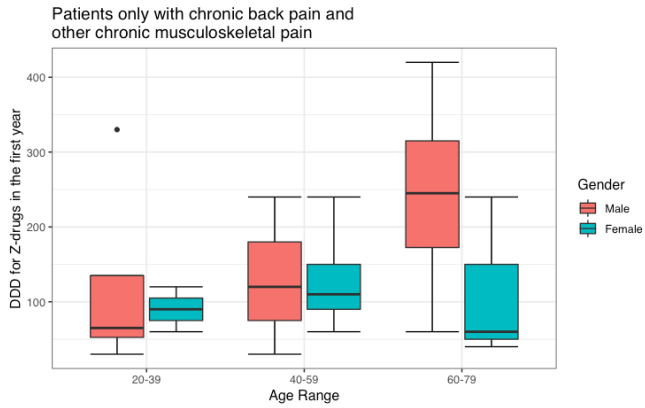

Figure B.6: Boxplot for DDD of Z-drugs in the first year for patients only with chronic back pain and other chronic musculoskeletal problem using Z-drugs for 3 years

Table B.12: DDDs of Z-drugs in the first year by different age groups and genders

	20-39		40-59		60-79	
	Male (n = 4)	**Female (n = 2)**	**Male (n = 3)**	**Female (n = 4)**	**Male (n = 4)**	**Female (n = 3)**
95%	291	291	228	222	1131	222
75%	135	135	180	150	735	150
50%	65	65	120	110	540	60
25%	52.5	52.5	75	90	405	50
5%	34.5	34.5	39	66	153	42

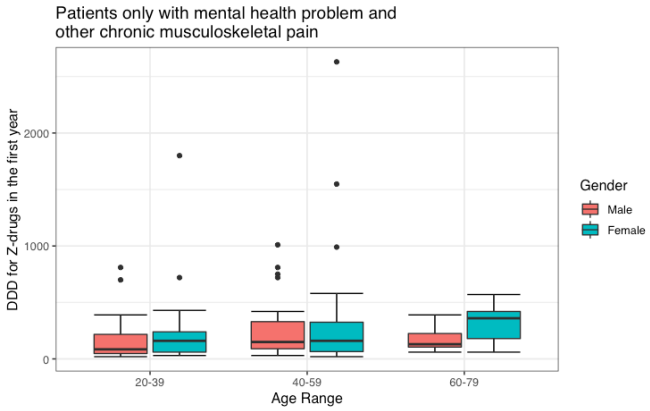

Figure B.7: Boxplot for DDD of Z-drugs in the first year for patients only with mental health problems and other chronic musculoskeletal problem using Z-drugs for 3 years

Table B.13: DDDs of Z-drugs in the first year by different age groups and genders

	20-39		40-59		60-79	
	Male (n = 20)	**Female (n = 21)**	**Male (n = 44)**	**Female (n = 75)**	**Male (n = 7)**	**Female (n = 17)**
95%	705.5	720	745.5	573	345	482
75%	217.5	240	330	325	225	420
50%	85	160	150	160	130	360
25%	47.5	60	90	65	105	180
5%	29.5	40	40	27	69	108

Boxplots with DDDs between years by age groups and genders:

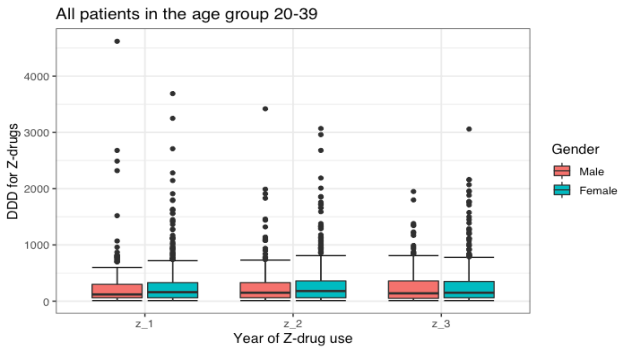

Figure B.8: Boxplot showing DDDs between years for all patients in the age group 20-39 using Z-drugs for 3 years

Table B.14: DDDs of Z-drugs between years

All patients 20-39						
	Z1		Z2		Z3	
	Male (n = 412)	**Female (n = 699)**	**Male (n = 412)**	**Female (n = 699)**	**Male (n = 412)**	**Female (n = 699)**
95%	645	930	690	921	720	811
75%	300	330	330	360	360	350
50%	120	160	150	180	140	150
25%	60	60	60	60	50	60
5%	20	20	20	20	20	20
Mean (SD)	**224.2 (353.9)**	**269.1 (365.5)**	**238.8 (313.8)**	**277.9 (355.7)**	**227.8 (262.6)**	**262.7 (340.3)**

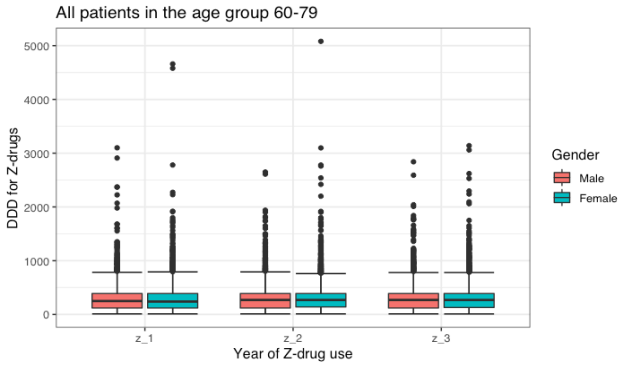

Figure B.9: Boxplot showing DDDs between years for all patients in the age group 60-79 using Z-drugs for 3 years

Table B.15: DDDs of Z-drugs between years

All patients 60-79						
	Z1		Z2		Z3	
	Male (n = 1940)	**Female (n = 3883)**	**Male (n = 1940)**	**Female (n = 3883)**	**Male (n = 1940)**	**Female (n = 3883)**
95%	750	690	750	720	770.1	709.2
75%	390	390	390	390	390	390
50%	250	240	270	270	270	270
25%	120	120	120	140	120	130
5%	30	40	30	30	30	30
Mean (SD)	303.3 (261.4)	296.6 (248)	304.3 (253)	296.3 (251.3)	302.5 (263)	293.5 (237)

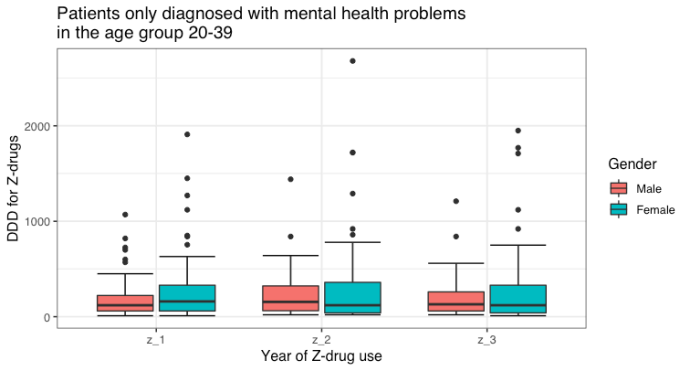

Figure B.10: Boxplot showing DDD between years for patients only diagnosed with mental health problems in the age group 20-39 using Z-drugs for 3 years

Table B.16: DDDs of Z-drugs between years

Only mental health problems 20-39						
	Z1		Z2		Z2	
	Male (n = 70)	**Female (n = 81)**	**Male (n = 70)**	**Female (n = 81)**	**Male (n = 70)**	**Female (n = 81)**
95%	655	850	581	920	528.5	920
75%	222.5	330	322.5	360	260	330
50%	120	160	155	120	130	120
25%	60	60	62.5	40	60	40
5%	20	20	20	20	20	20
Mean (SD)	189.5 (209.5)	261.1 (334.3)	218.6 (228.6)	279.2 (431.3)	193.7 (202.2)	267.5 (378.8)

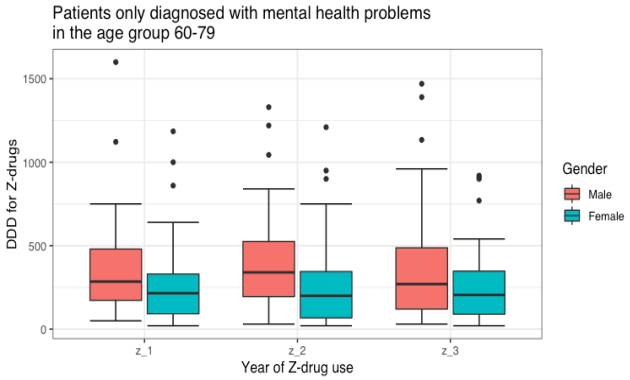

Figure B.11: Boxplot showing DDDs between years for patients only diagnosed with mental health problems in the age group 60-79 using Z-drugs for 3 years

Table B.17: DDDs of Z-drugs between years

Only mental health problems 60-79						
	Z1		Z2		Z3	
	Male (n = 36)	**Female (n = 50)**	**Male (n = 36)**	**Female (n = 50)**	**Male (n = 36)**	**Female (n = 50)**
95%	843	761	1088	832.5	1198	841.5
75%	480	330	525	345	487.5	347.5
50%	285	215	340	200	270	205
25%	172.5	92.5	195	67.5	120	90
5%	60	24.5	60	34.5	30	30
Mean (SD)	382.5 (321.8)	267 (240.9)	393.3 (316.7)	257.8 (249.1)	381.4 (361.7)	255.9 (226.7)

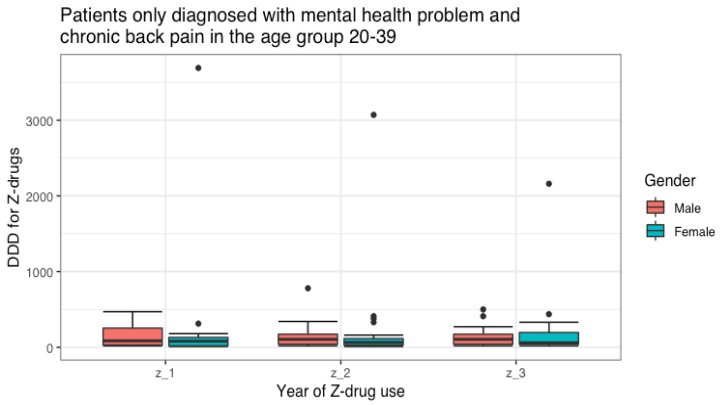

Figure B.12: Boxplot showing DDDs between years for patients only diagnosed with mental health problems and chronic back pain in the age group 20-39 using Z-drugs for 3 years

Table B.18: DDDs of Z-drugs between years

Only mental health problems and chronic back pain 20-39						
	Z1		Z2		Z2	
	Male (n = 16)	**Female (n = 26)**	**Male (n = 16)**	**Female (n = 26)**	**Male (n = 16)**	**Female (n = 26)**
95%	455	279	450	401.8	432.5	410.3
75%	252.5	130	172.5	115	172.5	195
50%	85	80	105	65	105	60
25%	30	20	40	30	40	40
5%	20	12.5	20	20	27.5	20
Mean (SD)	153.1 (155.9)	223.5 (710.5)	155.6 (187.7)	213.3 (592.8)	146.9 (140.5)	193.3 (415.5)

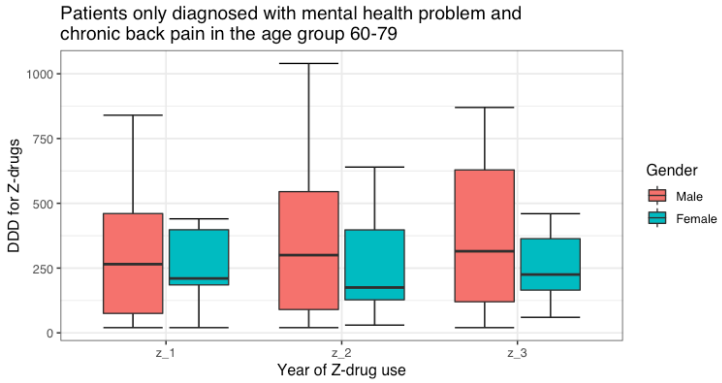

Figure B.13: Boxplot showing DDDs between years for patients only diagnosed with mental health problems and chronic back pain in the age group 60-79 using Z-drugs for 3 years

Table B.19: DDDs of Z-drugs between years

Only mental health problems and chronic back pain 60-79						
	Z1		Z2		Z3	
	Male (n = 14)	**Female (n = 10)**	**Male (n = 14)**	**Female (n = 10)**	**Male (n = 14)**	**Female (n = 10)**
95%	781.5	431	890.5	541	850.5	428.5
75%	460.5	398	545	397.5	629	363.5
50%	265	210	300	175	315	225
25%	75	185	90	127.5	120	165
5%	33	51.5	46	30	65.5	78
Mean (SD)	306.7 (262.3)	256.2 (147.7)	355.7 (318.9)	253 (199.4)	384 (310)	254.6 (133.7)

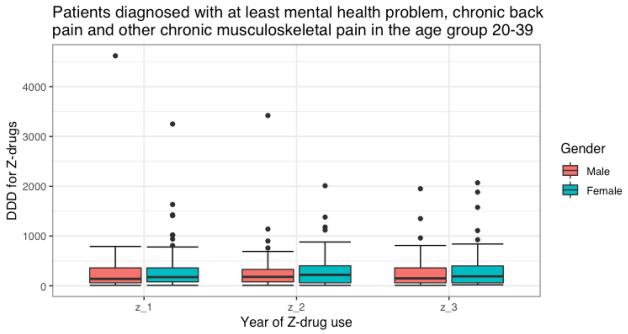

Figure B.14: Boxplot showing DDDs between years for patients diagnosed with at least mental health problem, chronic back pain and other chronic musculoskeletal problem in the age group 20-39 using Z-drugs for 3 years

Table B.20: DDDs of Z-drugs between years

Mental health problem, chronic back pain and other musculoskeletal pain 20-39						
	Z1		Z2		Z2	
	Male (n = 65)	**Female (n = 140)**	**Male (n = 65)**	**Female (n = 140)**	**Male (n = 65)**	**Female (n = 140)**
95%	756	816.5	746	781.5	782	767.2
75%	360	360	330	402.5	360	400
50%	140	175	180	220	150	190
25%	60	80	80	60	60	60
5%	20	20	20	20	20	20
Mean (SD)	293.1 (582.2)	289.7 (380.6)	285.2 (456)	294.7 (298.6)	255.6 (323.3)	290.1 (324.1)

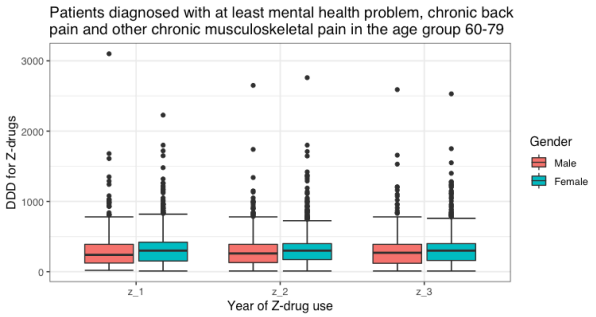

Figure B.15: Boxplot showing DDD between years for patients diagnosed with at least mental health problem, chronic back pain and other chronic musculoskeletal problem in the age group 60-79 using Z-drugs for 3 years

Table B.21: DDDs of Z-drugs between years

Mental health problem, chronic back pain and other musculoskeletal pain 60-79						
	Z1		Z2		Z3	
	Male (n = 375)	**Female (n = 902)**	**Male (n = 375)**	**Female (n = 902)**	**Male (n = 375)**	**Female (n = 902)**
95%	819	779	820	769.5	777.2	749.5
75%	390	420	390	400	390	400
50%	240	300	260	300	270	300
25%	123.5	152.5	130	172.5	120	160
5%	37	40	40	40	30	30
Mean (SD)	313.7 (291.2)	329.6 (245.6)	306.8 (268.1)	327.7 (249.7)	306.5 (266.7)	324.7 (242.6)