Determinants and consequences of long-term benzodiazepine use

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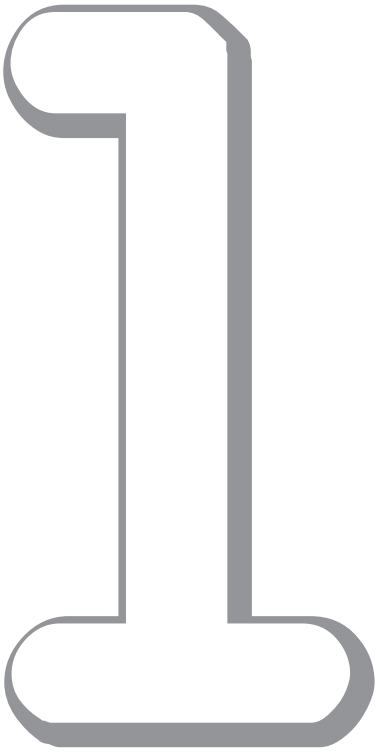
General Introduction



Benzodiazepines (BZDs) are a class of psychotropic drugs with anxiolytic, muscle-relaxant and hypnotic properties.[1] In clinical practice, they are mainly used to manage the symptoms of anxiety and insomnia.[1] BZDs are the most prescribed psychotropic drugs worldwide and although it has regularly been stated that prescription rates have declined during the past 15 years,[2] statistics reveal that the prevalence of BZD use has actually remained quite stable.[3] There is a broad evidence-based knowledge foundation for the effects of short-term use of BZDs, but studies in long-term users are less common. Instead, oftentimes, clinicians' observations seem to form the basis of ideas on long-term BZD use and related prescribing decisions. However, as many BZD users are long-term users, prescribing decisions for these patients should be based on clinical research conducted in representative samples. An obvious reason for the lack of randomized clinical long-term trials in chronic BZD users is not only of pragmatic but also of ethical nature. It is not justified to administer BZDs for more than a few weeks, due to the high risk of side effects and dependence development. Up to now, prospective research is lacking for a number of the possible determinants and consequences of long-term BZD use. Therefore, the thesis on hand aims to investigate the determinants and consequences of long-term BZD use in subjects at different stages of psychopathology and healthy controls.

This introduction consists of four parts: In part A, an overview of the indications, prevalence and subjects at risk of BZD use will be provided. The possible influence of the prescribers on BZD use will also be discussed. In part B, the working mechanism of BZDs and physiological consequences of long-term BZD use will be described. In part C, the cognitive side effects of the BZDs and especially their effects on reaction time (RT) will be addressed with a special focus on chronic use. Finally, in part D, the studied sample, the structure as well as the aims of this thesis will be outlined.

PART A) BZD USE, INAPPROPRIATE USE, AND THE INFLUENCE OF BZD PRESCRIBERS

Indications of BZD Use

In the Netherlands, BZDs are registered for the short-term treatment of insomnia and anxiety disorders.[1,4] Besides, BZDs are used as preoperative drugs and for emergency sedation as well as to treat epilepsy, alcohol withdrawal symptoms, febrile seizures, and acute insults. The British National Formulary divides BZDs into anxiolytics, used for the reduction of anxiety symptoms (ATC-code N05BA) and hypnotics (ATC codes N05CD for BZDs and N05CF for BZD related compounds) used for the short-term treatment of insomnia. This categorization is commonly used, but arbitrary, as both types of BZDs have similar actions. Anxiolytics will induce sleep when administered at night and hypnotics will have anxiolytic effects when used during the day at the respective dosages.[5] Differences between anxiolytics and hypnotics are related to their duration of action, which depends on the metabolic half-life and the presence of active metabolites. Nevertheless, also long-acting BZDs such as nitrazepam and flurazepam are considered as hypnotics, although they were proven to have residual effects the next day.[6] The most common BZDs in the Netherlands are summarized in table 1.[1,6,7]

Table 1: Common BZD Agonists

Drug	Trade name in the Netherlands	Approximate equivalent dose of 10mg diazepam	Mostly marketed as anxiolytic/ hypnotic
Alprazolam	Xanax	1mg	Anxiolytic
Bromazepam	Lexotanil	10mg	Anxiolytic
Brotizolam	Lendormin	0,25mg	Anxiolytic
Chlordiazepoxide	Chlordiazepoxide	20mg	Anxiolytic
Clobazam	Frisium, Urbadan	20mg	Anxiolytic
Clorazepate	Clorazepaat, Tanxene	13,3mg	Anxiolytic
Diazepam	Diazepam, Stesolid, Valium	10mg	Anxiolytic
Flunitrazepam	Flunitrazepam, Rohypnol	1mg	Hypnotic
Flurazepam	Dalmadorm, Flurazepam	30mg	Hypnotic
Loprazolam	Dormonoct	1mg	Hypnotix
Lorazepam	Lorazepam, Temesta	2mg	Anxiolytic
Lormetazepam	Loramet, Lormetazepam, Noctamid	1mg	Hypnotic
Midazolam	Dormicum	7,5mg	Hypnotic
Nitrazepam	Mogadon, Nitrazepam	10mg	Hypnotic
Oxazepam	Oxazepam, Seresta	33,3mg	Anxiolytic
Prazepam	Reapam	20mg	Anxiolytic
Temazepam	Normison, Temazepam	20mg	Hypnotic
Zolpidem	Stilnoct	20mg	Hypnotic
Zopiclone	Zimovane	13mg	Hypnotic

BZDs are registered[8] and proven effective for the short-term symptomatic relief of insomnia as they accelerate sleep onset, reduce nocturnal awakenings, and increase total sleep time.[1,9,10] This has been proven in several randomized controlled trials.[11-13] However, BZDs also reduce the duration of slow wave sleep and rapid eye movement sleep.[1,14] For these reasons in addition to BZDs' risk of side effects, tolerance, and

dependence development, prescription guidelines recommend to limit BZD prescriptions to the short-term treatment of severe insomnia, which is considered to be disabling or extremely distressing[1] and could not be relieved by sleep hygiene and information about the normal sleep cycle.[8] Guidelines recommend treating transient insomnia caused by a disruption of the circadian rhythm such as in overnight travel or shift work with an occasional BZD.[1] Short term insomnia due to temporary environmental stress may be treated by BZDs for a maximum of two weeks.[1] Chronic insomnia is usually secondary to other conditions, thus it is more effective to treat the cause of insomnia than the insomnia itself.[1] Further, BZDs do not seem to maintain effectiveness in longer-term treatment of sleep problems[1,15,16] and chronic use was found to be associated with complex changes of sleep architecture leading to poor quality of sleep.[6] Therefore, long-term BZD use is not recommendable.

Regarding anxiety, a large number of randomized controlled trials have proven the effectiveness of BZDs in the short-term, symptomatic treatment of social phobia,[17,18] general anxiety disorder,[19] panic disorder,[20,21,22] and acute states of anxiety. The United Kingdom Committee on Safety of Medicines advised to limit BZD prescriptions to two to four weeks for anxiety that is severe, disabling or causing unacceptable distress.[1] Single doses of BZDs may be used to prevent predictable, acute stress reactions such as air travel or dental appointments in phobic patients. Yet, psychological therapies are preferable in the long-run.[1] Very short-term treatment of one to seven days may be indicated for stress reactions after catastrophic events such as natural disasters and accidents, as spontaneous resolution is common.[1] BZDs are not recommended after the death of a loved person as they may inhibit the grieving process, but a few days of use may be justified.[1] Intermittent treatment of two to four weeks can be of value in episodic anxiety often observed in chronic generalized anxiety disorder, but the longer the duration of treatment the less the benefit.[1] The anxiolytic effects of BZDs may be more resistant to tolerance than the sedative, anticonvulsant or

muscle-relaxant effects and enduring anxiolytic effectiveness for two to six months was proven by several clinical trials.[23-25] In contrast, other studies did not detect differences between BZDs and placebo in long-term use,[26] indicating that the anxiolytic effect is not maintained. Furthermore, long-term BZD users were regularly found to suffer from severe anxiety and insomnia although these are the symptoms that BZDs are supposed to reduce. This suggests that BZDs do not sufficiently reduce insomnia and anxiety symptoms (anymore) in long-term users. However, as results are inconsistent, it is unclear when tolerance to BZDs anxiolytic effects develops and if BZDs are effective in the reduction of stress and anxiety symptoms when used chronically.

The Prevalence of BZD Use

The prevalence of BZD use in the Netherlands has been quite stable over the past 15 years. In 1996, 1.3 million individuals used BZDs with the ATC codes N05BA, 0.8 million used BZDs with the ATC code N05CD, and 0.1 million used BZDs with the ATC code N05CF.[3] These numbers cannot be added as many BZD users concomitantly use different types of BZDs. Interestingly, the number of BZD users had hardly changed 12 years later when 1.2 million (ATC code N05BA), 0.7 million (ATC code N05CD) and 0.2 million (ATC code N05CF) subjects used the different groups of BZDs.[3] In 2010 – only two years later – these numbers differed dramatically: Only 0.3 million (ATC code N05BA), 0.1 million (N05CD), and 0.4 million (N05CF) subjects used BZDs.[3] This decrease of the "official" BZD use was due to a Dutch governmental measure in January 2009 that aimed to reduce unnecessary and inappropriate BZD use and its accompanying costs.[27,28] Since then, BZDs are only compensated by Dutch health care insurance if patients must use BZDs due to lacking alternatives (epilepsy, treatment resistant anxiety, psychiatric comorbidity, palliative sedation).[27,28] Yet, the Dutch foundation of pharmaceutical core numbers stated that the much lower prevalence numbers did not represent the true user numbers. Instead, the majority of users had not discontinued

their BZD use but paid for the drugs themselves.[3] Accordingly, the actual number of BZD users in the Netherlands was estimated at 1.5 million,[29] which corresponds to a prevalence rate of 9.0% (for the total Dutch population of 16,6 million people) and indicates that BZD use has not decreased much in the past 20 years.[30] The BZD use in the Netherlands seems to be comparable to the use in other countries. Lader et al. reviewed papers of different countries and reported that the prevalence rates of BZD use range between 2.2% and 17.6%.[6]

The Initiation of BZD Use

As the indications for BZD use are restricted, even in a population of subjects who mainly suffer from depression and/or anxiety, it is interesting to identify the determinants of BZD use. It will provide clinicians with a clearer picture of actual BZD use and how far that behaviour diverges from the treatment guidelines. Longitudinal research on new-onset BZD use is scarce and the identified predictors differ between studies. In these studies, the initiation of BZD use was found to be predicted by female gender,[31] older age,[31] divorce,[31] psychopathology,[32] insomnia,[33] alcohol abuse,[32] antidepressant use,[32] smoking,[33] poor physical health,[33] and joint pain.[33] These studies were restricted to very specific samples such as retired workers[31] and elderly subjects.[32] Additionally, the associations of changes in psychopathology over time and life events with BZD use have not been studied in longitudinal research, although they may very well precede transitions in BZD use. In order to identify the independent determinants of the initiation of BZD use, we included the previously identified determinants of BZD use plus a number of new determinants into a multivariate model. We were also interested if the predictors of BZD use in a sample mainly consisting of anxious and depressed subjects would be similar to those identified in the previous samples (which were constituted by very specific groups of subjects such as elderly persons or retired workers).

Chronic BZD Use

The persisting high prevalence of (chronic) BZD use despite the limited indications makes it interesting to determine its correlates. Cross-sectional studies identified several sociodemographic (sex,[34] age,[34] education,[34] unemployment[35]), psychological (psychopathology,[35] antidepressant use,[35] neuroticism[36]), and physical (chronic illnesses,[36] pain,[37] GP visits[38]) correlates of BZD use. However, these studies differed in the correlates they included so that findings were not always comparable. Further, they did not always conduct a multivariate analysis[34,38] so that the independent correlates of BZD use could not be identified. Therefore, a study which includes all important previously identified correlates of BZD use in one multivariate model is needed, in order to identify the independent correlates of BZD use. However, cross-sectional research provides no information of the order in which the investigated variables occur, so that it is unclear if an identified correlate actually is a risk factor or otherwise related to BZD use. Longitudinal studies are superior as they permit to identify the risk factors that precede chronic BZD use. Previous longitudinal research identified a number of sociodemographic (gender,[39] age,[33,40,41] being divorced,[39]), health related (psychopathology,[42] insomnia,[39,42] poor physical health,[39,43] number of GP contacts,[39] pain,[33] chronic diseases,[44] antidepressant use[32]) and BZD use related (dosage,[43] duration,[43] half-life,[41] past use, [40,42,44,45] daily use,[40] hypnotic use[43]) predictors of continued BZD use.

However, again, findings were inconsistent between studies, possibly due to the investigation of different and small sets of determinants per study, distinct definitions of the outcome variable (such as three months[43] /six months[33]/ three years[39] of BZD use, psychotropic use[46]) as well as different measurement methods of BZD use (pharmacy records,[33] observing medication containers,[39] self-report[46]). Further, studies focused on different study samples (such as elderly subjects[33,39,46] or BZD users only[43]) which may also have differentially influenced the results. Changes of psychopathology and life events have not been investigated

yet as possible determinants, although they might precede transitions in BZD use. Therefore, to identify the risk factors of transitions in BZD use, prospective research is needed, which includes the most important predictors identified in previous research, plus those that have not been considered previously, and investigates them in a multivariate model.

Inappropriate BZD Use

BZDs are relatively safe when an overdose is taken, and symptoms of severe poisoning are rare in young, healthy adults.[47] However, hypotension and coma have been reported in elderly subjects and children[48,49] and seniors were repeatedly found to experience cognitive impairments, psychomotor slowing, and reduced functional autonomy subsequent to BZD use.[50] Further, higher doses of BZDs were found to cause respiratory depression and may therefore be dangerous to patients with severe chronic obstructive pulmonary disease.[51] Younger adults may also experience complications when a BZD overdose is combined with alcohol, opiates, and tricyclic antidepressants. BZD use was also found to strongly increase suicidal and non-suicidal deaths in patients suffering from schizophrenia.[52] Long-term use was associated with the development of dependence as well as lasting memory impairments.

To prevent these unwanted effects, international prescription guidelines recommend cautious prescription of BZDs with dosages lower or equal to the defined daily dosage (as developed by the World Health Organization) for a maximum duration of two weeks for insomnia and two months for anxiety.[4,8] Still, BZD users and prescribers do not always adhere to these guidelines and chronic BZD use is a common phenomenon. In 2009, the average BZD user in the Netherlands received 175 daily dosages, equalling approximately six months of average BZD use.[3] Research has also shown that many BZD users receive prescriptions for more than one type of BZD, although they all have comparable effects (in different potencies).[53] Using several BZDs concomitantly for different

indications (e.g. anxiety, sleep and muscle spasms) can easily and unnecessarily lead to dose escalation.

The identification of subjects at risk of inappropriate BZD use would allow medical doctors to make more balanced prescribing decisions. Up to now, only the correlates of long-term use were studied. In these studies, sex,[54,55] age,[54,55] education,[56] psychological[33,57] and physical health,[33,57] antidepressant use,[57] daily BZD use,[40] and use of higher potency BZDs[41] were identified as important correlates of long-term BZD use. Research on the correlates of inappropriate use as a whole (including dosage and concomitant use of >1 type of BZD) does not exist yet, although these guideline deviations regularly occur. Therefore, research on the correlates of inappropriate BZD use is needed.

BZD Dependence

When BZDs were originally introduced in clinical practice, they were thought to be free of addictive properties. However, since the early 1970s it is apparent that BZDs can produce physiological dependence and withdrawal symptoms. According to the Diagnostic and Statistical Manual of Mental Disorder Fourth Edition - Text Revision (DSM-IV-TR) substance dependence (including BZD dependence) is defined as a maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring any time in the same 12-month period (Table 2).

Research suggests that a substantial proportion of users will develop BZD dependence, also at low doses.[58,59] With 9.5% - 40.0% of outpatient BZD users developing dependence, the prevalence is high.[6,58-61] Nevertheless, clinicians often seem to overlook BZD dependence,[62] downplay its importance[63] or fail to discuss it with their patients.[63] According to the CASA National Survey of Primary Care Physicians and Patients on Substance Abuse, less than one third of primary care physicians screen for substance abuse.[64] The generation of a risk profile of subjects vulnerable of BZD dependence may help the treating GPs to

Table 2: DSM-IV-TR Criteria of Substance Dependence

Tolerance (marked increase in amount; marked decrease in effect)
Characteristic withdrawal symptoms; substance taken to relieve withdrawal
Substance taken in larger amount and for longer period than intended
Persistent desire or repeated unsuccessful attempt to quit
Much time/activity to obtain, use, recover
Important social, occupational, or recreational activities given up or reduced
Use continues despite knowledge of adverse consequences (e.g., failure to fulfill role obligation, use when physically hazardous)

prevent BZD dependence in certain subjects or at least to identify the problem at an early stage and discuss it with the patient.

In previous research, BZD dependence was found to be associated with sociodemographic factors (female gender,[65] lower age,[66] non-Dutch cultural origin,[66] and retirement[66]), psychological and physical health factors (negative mood,[67] depression,[66,68] anxiety,[65,66,68] antidepressant use,[69] hostility,[66] a lower quality of life,[68] and somatization[67]), addiction related factors (treatment for dependence[66]), and BZD use related factors (a high daily dosage[66,69] and long-term BZD use[66,69]). However, findings differed between studies, amongst others due to differing samples[65,66,68,69] and definitions of BZD dependence.[65-70] Most importantly, the majority of the studies applied dichotomous (yes/no) definitions of dependence,[65,68] while the clinical expression of BZD dependence is better modeled using several subscales[70] and severity dimensions such as in the BZD Dependence Self-Report Questionnaire (Bendep-SRQ).[71]

Only one previous study has investigated the correlates of these three subscales of the Bendep-SRQ.[66] Higher age, depressive disorder, duration and dosage of BZD use were associated with higher scores on problematic use.[66] Anxiety disorder and a longer duration of BZD use were associated with more preoccupation.[66] Lower age, retirement, duration of BZD use and a higher dosage were associated with more

lack of compliance.[66] Being an outpatient in a substance addiction center was associated with higher scores on all three subscales.[66] However, this study did not examine the impact of several potential physical and addiction-related correlates such as chronic illnesses, pain, and alcohol dependence. For this reason, a study determining the independent sociodemographic, psychological, physical, addiction-related, and BZD use-related correlates of the BZD dependence severity dimensions is needed.

GP Characteristics, Patient Characteristics, and BZD Use

GPs may contribute to the inappropriate BZD use of their patients. However, in the previous investigations of risk factors of patient BZD use, the focus was mainly on patient characteristics while GP characteristics received less attention. Existing research on the physician correlates of patient BZD use was mainly of qualitative nature.[63,72-78] These studies reported that the majority of physicians were aware of and supported the treatment guidelines. [73,75,77] Yet, BZDs were frequently and inappropriately prescribed due to a lack of time,[72,74,79-81] alternatives,[77,79,80,82] and skills,[74,79-81] the idea that BZDs are the appropriate treatment for vulnerable patients,[73,79,82] and the wish to maintain a good-doctor patient relationship.[74,75,80,81]

Quantitative studies on the physician characteristics associated with patient BZD use were scarce. Physician correlates of BZD use were male gender,[83,84] personal usage of BZDs,[85] being a general practitioner (as opposed to a psychiatrist),[83,85] allowing patients to influence prescription decisions,[84] prolongation of prescriptions without direct doctor-patient contact,[84] and multiple drug prescribing.[86] Several studies did not identify any significant physician factors of BZD use[87,88] or found inconsistent results.[83-86,89] Quantitative studies on physician correlates of inappropriate BZD use have not been conducted yet. However, one study investigated the correlates of long-term BZD use and found that

practice and patient characteristics were more important predictors than physician characteristics.[90]

Most of the above mentioned studies did not correct for patient characteristics[83-85] so it is unclear if the differences found were due to variation between physicians or due to differences between the treated patients. The attitudes of physicians towards depression and anxiety, guideline implementation, and collaboration with health care specialists have also received little attention,[83,87,89,90] although these attitudes may influence the patients' BZD use. Therefore, a study which investigates the general practitioner (GP) correlates of patient BZD use and inappropriate BZD use and corrects for important patient correlates of BZD use is needed in order to tell whether GP characteristics affect patient BZD use or if it is rather due to certain characteristics of the treated patients that GPs prescribe BZDs (inappropriately).

PART B) THE BIOLOGICAL CONSEQUENCES OF BZD USE

The Working Mechanism of BZDs

BZDs exert their action by binding to the receptor for gamma-aminobutric acid (GABA) and potentiating the effect of the inhibitory neurotransmitter GABA. There are three types of GABA-receptors: A, B, and C. The BZDs bind to $GABA_A$, while baclofen (Lioresal) binds to $GABA_B$.[91] GABA is the most abundant inhibitory neurotransmitter in the human central nervous system.[92] Depending on the brain region 20-50% of all neurons use GABA as neurotransmitter.[91,93] $GABA_A$ receptors are ion channels through which chloride anions pass when GABA binds to the $GABA_A$ receptor.[91] This leads to a hyperpolarization of the postsynaptic neuron, and renders it less sensitive to excitatory neurotransmitters so that neuronal activity is inhibited. BZDs enhance the inhibitory effect of GABA as they increase the frequency of GABA induced chloride channel openings.[91] This reduces the turnover of several neurotransmitters

involved in emotional expression such as norepinephrine and serotonin and has a calming effect on many functions of the brain.[94] The main sites of action of the BZDs are in the spinal cord, where BZDs mediate muscle relaxation, the brain stem and the cerebellum, where they cause ataxia, and the limbic and cortical areas, where they are involved in emotional experience and behaviour.[6]

The $GABA_A$ receptor consists of five subunits and was found to be assembled from a family of at least 15 subunits (α1-6, ß1-3, γ1-3, θ, and p1-2) into different receptor complexes in rats.[95] The most common receptors consist of two alphas, two betas and one gamma (α2ß2γ).[96] $GABA_A$ receptors that are made of different subunit combinations differ in properties, distributions in the brain and clinical effects. The α1 subunit is the most abundant in most areas of the adult brain.[97] Yet, in the hypothalamus and the hippocampus, α2 is the most dominant subunit,[97,98] while in the deep cortical layers α3 is the major subunit.[98] Hence, different BZDs can have different affinities for different $GABA_A$ receptor subunit combinations, the activation of which may result in different pharmacological actions.[99] BZDs bind at the interface of the α (α1, α2, α3, or α5) and the γ subunit of the $GABA_A$ receptor.

Studies in knock-out mice investigated the effect of BZDs on certain $GABA_A$ receptor subtypes. These studies found that agonists for α1 were associated with hypnotic, amnesic, anticonvulsive and addictive effects,[96] agonists for α2 mediated anxiolytic and myorelaxant effects,[96] agonists for α3 subunits were associated with anxiolytic and analgesic effects,[96] and inverse agonists for α5 improved learning and memory.

Possible (Long-Term) Effects on the Hypothalamic-Pituitary-Adrenal (HPA) axis

The hypothalamic - pituitary - adrenal (HPA) axis is a complex set of direct influences and feedback interactions among the hypothalamus, the pituitary gland, and the adrenal glands. It controls reactions to stress and regulates many body processes, including digestion, the immune

system, mood and emotions, sexuality, energy storage and expenditure. It plays a central role in the body's neuroendocrine reaction to stress.[100]

As BZDs bind to $GABA_A$ receptors, which are densely located in the paraventricular nucleus (PVN) of the hypothalamus,[97,98] they may directly affect the HPA axis. Especially the α2 subunit of the $GABA_A$ receptor, which has been associated with the anxiolytic effects of BZDs, has been found to be abundant in the hypothalamus.[97] Possibly, BZDs inhibit the production of the corticotrophin-releasing-hormone (CRH) via their action on the $GABA_A$ receptor in the PVN of the hypothalamus, leading to less secretion of the adrenocorticotropic hormone (ACTH) in the pituitary gland, and to less production of cortisol in the adrenal cortices. This effect on the HPA axis may underlie BZDs' anxiolytic and stress reducing action.

A number of studies investigated the acute effects of BZDs on the HPA axis and mostly reported decreased cortisol levels after administration of BZDs.[101-105] This suggests that BZDs acutely suppress the HPA axis. These suppressed cortisol levels were found to increase again 30 minutes to 2,5 hours later, indicating that this effect is transient.[106,107]

Whether BZDs acute cortisol suppressant effect is maintained in long-term use, received less attention in the past. There was only one small cross-sectional study which reported similar cortisol levels in long-term BZD users (> 3 months) and non-users.[108] This implies that BZDs do not maintain their full cortisol-suppressing effects during longer term use. In contrast, an additional dosage of BZDs (on top of the BZD dosage that chronic users took on a daily basis) still affected the HPA axis in chronic users. Additional research is needed in order to investigate whether tolerance to BZDs effects on the HPA axis develops in chronic BZD use.

Possible (Long-Term) Effects on the Autonomic Nervous System

The autonomic nervous system (ANS) consists of the sympathetic nervous system (SNS), which stimulates "rest-and-digest" activities,

and the parasympathetic nervous system (PNS), which mobilizes the fight-or-flight response. In research, PNS activity is often measured through respiratory sinus arrhythmia (RSA) which is an index of heart rate variability (HRV).[109] SNS activity can be measured through the pre-ejection period (PEP) which is a widely used, valid index of sympathetic effects on cardiac contractility.[110,111] Heart rate (HR) reflects the control of PNS and SNS on the heart.[109,111]

Based on animal research, BZDs were suggested to suppress (stress-induced) sympathetic activation by enhancing the sympatho-inhibitory effects of GABA on presympathetic neurons in the PVN of the hypothalamus.[112,113] Alternatively, BZDs have been hypothesized to enhance direct GABAergic inhibition of cardiac vagal neurons and GABAergic inhibition in the nucleus tractus solitarii and thereby decrease HRV.[114] However, BZDs may also affect the ANS via GABA in other brain structures (such as nucleus ambiguous,[115] caudal ventrolateral medulla,[115] rostral ventrolateral medulla,[115] medullary raphe nuclei[116]), as GABA is localized in many discrete autonomic centers of the brain. The above mentioned hypotheses have been investigated in short-term intervention studies with humans with the following results. In line with the hypothesis that BZDs suppress SNS activity, BZDs were found to suppress stress-induced increases of sympathetic activity.[117-119] In contrast, in other research studies BZDs heightened sympathetic outflow,[114] did not have any effects on the SNS[120] or increased HR.[114,121-125] During rest, BZDs were either reported to decrease sympathetic tone[126-128] or not to have any effect at all.[120,124,129,130] Corresponding to the hypothesis that BZDs have vagolytic effects, BZDs were commonly found to attenuate HRV[114,121,122,124,125,131,132] and to increase HR.[114,121-125] Only two studies reported elevated HRV[128,133] and HR[120] after BZD administration.

Opposite to intervention studies, observational research on the effects of BZDs on the ANS is less common. BZDs' effects on the SNS activity have not been investigated yet. Regarding PNS activity, cross-sectional research of our own group did not find significant differences

in HRV and HR between BZD users and non-users.[109] The discrepancy of this finding with previous research may be due to the joint investigation of different types of BZDs with possibly opposing effects,[128] which may have covered BZDs' effects on the ANS in long-term users. Alternatively, only frequent BZD use or high BZD dosages may lead to alterations of ANS activity. Finally, long-term users may develop tolerance to the effects of BZDs on the ANS so that they no longer differ from non-users.

As BZDs effects on the SNS as well as the potential effects of type of BZD, dosage, duration and frequency of BZD use on the ANS have not been studied previously, additional research is needed. Further, longitudinal research on BZDs effects on the ANS is eligible in order to validate cross-sectional results.

PART C) SEDATIVE AND ATTENTION IMPAIRING EFFECTS OF BZDS

Cognitive Effects of BZDs in short-term and long-term Use

BZD use interferes with multiple cognitive functions. The most common problems of short-term BZD use are unintended subjective sedation[134] (e.g., sleepiness and mental slowness), objective sedation[135] (e.g., cognitive processing speed and psychomotor slowing), inattention,[136] and anterograde impairments of memory.[136,137] Increased sedation and altered psychomotor skills impair everyday tasks such as driving or operating machinery.[138] Therefore, BZD use increases the risk of (traffic) accidents, (workplace) injuries and falls with possibly resulting hip fractures.[139] This risk rises at higher age and increased doses and when BZD are used concomitantly with alcohol.[140,141]

While the side effects of BZD use in short-term users are firmly established,[136] research in chronic users is less frequent. The existent research revealed that tolerance to BZDs side effects seems to develop (differentially) over time.[142] Memory deficits were found to persist in long-term use on most memory tasks,[142-144] indicating that tolerance to these

effects never fully develops. Tolerance to the subjective and objective sedative effects of BZDs was detected in long-term users[142,144] and experimental research reported that tolerance began to develop already after two weeks of use. Other research studies found sustained attention impairments in chronic BZD users,[145] but no impairments of simple reaction time.[145]

BZDs effects on objective sedation and attention impairments are often measured by 'reaction time' (RT),[146,147] which is defined as the time interval between a sensory stimulus and response.[148,149] Prolonged RTs in BZD users would indicate sedation or inattention or both.[150] Only a few studies investigated the effects of long term use on RT and reported inconsistent results. One cross-sectional, observational study did not detect longer RTs in chronic BZD users as compared to healthy controls.[151] In contrast, another study found longer RTs in chronic BZD users with anxiety than in healthy non-users,[150] but did not investigate whether the increased RTs were due to psychopathology or the use of BZDs.[150] As psychopathology was found to increase RT in previous research, this may be the reason for the increased RT detected in this study. Consistently, a different study found longer RTs in depressed subjects (half of whom used BZDs) as compared to healthy volunteers.[152] When analyses were repeated in the depressed group only, RTs did not differ between BZD-users and non-users.[152] This suggests that the increased RTs were due to psychopathology rather than BZD use.

This longitudinal research has several limitations. Most studies investigated a small number[142] of healthy volunteers[153] for a duration shorter than three months[153], although the majority of BZD users suffers from psychopathology and administers BZDs for a much longer duration of use. Further, these studies did not correct for established confounders of BZD use and RT (level of education, psychopathology,[150,154] physical health[150,152] and antidepressant use[150]). Therefore, observational research that investigates a large sample representative of the average BZD user (i.e. long duration of use, comorbid psychopathology) and corrects for

important confounders is needed in order to determine whether in long-term BZD use the effects of BZD on RT remain or tolerance develops.

PART D) STUDIED SAMPLE AND OUTLINE OF THE THESIS

The Netherlands Study of Depression and Anxiety

The present thesis is based on a large depression and anxiety cohort: The Netherlands Study of Depression and Anxiety (NESDA). NESDA is an ongoing, multicenter, longitudinal, observational cohort study of 2981 adults aged 18-65 years. The major aims of the NESDA study were: 1) describing the long-term prognosis of depression and anxiety disorders, 2) examining the determinants and consequences of depression and anxiety disorders, and 3) evaluating patients' expectations, evaluations and provision of mental health care and their association with the long-term course and consequences of these disorders.[155] NESDA was designed to be representative of individuals with depressive and anxiety disorders in different health care settings and different developmental stages of illness.[155] Therefore, subjects with no symptoms ('controls'), those with earlier episodes or at risk, and those with current depression and/or anxiety disorders were recruited from two population studies (the 'Adolescents at Risk of Anxiety and Depression' study, n=261 and the 'Netherlands Mental Health Survey and Incidence Study' n=303), 65 general practices (n=1610), and specialized mental health care institutions (n=807) throughout the Netherlands.[155] The mean age of the study sample was 41.9 years at baseline (standard deviation [SD] = 13.0) and 66.4% was female.

The NESDA interviews were performed by trained interviewers and recorded on tape in order to secure quality of data. The baseline interview took place between 2004 and 2007, had a duration of 3 – 4 hours, and consisted of a blood draw, autonomic nervous system measurements, saliva sampling, a medical exam, an in-person interview, computer tasks,

and self-report questionnaires. The study protocol was approved by the ethical review board of each participating centre and all subjects signed an informed consent at the baseline assessment. A detailed description of the NESDA rationals, methods, and measures can be found elsewhere.[155] After two and four years, a face-to-face follow-up was conducted with a response of 87.1%.[156] During this second measurement most of the baseline assessments were repeated.[157]

Benzodiazepine Use in NESDA

BZD use at baseline and follow-up (including z-drugs; anatomical therapeutic codes [ATC codes] N05BA, N05CD, N03AE01, and N05CF) was defined as having used BZDs (daily or less often) in the month prior to the baseline and follow-up interview respectively. BZD use was recorded by investigation of drug containers or self-report (if drug containers had been forgotten). Besides BZD use in general, five indicators of BZD use were investigated: type of BZD, frequency of BZD use, daily BZD dosage, duration of BZD use, and BZD dependence severity.

Aim

The main questions of this thesis are:

1) What are the correlates of BZD use in general, inappropriate use and dependence and what physician characteristics are associated with patient BZD use?
2) Is long-term BZD use associated with alterations of the HPA axis or the ANS?
3) Is BZD use associated with prolonged RTs in chronic users?

Outline of the Thesis

The main objective of this thesis is to describe the epidemiology of long term BZD use as well as its long term consequences. This thesis is structured into three sections: In section one, the correlates of BZD use, new use, chronic

use, inappropriate use, and BZD dependence severity are investigated. The possible influence of the prescribing physicians on patient BZD use is also considered. In section two, the focus is on the physiological consequences of long-term BZDs use on the HPA axis and the ANS. In section three, cognitive effects of BZDs in long-term users are addressed.

Section 1

Chapter 2 describes the cross-sectional sociodemographic, psychological and physical correlates of BZD use and inappropriate BZD use.

Chapter 3 addresses the most important risk factors of initiated and continued BZD use during a two-year follow-up period.

Chapter 4 investigates the cross-sectional correlates of BZD dependence severity as measured with the Bendep-SRQ.[58]

Chapter 5 presents the general practitioner correlates of patient BZD use and inappropriate use.

Section 2

Chapter 6 covers the cross-sectional association between chronic BZD use and various salivary cortisol measures. The question is whether tolerance to the cortisol suppressant effects of BZDs arises in long-term BZD use.

Chapter 7 explores the relationship between transitions in BZD use and changes on various autonomic nervous system measures during a two-year follow-up.

Section 3

Chapter 8 examines the association between long-term BZD use and reaction time as measured by the implicit association task (IAT)[158] during a two-year follow-up. We aimed to elucidate whether BZDs sedative and attention impairing effects remain or tolerance develops in long-term use.

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