Determinants and Consequences of long-term Benzodiazepine Use

Leonie Manthey

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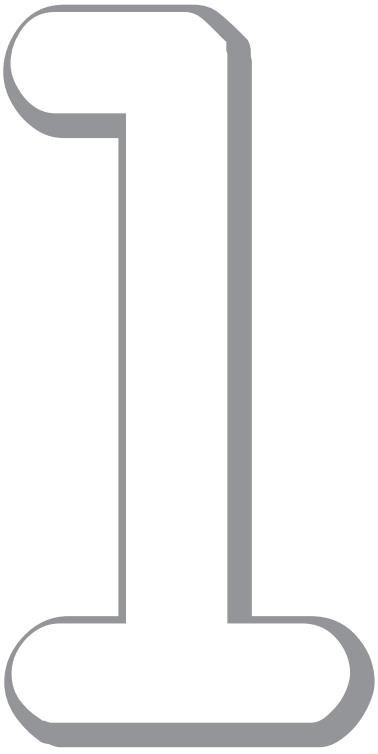

Benzodiazepines (BZDs) are a class of psychotropic drugs with anxiolytic, muscle-relaxant and hypnotic properties.[1] In clinical practice, they are mainly used to manage the symptoms of anxiety and insomnia.[1] BZDs are the most prescribed psychotropic drugs worldwide and although it has regularly been 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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Correlates of (inappropriate) Benzodiazepine Use: the Netherlands Study of Depression and Anxiety (NESDA)

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ABSTRACT

Aim: Results on correlates of benzodiazepine (BZD) use in general and inappropriate use were inconsistent and mostly univariate. The relative importance of sociodemographic, psychological and physical correlates has never been investigated in a comprehensive, multivariate model.

Methods: We included 429 BZD users and 2423 non-users from the Netherlands Study of Depression and Anxiety (NESDA) in order to investigate sociodemographic, psychological and physical correlates of BZD use and inappropriate use by logistic and linear regression analyses.

Results: BZDs were used by a considerable proportion of the 2852 NESDA participants (15.0%). BZD use was independently associated with older age, singleness, unemployment, treatment in secondary care, higher medical consumption, (more severe) anxiety, depression (OR[95%CI]=1.95[1.29,2.93]), comorbidity, insomnia, SSRI (OR[95%CI]=2.05[1.55,2.70]), TCA, and other antidepressant (OR[95% CI]=2.44[1.64,3.62]) use. Overall, BZD use was rarely in accordance with all guidelines, mainly because most users (82.5%) exceeded the recommended duration of safe use. Inappropriate use was independently associated with older age (β = 0.130) and chronic illnesses (β = 0.120). Higher scores on agreeableness were associated with less inappropriate use.

Conclusions*:* Mentally or physically vulnerable subjects were most likely to use BZDs. The most vulnerable (i.e. old and physically ill) BZD users were at highest risk of inappropriate BZD use. Without further evidence of BZDs effectiveness in long-term use, caution in initiating BZD prescriptions is recommended, particularly when patients are chronically ill and old, as those are most likely to display inappropriate use.

INTRODUCTION

Benzodiazepines (BZDs) are commonly prescribed as a treatment of anxiety and insomnia.[2-5] Remarkably, BZDs are also inappropriately used for pain,[6] somatic illnesses,[1] and less specific stress responses.[7,8] Although there is still controversy about the potential for abuse, dependence, withdrawal symptoms, and side effect, prevalence rates of BZD use are high and vary between 7.5% and 21.3% across countries.[9-12] Due to these high prevalence rates, it is informative to obtain a profile of the average BZD user. Specific subject characteristics such as sociodemographic factors (female sex,[5,12-15] older age,[3,5,12-16] lower education,[14] and unemployment[12,13,15]), psychological characteristics (worse mental health,[3,13,15-17] antidepressant use,[13,18] and elevated neuroticism[14,15,17]) and physical health factors (chronic illnesses or other physical health problems,[1,13-18] higher medical consumption,[18] and pain complaints[6]) were found to be associated with BZD use in previous studies. A number of these variables,[5,12,13] but not all,[14,15,17] were identified as important correlates of BZD use in the majority of studies. Several studies did not look at the determinants independently by using a multivariate analysis[3,5,14,17,18] and no joint investigation of all determinants has been conducted yet.

When BZDs are used as indicated, i.e. at standard therapeutic doses, during a short time period, and only one type of BZD at a time, treatment is usually without strong side effects.[19] Inappropriate BZD use is accompanied by adverse health consequences including cognitive impairment, risk of falling, traffic accidents, and dependence.[6,20-23] Further, there is little evidence for the effectiveness of BZDs during chronic use.[24] Therefore, several national and international guidelines were formed that – although showing some differences– all recommended a conservative practice of prescription, including short-term use.[25-27] However, more than 20 years after the notion that long-term BZD use should be discouraged, still more than 50% of current BZD users are chronic users (i.e., using BZDs for more than 3 months).[12,28,29] To prevent

inappropriate use, it is important to determine which users become inappropriate users. To date, the determinants of inappropriate use have not been investigated. Only the determinants of long-term use have been studied, yet with inconsistent results and without considering the other aspects of inappropriate use (i.e., dosage and number of BZD types used). In those studies, sex,[29-31] age,[28-33] education,[32] psychopathology,[32-34] physical health,[30,33,34] pain complaints,[34] daily BZD use,[28] use of higher potency BZDs,[31] and antidepressants[33] were identified as correlates of long-term BZD use.

To the best of our knowledge, we are the first study to investigate the relative importance of a comprehensive set of potential correlates of BZD use and inappropriate use in a study among 2852 subjects at various stages of psychopathology participating in the Netherlands Study of Depression and Anxiety (NESDA). We first explored the sociodemographic, psychological and physical correlates of BZD use. Second, we investigated (the correlates of) inappropriate use according to international guidelines.[25-27]

MATERIALS AND METHODS

Subjects

Subjects participated in the baseline assessment of the Netherlands Study of Depression and Anxiety (NESDA), an 8-year longitudinal cohort study of 2981 respondents aged 18 to 65 years.[35] NESDA was designed to be representative of individuals with depressive and/or anxiety disorders in different health care settings and developmental stages of illness.[35] Psychiatric status did not seem to be predictive of the initial (non)-response in the NESDA study. (Non)-response was driven by age and sex, i.e. older women more often participated in the NESDA study and young men less often.[35] Subjects were recruited from the community, general practice and specialized mental health care institutions throughout the Netherlands. They completed a medical exam, an in-person interview,

and several 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.

We excluded subjects with one or more missing values on BZD use, inappropriate use, sociodemographic, psychological or physical characteristics (n=94). An exception was made for missing values on the Insomnia Rating Scale (IRS) where mean imputation was used due to the high number of missings (n=300). We also excluded subjects with epilepsy (n=29), as epilepsy is an indication that justifies prolonged BZD use.[36]

To obtain an indication of the main correlates of BZD use (aim [1]), two groups were defined: subjects who reported BZD use in the month prior to the baseline interview ('BZD users', n=429) and those reporting no use of BZDs in the last month ('non-users', n=2423). For the investigation of appropriateness of BZD use (aim [2]) only BZD users were considered and further categorized according to appropriateness of BZD use.

Benzodiazepine Use

Two indicators of BZD use were investigated: BZD use and appropriateness of BZD use.

BZD use during the month prior to baseline interview was registered by observation of drug containers brought to the interview (in 73.4% of cases) or self-report (in 26.6% of cases). Information was collected about name, dose, number of tablets, and duration of BZD use. Medication was coded according to the Anatomical Therapeutic Code/ Defined Daily Dose (ATC/DDD) system developed by the World Health Organization (WHO) collaborating Centre for Drug Statistics Methodology. BZDs were classified as ATC-coded groups N05BA, N05CD, N05CG, and N03AE01. The so called "Z-drugs", of which in the Netherlands only zopiclone and zolpidem (ATC code N05CF) are available, were also included in our analyses, as studies on long-term adverse effects,

withdrawal and tolerance development for these drugs are still lacking. The daily BZD dose was computed according to the coding system of the ATC and DDD system.[37] The Mean Daily Dose was calculated by dividing individual daily doses (in mg) of BZDs by the DDD for the particular BZD.[38] For patients using BZDs other than diazepam, an equivalent daily dose was calculated with the conversion tables commonly used by general practitioners' (GPs)[39] and 10 mg of diazepam were regarded equivalent to 1 mg alprazolam, 10 mg bromazepam, 0.25 mg brotizolam, 20mg clobazam, 20 mg chlordiazepoxide, 13.3 mg clorazepate, 8 mg clonazepam, 30 mg flurazepam, 1 mg loprazolam, 2 mg lorazepam, 1 mg lormetazepam, 7.5 mg midazolam, 10 mg nitrazepam, 33 mg oxazepam, 20 mg prazepam, 20 mg temazepam, 20 mg zolpidem and 13 mg zopiclone. Dosages were summed when more than one BZD was used. Types of BZDs were subdivided into short acting ($t_{1/2}$ < 24h) and long acting ($t_{1/2}$ ≥ 24h) BZDs. Duration of use was categorized as short-term (≤ 3 months) or long-term (> 3 months). The number of different types of BZDs used was categorized into 1, 2, or 3. BZDs were further divided into anxiolytics (ATC code N05BA, n=263) and hypnotics (ATC codes N05CD and N05CF, n=147).

Appropriateness of use was based on the Dutch practice guidelines for anxiety and insomnia[26,27] and the British *National Institute of Health and Clinical Excellence* treatment guidelines for general practitioners.[25] The following criteria for appropriate use were derived:

1. mean daily dosage ≤ DDD as defined by the WHO
2. duration of benzodiazepine use ≤ 3 months in case of no concomitant antidepressant (AD) use and ≤ 2 months in case of concomitant AD use
3. only one type of BZDs is used at a time

Based on the number of appropriateness criteria not met by a subject, an inappropriateness score (range 0 – 3) was calculated. An inappropriateness score of 0 indicated that a subject met all three appropriateness criteria (i.e. appropriate use) whereas an inappropriateness score of 3 indicated

that none of the appropriateness criteria was met (i.e. highly inappropriate use).

Demographic, Psychological and Physical Characteristics

Based on previous studies, various potential correlates of BZD use and appropriateness of BZD use were included and grouped into: sociodemographic characteristics (age, gender, education, marital status, and work status), psychological characteristics (current psychopathology, health care setting, severity of anxiety or depression symptoms, insomnia, antidepressant use, and personality traits) and physical characteristics (number of chronic diseases, medical consumption; pain complaints, and smoking).[5,12-15,29,32-34,40]

Sociodemographic characteristics- Gender, age, education level (in years), work status (employed vs. unemployed), and partner status (living with partner vs. single) were reported in the baseline interview.

Psychological characteristics- In NESDA, depressive (dysthymia or Major Depressive Disorder, MDD) and anxiety (panic disorder with or without agoraphobia, generalized anxiety disorder or social phobia) diagnoses were measured by the Composite International Diagnostic Interview (CIDI, life time version 2.1), which classifies diagnoses according to the DSM-IV criteria. Current diagnoses were defined as those in the last year. The severity of generalized anxiety and panic symptoms were assessed with the Beck Anxiety Inventory (BAI).[41] The presence of insomnia was determined using the Insomnia Rating Scale (IRS).[42] The severity of depressive symptoms was measured by the cognitive/mood scale of the Inventory of Depressive Symptomatology Self Report (IDS-SR).[43] In order to avoid overlap with the BAI and IRS, we did not include the anxiety/arousal and sleep scales of the IDS-SR. So as to make the score of BAI, IDS-SR and IRS comparable, z-scores were calculated and z transformed values were used for regression analyses. Personality traits were assessed with the Neuroticism Extraversion Openness-Five Factor Inventory (NEO-FFI), a 60-item questionnaire measuring five personality

domains: neuroticism, extraversion, agreeableness, conscientiousness, and openness to experience.[44] Antidepressant use was reported during the interview. The ATC-coded groups N06AA, N06AB, N06AF, N06AX and N06AG were classified as antidepressants.

Physical characteristics - An inventory of somatic diseases was made by detailed questions of the presence of the following chronic illnesses: chronic lung disease, heart condition, diabetes mellitus, stroke, arthritis, rheumatism, cancer, hypertension, ulcer, intestinal problems, liver disease, chronic fatigue syndrome, allergy, thyroid gland, head injury or other injuries. Based on the number of chronic diseases a subject suffered from, a score ranging from 0 to 17 was calculated. Medical consumption was defined as the number of GP consultations in the six months prior to the interview, as assessed with the Perceived Need for Care Questionnaire (PNCQ).[45] Pain complaints were measured with the Chronic Graded Pain Scale and pain severity (consisting of pain intensity and disability) was summarized by the Chronic Pain Grade according to Korff et al., which is a score ranging from 0 to 4.[46] Smoking was reported during the interview.

Statistical Analyses

Sample characteristics and characteristics of BZD use were expressed by frequencies, means or medians, and compared using $\chi 2$ statistics (for categorical variables), analysis of variance (ANOVA, for normally distributed, continuous variables), and Mann-Whitney U-test (for non-normally distributed, continuous variables). Non-normally distributed values were naturally log transformed for regression analyses.

Univariate logistic and linear regression analyses were carried out to identify correlates of BZD use (vs. non-use as the reference category) and inappropriate use (inappropriateness score ranging from 0-3). Odds ratios with 95% confidence intervals (OR [95 % CI]) and standardized betas (β) were provided as outcome measures. All independent variables with $P < 0.10$ in univariate analyses were entered in the multivariate regression

models. The P value was set at $P < 0.10$ (instead of $P < 0.05$) in order to avoid missing important determinants of BZD use that do not reach significance in univariate analysis at $P < 0.05$ but will when correcting for possible confounders in multivariate analyses. The following variables were considered: [1] demographic variables: gender, age, education level, work status, and partner status, [2] psychological characteristics: current psychopathology, health care setting, severity of anxiety and depression symptoms, insomnia, antidepressant use, and personality traits, [3] physical characteristics: number of chronic diseases, medical consumption, pain complaints and smoking. The analysis was adjusted for sex and age. Significance in the multivariate model was inferred at $P <0.05$.

Finally, we compared anxiolytic and hypnotic users on possible characteristics of BZD use using $\chi 2$ statistics (for categorical variables), ANOVA (for normally distributed, continuous variables), and Mann-Whitney U-test (for non-normally distributed, continuous variables) to find out whether there would be group differences. Significance was inferred at $P < 0.05$. All analyses were conducted with SPSS 16.0 for Windows.

RESULTS

Characteristics of BZD Use

Of the 2852 subjects, 429 (15.0%) had used a BZD in the past month. Table 1 shows the sociodemographic, psychological, and physical characteristics of BZD users as compared to non-users.

BZD users were older (mean 46.3 vs. 41.2 years, $P<0.001$), more likely to be single (36.4% versus 29.6%, $P=0.005$), and more likely to be unemployed (51.7% vs. 28.4%, $P<0.001$). Further, BZD users displayed worse physical (3.0 vs. 2.0 medical consumption, $P<0.001$) and psychological health (BAI score of mean 20.0 vs. 8.0 respectively, $P<0.001$).

TABLE 1. Characteristics of Benzodiazepine (BZD) User Groups (n=2852)

	Non-Users n= 2423	BZD Users n=429	P-value
Sociodemographics			
Sex (% female)	66.1	68.1	0.43
Age (years)	41.2 (40.7 – 41.7)	46.3 (45.0 – 47.5)	<0.001
Partner status (% single)	29.6	36.4	0.005
Employment status (% not working)	28.4	51.7	<0.001
Education level (years)	12.0 (10.0 – 15.0)	11.0 (9.0 – 15.0)	<0.001
Treatment in secondary care (%)	24.2	49.0	<0.001
Physical health			
Medical consumption	2.0 (1.0 – 3.0)	3.0 (2.0 – 5.0)	<0.001
Chronic illnesses	1.8 (1.8 – 1.9)	2.5 (2.3 – 2.6)	<0.001
Pain	1.5 (1.5 – 1.6)	2.1 (2.0 – 2.2)	<0.001
Smoking (%)	28.9	24.2	0.05
Psychological Characteristics			
Current Diagnosis (%)			<0.001
MDD Only	15.1	17.5	
Anxiety Only	14.6	18.2	
Comorbid disorder	23.1	49.0	
IRS	8.0 (4.0 – 10.0)	10.0 (8.0 – 15.0)	<0.001
BAI	8.0 (3.0 – 16.0)	20.0 (10.0 – 28.0)	<0.001
IDS-SR Mood/Cognition Scale	5.0 (2.0 – 11.0)	12.0 (6.0 – 16.5)	<0.001
Antidepressant use (%, past month)			<0.001
SSRI	13.9	34.5	
TCA	2.1	6.1	
Others	4.2	14.0	
Personality Characteristics			
Neuroticism	23.5 (23.1 – 23.8)	28.7 (27.9 – 29.6)	<0.001
Extraversion	25.4 (25.1 – 25.7)	21.8 (21.1 – 22.4)	<0.001
Openness	26.4 (26.2 – 26.7)	25.3 (24.7 – 25.9)	<0.001
Agreeableness	31.9 (31.7 – 32.1)	31.2 (30.7 – 31.7)	0.02
Conscientiousness	30.5 (30.2 – 30.7)	28.8 (28.2 – 29.3)	<0.001

BAI indicates Beck's anxiety index; IDS-SR indicates Inventory of Depressive Symptomatology; IRS indicates Insomnia Rating Scale: MDD indicates Major Depressive Disorder; SSRI indicates Selective Serotonin Reuptake Inhibitor; TCA indicates Tricyclic Antidepressant. Means (95% confidence intervals) are given for age, chronic illnesses, pain, and personality traits. Medians (interquartile range) are given for education level, medical consumption IRS, BAI, and IDS as these values are not normally distributed. Percentages are given for categorical variables. *P* is derived by analysis of variance (ANOVA) for quantitative, normally distributed variables, Mann Whitney U-test for continuous, non-normally distributed variables, or χ^2 statistics for categorical variables. Significance is inferred at P<0.10.

Table 2 shows the effect of putative correlates of BZD use as opposed to non-use among all subjects. Univariate P values of these analyses are shown in Table 1 which comprises group comparisons conducted with ANOVAs. An ANOVA results in exactly the same P value as a regression analysis.

In multivariate analyses, the following variables were significant correlates of BZD use: older age (OR=1.48), singleness (OR=1.34), unemployment (OR=1.56), treatment in secondary care (OR=1.55), higher medical consumption (OR=1.41), a diagnosis of depression (OR=1.56), anxiety (OR=1.95) and comorbidity (OR=1.78), higher scores on the IRS (OR=1.35) and BAI (OR=1.65) questionnaires, use of SSRIs (OR=2.05), TCAs (OR=1.84), and other antidepressants (OR=2.44).

In the comparison between anxiolytic and hypnotic users, groups were similar on most variables, except of the following: Anxiolytic users were younger (45.3 vs. 47.8, P=0.04), had more often a diagnosis of anxiety (25.2 vs. 14.9%, P=0.02), less often a diagnosis of depression (15.9 vs. 28.9%, P=0.009), had lower scores on insomnia (9.0 vs. 13.0, P≤0.001), and higher scores on agreeableness (31.8 vs. 30.5, P=0.02, data not shown).

Appropriateness of BZD Use

In Table 3, we present the characteristics of BZD use among the 429 BZD users. The median daily dosage used was 2.5 mg of diazepam equivalents (interquartile range [IQR]: 0.7 – 6.0) and the median duration of BZD use was 24 months (IQR: 5.0 – 84.0). The most frequently used BZD was oxazepam (44.3%), followed by temazepam (14.9%), diazepam (14.7%) and alprazolam (6.1%).

Only 17.5% of all BZD users took BZDs for the appropriate duration of three months whereas 82.5% of users took BZDs for a much longer period. The remaining appropriateness criteria were met more frequently. The majority of the BZD users (86.0%) did not exceed the recommended DDD as defined by the WHO and 84.4% of users had only

TABLE 2. Determinants of Benzodiazepine Use as opposed to Non-Use: Results from Univariate and Multivariate logistic Regression Analyses (n=2852)

	Univariate analysis odds ratio (95% CI)	P-value*	Multivariate analysis odds ratio (95% CI)	P value**
Sociodemographics				
Sex (female)	1.09 (0.88 – 1.36)	0.43	1.09 (0.84 – 1.42)	0.53
Age (per 10 years)	1.34 (1.22 – 1.48)	<0.001	1.48 (1.34 – 1.63)	<0.001
Partner status (single)	1.36 (1.10 – 1.69)	0.005	1.34 (1.05 – 1.71)	0.02
Employment status (not working)	2.71 (2.20 – 3.33)	<0.001	1.56 (1.22 – 1.99)	<0.001
Education level (years)	0.30 (0.20 – 0.43)	<0.001	0.89 (0.56 – 1.43)	0.64
Health care setting (secondary care)	3.00 (2.43 – 3.71)	<0.001	1.55 (1.16 – 2.07)	0.003
Physical health				
Medical consumption	2.39 (2.04 – 2.79)	<0.001	1.41 (1.17 – 1.69)	<0.001
Chronic illnesses	1.28 (1.20 – 1.35)	<0.001	1.02 (0.95 – 1.11)	0.54
Pain	1.63 (1.49 – 1.79)	<0.001	1.09 (0.97 – 1.23)	0.13
Smoking	0.79 (0.62 – 1.00)	0.05	0.96 (0.73 – 1.26)	0.77
Psychological Characteristics				
Current Diagnosis				
MDD Only	1.19 (0.91 – 1.56)	0.21	1.56 (1.02 – 2.40)	0.04
Anxiety Only	1.30 (1.00 – 1.71)	0.06	1.95 (1.29 – 2.93)	0.001
Comorbid disorder	3.20 (2.59 – 3.95)	<0.001	1.78 (1.17 – 2.70)	0.008
IRS	2.13 (1.85 – 2.45)	<0.001	1.35 (1.16 – 1.56)	0.001
BAI	2.72 (2.37 – 3.13)	<0.001	1.65 (1.34 – 2.03)	<0.001
IDS-SR Mood/Cognition Scale	2.29 (2.00 – 2.62)	<0.001	0.90 (0.72 – 1.13)	0.36
Antidepressant use (past month)				
SSRI	3.27 (2.60 – 4.12)	<0.001	2.05 (1.55 – 2.70)	<0.001
TCA	3.06 (1.88 – 4.98)	<0.001	1.84 (1.07– 3.16)	0.03
Others	3.74 (2.67 – 5.24)	<0.001	2.44 (1.64 – 3.62)	<0.001
Personality Characteristics				
Neuroticism	1.07 (1.06 – 1.08)	<0.001	0.99 (0.97 – 1.02)	0.61
Extraversion	0.93 (0.92 – 0.95)	<0.001	1.00 (0.98 – 1.02)	0.78
Openness	0.97 (0.95 – 0.99)	<0.001	0.99 (0.97 – 1.01)	0.29
Agreeableness	0.98 (0.96 – 1.00)	0.02	1.01 (0.99 – 1.04)	0.26
Conscientiousness	0.96 (0.94 – 0.97)	<0.001	1.00 (0.98 – 1.02)	0.92

BAI indicates Beck's anxiety index; IDS indicates Inventory of Depressive Symptomatology; IRS indicates Insomnis Rating Scale; MDD indicates Major Depressive Disorder; SSRI indicates Selective Serotonin Reuptake Inhibitor; TCA indicates Tricyclic Antidepressant. All variables with P<0.10 in univariate analyses are entered in the multivariate model. Significance is inferred at P < 0.05 in the multivariate model.*: The P values are optained by univariate analyses. ** : The P values are obtained by multivariate analyses.

TABLE 3. Characteristics and Appropriateness of Benzodiazepine (BZD) Use (n=429)

Benzodiazepine Use	
Type of BZD	
Short acting (%, $t_{1/2}$ < 24h)	81.1
Long acting (%, $t_{1/2}$ ≥ 24h)	18.9
Mean daily dose (mg / day)[1]	2.5 (0.7 – 6.0)
Duration of use (months)	24.0 (5.0 – 84.0)
Daily BZD use (%)	38.5
Number of different types of BZDs used concomitantly (%)	
1	84.4
2	14.0
3	1.6
Most frequently used BZDs (%)	
Oxazepam	44.3
Temazepam	14.9
Diazepam	14.7
Alprazolam	6.1
Lorazepam	4.2
Zopiclone	3.7
Appropriate BZD use	
Mean Daily Dose/ DDD[2] ≤ 1(%)	86.0
Duration of use ≤ 3 months (%)	17.5
Use of only 1 type of BZD (%)	84.4
Inappropriateness score[3] (%)	
0	15.2
1	64.3
2	13.8
3	6.8

[1]Expressed as diazepam equivalents, [2] DDD indicates defined daily dose (DDD for diazepam: 10 mg / day), [3] an appropriateness score of 0 indicates that all appropriateness criteria are met (appropriate use), an appropriateness score of 3 indicates that none of the criteria is met (inappropriate use)

Median (interquartile range) is given for mean daily dose and duration of use. Percentages are given for categorical variables.

TABLE 4. Determinants of Inappropriate[1] Benzodiazepine (BZD) Use: Results from Univariate and Multivariate Linear Regression Analyses (n=429)

	Univariate Analysis β	**P value**	**Multivariate Analysis** β	**P value**
Sociodemographics				
Sex (female)	-0.003	0.96	0.018	0.72
Age (years)	0.153	0.001	0.130	0.008
Partner status (single)	0.065	0.18		
Employment status (not working)	0.114	0.02	0.073	0.14
Education level (years)	-0.078	0.11		
Health care setting (secondary care)	0.010	0.84		
Physical health				
Medical consumption	-0.043	0.37		
Chronic illnesses	0.173	<0.001	0.120	0.02
Pain	0.078	0.11		
Smoking	-0.034	0.48		
Psychological Characteristics				
Current Diagnosis (%)				
MDD Only	-0.067	0.16		
Anxiety Only	-0.028	0.56		
Comorbid disorder	0.060	0.21		
IRS	0.013	0.79		
BAI	0.075	0.12		
IDS-SR Mood/Cognition Scale	0.076	0.12		
Personality Characteristics				
Neuroticism	0.008	0.87		
Extraversion	-0.113	0.02	-0.043	0.40
Openness	-0.098	0.04	-0.065	0.18
Agreeableness	-0.126	0.009	-0.111	0.03
Conscientiousness	-0.017	0.73		

BAI indicates Beck's anxiety index; IDS-SR indicates Inventory of Depressive Symptomatology Self Report; IRS indicates Insomnia Rating Scale; MDD indicates Major Depressive Disorder; SSRI indicates Selective Serotonin Reuptake Inhibitor; TCA indicates Tricyclic Antidepressant.[1] Inappropriate BZD use is calculated with an inappropriateness score. An inappropriateness score of 0 indicates that all appropriateness criteria are met, an inappropriateness score of 3 indicates that none of the criteria is met. All variables with $P < 0.10$ are entered in the multivariate model. Significance in the multivariate analysis is inferred at $P < 0.05$.

a prescription for one type of BZD at a time. However, mainly due to the high duration of BZD use of most users, only 15.2% of BZD users met all three appropriateness criteria, whereas 64.3% met two criteria, 13.8% met one and 6.8% of users did not meet any criterion (highly inappropriate use).

Table 4 shows the effect of potential correlates of inappropriate BZD use among all BZD users. Age (β = 0.130) and chronic illnesses (β = 0.120) were significantly associated with higher inappropriate BZD use. Higher scores on agreeableness were associated with lower inappropriate use (β = -0.111).

DISCUSSION

BZDs were used by a considerable proportion of the 2852 NESDA participants (15.0%). BZD use was independently associated with older age, singleness, unemployment, treatment in secondary care, high medical consumption, (more severe) anxiety, depression, comorbidity, (more severe) insomnia, and antidepressant use. Inappropriate BZD use was independently associated with older age and chronic illnesses. High scores on agreeableness were associated with less inappropriate use. Overall, BZD use was rarely in accordance with all guidelines, mainly because most users (82.5%) exceeded the recommended maximum duration for safe use.

Although the uncritical enthusiasm about BZD use is over since many decades,[30,47,48] BZDs are still not only used for the treatment of severe insomnia and anxiety (other than epilepsy), but also to alleviate stress caused by adverse life circumstances such as unemployment[49] as well as pain[6] and other somatic complaints.[1] Largely corresponding to earlier findings, our results show that mainly the physically and mentally more vulnerable, e.g., the old,[5,13,29] unemployed,[12,13,15] psychologically,[3,13,15-17,32-34] and physically[14,18,34] ill subjects are using BZDs and use these BZDs inappropriately. There seems to be a tendency from

relatively invulnerable subjects being non-users, mildly vulnerable being users and highly vulnerable being inappropriate users. Consistently, vulnerable subjects reported lower perceived support[50,51,52] as well as more maladaptive coping strategies[18,32,50-53] and were found to display more emotional arousal when facing stressful events as compared to less vulnerable subjects.[49] They might substitute those deficits by BZDs[49,52] and be more likely to ask their medical doctors (MDs) for tranquillizers to alleviate their distress. MDs themselves might also be more likely to prescribe BZDs to vulnerable subjects as compared with all other problems those people have due to unemployment, chronic illnesses and psychopathology, BZD use seems to be the least concerning issue. A number of qualitative research studies investigated the prescription habits of MDs and found that the majority of questioned MDs were aware of the guidelines[54,55] and supported conservative prescription practice of BZDs.[54] A reported reason for prescribing nonetheless was feeling poorly equipped to solve the emotional problems of their troubled patients,[56] but wanting to alleviate their distress[55] and maintain a good doctor-patient relationship.[54,55] If MDs received more (psychological) education on how to communicate their reasons for declining prescriptions to the patients, they might prescribe less and initiate BZD discontinuation more often.[54,56,57]

As could be expected, anxiolytic BZDs were more often used in cases of anxiety disorders, and hypnotic BZDs more often in cases of insomnia. However, it also seems that the drugs are insufficient to provide therapeutic relief as otherwise lower anxiety and insomnia scores were to be expected in the respective groups. Group differences on age and agreeableness were unexpected and difficult to explain.

In general, the high percentage of inappropriate users in NESDA is disconcerting. The majority (84.8%) of users did not use BZDs according to international guidelines,[25-27] mainly due to exceeding the maximum duration of recommended use. This is striking considering that for more than 20 years BZDs have been known to cause side effects and

dependence and evidence for the drug's effectiveness in long-term use is controversial.[7,8] In addition, several NESDA subjects surpassed the recommended daily dosage (14.0%) and used more than one type of BZD concomitantly (15.6%). Dosage escalation is generally unsafe, as side effects become more pronounced and can have adverse consequences ranging from low performance at work to falls and traffic accidents.[6,20-22] BZDs should be reserved for the severely anxious who have tried AD medication with no effect and have BZDs as last treatment option. However, BZD prescriptions cannot be discontinued without providing patients with alternative coping strategies. Training should be conducted to strengthen BZD users' coping skills,[11,58] self-efficacy and positive outcome expectations[11] and to lessen their disengagement beliefs[11] as such efforts may increase the chance of successful BZD discontinuation.[11,58] In spite of all objections and in view of the restricted financial resources in the health sector, it is clear that prescribing BZDs takes less time than providing psychological support.[7,55] Therefore, BZD use should be targeted with relatively quick and cheap methods that have been developed (e.g., computer-tailored education,[11] discontinuation letters[59]) and found to increase effectively BZD cessation rates.[11,59]

The present study has some limitations. The cross-sectional design does not allow us to make causal inferences on whether determinants preceded BZD use or vice versa. Although participants were asked to bring drug containers to the interview, one fourth of the subjects did not adhere to that and reported medication use from memory leading to a potential recall bias. The 84.8% inappropriate user number is probably an overestimation, as long-term users were more likely to be included in the user group than short-term users due to the cross-sectional design. A strong aspect of our study is the conductance of a multivariate analysis across a comprehensive set of possible determinants of BZD use. Furthermore, we included all aspects of inappropriate BZD use in a large sample composed of subjects with a range of psychopathology.

In conclusion, this study revealed three major points: 1) the vast majority of NESDA subjects displayed inappropriate BZD use, mainly due to exceeding the maximum duration of recommended use; 2) it is primarily the physically or mentally vulnerable subjects who use BZDs, and 3) the most physically ill of the BZD users are at highest risk for inappropriate use. Without further evidence for the effectiveness of BZDs in long-term use, caution in initiating BZD prescriptions is recommended, particularly when patients are chronically ill and old, as these subjects are most likely to display inappropriate use.

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Determinants of Initiated and Continued Benzodiazepine Use in the Netherlands Study of Depression and Anxiety (NESDA)

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ABSTRACT

Background: Longitudinal research on determinants of initiated and continued benzodiazepine (BZD) use is inconsistent and has identified many possible determinants. It is unclear which of those are most important in the prediction of BZD use. We aimed to identify the most important predictors of initiated and continued BZD use. Therefore, we analyzed the most consistently identified determinants from previous research plus some new determinants.

Method: We identified baseline and 2-year longitudinal predictors of initiated BZD use (vs nonuse) among 2205 baseline BZD nonusers, and of continued use (vs discontinued use) among 369 baseline BZD users in the Netherlands Study of Depression and Anxiety using logistic regression analyses.

Results: During follow-up, BZD use was initiated by 4.9% of BZD nonusers at baseline. Initiated use was predicted by insomnia (odds ratio [OR]=1.60), enduring anxiety symptoms (OR=2.02), entering secondary care during follow-up (OR=2.85), and past BZD use (OR=3.57). Positive life events during follow-up reduced the likelihood of BZD initiation (OR=0.76). Of BZD users at baseline, 54.2% continued use during the entire follow-up period. Continuation of BZD use was predicted by higher age (OR=1.03), severe anxiety (OR=1.85), and a long duration of BZD use (OR=1.54). Leaving secondary care was associated with less continued BZD use (OR=0.29).

Conclusion: Insomnia and anxiety were the main risk factors of initiated use, whereas advanced age and anxiety severity were the main risk factors of continued use. Gender, education, pain, and physical health seemed to be less important.

INTRODUCTION

Benzodiazepines (BZDs) are an effective short-term treatment option for symptoms of anxiety and insomnia.[1-3] Although BZDs are often the indicated treatment,[4] they are also inappropriately used for psychosocial problems,[5] pain,[6] and somatic complaints.[3,7] As BZDs are associated with dose- and concentration related side effects and physiological dependence,[1,3,8] guidelines advise short-term use.[4,9,10] Still, many BZD users are long-term users.[6] The existence of chronic and inappropriate BZD prescriptions call for the identification of risk factors of initiation and continuation of BZD use.

Cross-sectional research has identified many correlates of BZD use, but could not establish the temporal order of events.[11] Longitudinal analyses permit to establish the order of events and to identify true risk factors of BZD use. In longitudinal studies, initiated BZD use was predicted by female gender,[12] older age,[12] divorce,[12] psychopathology,[13] insomnia,[14] alcohol abuse,[13] antidepressant use,[13] smoking,[14] poor physical health,[14] and joint pain.[14] Continued BZD use was predicted by older age,[14] female gender,[15] divorce,[15] psychopathology,[16] poor health,[17] pain,[14] number of GP contacts,[15] insomnia,[15] a history of BZD use,[17] daily BZD use,[18] use of higher potency BZDs,[19] long duration of BZD use,[20] high BZD dosage,[20] and hypnotic use.[20] Living alone was associated with a decreased risk of continued BZD use.[14] However, findings are inconsistent across studies, possibly due to the investigation of only a few determinants per study,[12] distinct definitions of the outcome variable (psychotropic use,[12] BZD use,[18] onset of use,[16] onset of chronic use[14]), dissimilar data collection (pharmacy databases,[18] self-report [21]), differing study samples (all ages,[22] old subjects [5]) and included determinants. Thus, it remains unclear which of the above mentioned predictors are most important in the prediction of BZD use. Additionally, the associations of course of psychopathology and life events with BZD use have not been studied in longitudinal research yet.

We aimed to identify the (most important) independent risk factors of initiated BZD use and continued BZD use during a 2-year follow-up period. Therefore, we included the above described previously investigated predictors of BZD use and several not previously investigated determinants (e.g., course of psychopathology and life events) in order to investigate which variables would fall off (and thus be less relevant) and which would remain significant in the a multivariate model.

MATERIALS AND METHODS

Subjects

Subjects participated in the baseline and 2-year assessment of the Netherlands Study of Depression and Anxiety (NESDA), an ongoing 8-year longitudinal cohort study of 2981 respondents aged 18 through 65 years.[23] NESDA was designed to be representative of individuals with depressive and/or anxiety disorders in different health care settings and developmental stages of illness. Therefore, subjects with no symptoms ("controls"), those with earlier episodes or at risk, and those with a depressive or anxiety disorder were recruited from the community, general practices and specialized mental health care institutions throughout the Netherlands.[23] The baseline assessment included a medical exam, an in-person interview, and self-report questionnaires.[23] The study protocol was approved by the Ethical Review Board of each participating center and all subjects signed an informed consent at the baseline assessment.[23] After 2 years, a face-to-face follow-up was conducted.[24] Data from baseline and follow-up were used in this analysis. We excluded subjects with lacking follow-up data (n=385) and those with epilepsy (n=22), as epilepsy can be an indication for long-term BZD use.[25] Missing data were imputed by the mean for 4.2 % of data points. Imputation did not importantly change our results. After exclusion, 2574 subjects remained and comprised the sample of the following analyses.

To identify the determinants of initiated BZD use, only subjects who did not use BZDs at baseline were included (n=2205). They were divided into subjects who initiated BZD use in the time interval between baseline and follow-up ("initiated use", n=103) and those who did not ("nonuse", n=2102). For the investigation of continued BZD use, only subjects who used BZDs at baseline were included (n=369) and divided into subjects who still reported BZD use at follow-up ("continued use", n=200) and subjects who had discontinued use between baseline and follow-up ("discontinued use", n=169).

MEASURES

BZD Use

BZD use at baseline/follow-up (including z-drugs; Anatomical Therapeutic Codes [ATC codes] N05BA, N05CD, N03AE01 and N05CF[26]) was defined as having used BZDs (daily or less often) in the month before the baseline/follow-up interview. It was registered by observation of drug containers brought to the interview (in 74.3% of cases) or self-report. Information was collected about name, dose, number of tablets, frequency and duration of BZD use.[11]

Possible Determinants of Initiated and Continued BZD Use

To extract a set of the most important determinants of initiated and continued BZD use, the following variables were selected:

1) baseline characteristics (sociodemographic, physical, and psychological characteristics),
2) characteristics of BZD use (daily use, dosage, duration, half-life, number of different BZDs, and dependence), and
3) longitudinal characteristics (duration of psychopathology symptoms during follow-up, life events during follow-up, changes in treatment setting, insomnia, and chronic illnesses).

Baseline characteristics and characteristics of BZD use had been investigated in the past whereas no previous research has studied the above mentioned longitudinal characteristics of BZD use.

Baseline Characteristics

Sociodemographic characteristics. Gender, age, education level (in years), work status (employed, retired/working in household, unemployed/sick leave/disabled), partner status (partner, single, widowed/divorced), and living status (living together with at least 1 person versus living alone) were reported in the baseline interview.

Psychological characteristics. Six-months depressive and anxiety disorders were measured by the Composite International Diagnostic Interview (life time version 2.1) at baseline, which classifies diagnoses according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria. Severity of anxiety symptoms was assessed with the Beck Anxiety Inventory.[27] The presence of insomnia was determined using the Insomnia Rating Scale.[28] The severity of depressive symptoms was measured by the cognitive/mood scale of the Inventory of Depressive Symptomatology Self Report.[29] Locus of control was assessed by a 5-item mastery scale.[30] Personality traits were assessed with the Neuroticism Extraversion Openness-Five Factor Inventory.[31] Antidepressant use (with ATC codes N06AA, N06AB, N06AF, N06AX or N06AG) was reported during the interview.

Physical characteristics. An inventory of somatic diseases was made by counting the number of chronic illnesses a subject experienced at the baseline assessment.[11] The number of GP consultations in the 6 months before baseline assessment was assessed with the trimbos/iMTA questionnaire for costs associated with psychiatric illness.[32] Pain complaints were measured with the Chronic Graded Pain Scale.[33] Smoking was reported during the interview. Alcohol dependence was assessed with the corresponding Composite International Diagnostic Interview section.[34]

Characteristics of BZD Use at Baseline

As characteristics of use were associated with continued use in previous research,[18,19] mean daily dose, frequency of use, half-life, number of different types of BZDs used, and BZD dependency were included as possible predictors of continued BZD use.[11]

Longitudinal Characteristics (Measured During the 2-year Follow-Up)

Duration of psychopathology symptoms. The percentage of time during follow-up with symptoms of at least mild severity was calculated using the Life Chart Interview.[35] Three categories were established: 1) no anxiety/depressive symptoms during follow-up, 2) less than half of follow-up anxiety/depressive symptoms, and 3) more than half of follow-up anxiety/depressive symptoms.

Life events. The incidence of 12 negative life events during follow-up was assessed with the List of Threatening Events Questionnaire.[36] The List of Threatening Events Questionnaire was extended by 7 items referring to positive life events: (1) "immediate family member recovered from serious illness", (2) "met a new partner", (3) "became friends", (4) "have been on holiday", (5) "new job or important promotion", (6) "education completed", and (7) "be better off financially". Numbers of negative and positive life events during the follow-up period were summed separately in order to derive separate measures for the number of negative and positive life events.

Other longitudinal measures. Severity of insomnia and number of chronic illnesses at follow-up were assessed using similar methods as at baseline. For insomnia severity and chronic illnesses a change score was calculated by subtracting the baseline value from the follow-up value. A higher score indicated worsening of illnesses/insomnia from baseline to follow-up and vice versa. Treatment setting (primary vs secondary care) was established at baseline and follow-up. Transitions in treatment setting were divided in 4 categories: 1) primary care only, 2) entry of

secondary care during follow-up, 3) exit of secondary care during follow-up, and 4) secondary care only.

STATISTICAL ANALYSES

Sample characteristics were expressed by frequencies or means and compared using $\chi 2$ statistics and analysis of variance (ANOVA). Univariate logistic regression analyses were carried out to identify predictors of initiated BZD use (vs nonuse [reference]) among baseline BZD nonusers and continued use (vs discontinued use [reference]) among baseline BZD users. Variables with $P < 0.10$ in univariate analyses were entered in the multivariate regression models. In these analyses, baseline characteristics, longitudinal characteristics and characteristics of BZD use (only for analysis of continued use, except of history of BZD use which was only entered in the analysis of initiated use) were considered. All analyses were adjusted for gender and age. Analyses were conducted with SPSS 16.0 for Windows. Significance was inferred at $P < 0.05$.

RESULTS

BZD Use

The prevalence rates of BZD use at baseline and follow-up were 14.3% and 11.8%, respectively. During follow-up, 4.9% of nonusers initiated BZD use. Of the BZD (n=369) users at baseline, 54.2% continued use during the entire follow-up period. At baseline, there were 135 daily BZD users and 234 infrequent users, of whom 49.1% used BZDs as needed. At follow-up, there were 89 daily users and 214 infrequent users, of whom 59.3% used as needed. Short-acting BZDs were most often used, with on average 20.7% using long-acting BZDs at baseline and follow-up.

Predictors of Initiated BZD Use

Table 1 shows the baseline and longitudinal characteristics of baseline nonusers who initiated BZD use in the follow-up period (4.6%) or remained nonusers. In multivariate analyses, higher baseline insomnia (OR=1.60), anxiety symptoms for more than half of the follow-up time (OR=2.02), entering secondary care during follow-up (OR=2.85), and past BZD use (OR=3.57) were independent predictors of initiated BZD use. A higher number of positive life events experienced during follow-up decreased the probability of BZD use initiation (OR per positive life event=0.76).

Predictors of Continued BZD Use

In Table 2, we present the characteristics of subjects who continued BZD use (n=200) as compared with those who discontinued BZD use (n=169) as investigated in subjects who were using BZDs at baseline (n=369). In multivariate analyses, older age (OR per year=1.03), higher anxiety severity (OR per Beck Anxiety Inventory point=1.85), and a longer duration of BZD use at baseline (OR per month=1.54) predicted the continuation of BZD use. Leaving secondary care treatment during the follow-up time was associated with a lower OR of continued BZD use (OR=0.29).

TABLE 1. Baseline and Longitudinal Characteristics of Nonusers (at Baseline) Who Initiated Versus Did Not Initiate BZD Use (n=2205)

	No Initiated Use n= 2102	**Initiated Use n=103**	***P****	**Multivariate OR for Initiated Use**	***P*** **
Baseline characteristics					
Sociodemographics					
Sex (% female)	65.9	64.1	0.71	0.81 (0.51-1.27)	0.35
Age (years)	41.2 (40.6-41.7)	44.3 (41.8-46.9)	0.02	1.01 (0.99-1.03)	0.50
Partner status (%)					
Current partner	70.6	62.1	0.12		
No current partner	21.3	25.2			
Widowed / divorced	8.0	12.6			
Living status (% alone)	27.2	33.0	0.20		
Employment status (%)			0.005		
Employed	64.6	49.5			
Pension/housewife	3.6	6.8		2.25 (0.88-5.78)	0.09
Unemployed / sick	31.8	43.7		1.23 (0.78-1.96)	0.38
Education level (years)	14.1 (14.0-14.2)	13.3 (12.8-14.0)	0.02	0.73 (0.29-1.84)	0.51
Physical health					
Medical consumption	3.9 (3.8-3.9)	4.3 (4.0-4.7)	0.02	0.85 (0.54-1.33)	0.47
Chronic illnesses	3.5 (3.4-3.6)	3.9 (3.6-4.2)	0.005	1.12 (0.60-2.06)	0.73
Pain	3.4 (3.3-3.4)	3.8 (3.6-4.0)	<0.001	1.79 (0.75-4.29)	0.19
Smoking (%)	29.6	28.2	0.75		
Alcohol dependence (%)	26.2	32.0	0.19		
Psychological Characteristics					
Six months diagnosis (%)			<0.001		
No diagnosis	53.3	27.2			
MDD only	14.1	12.6		0.81 (0.36-1.84)	0.61
Anxiety only	15.0	26.2		1.56 (0.79-3.09)	0.20
Comorbid disorder	17.6	34.0		1.01 (0.40-2.56)	0.98
Insomnia rating scale	8.3 (8.1-8.5)	11.3 (10.2-12.5)	<0.001	1.60 (1.17-2.18)	**0.003**
Beck Anxiety Inventory	8.8 (8.5-9.1)	14.0 (12.0-16.5)	<0.001	1.07 (0.74-1.54)	0.72
IDS Mood/Cognition Scale	6.5 (6.3-6.8)	9.2 (8.0-10.6)	<0.001	0.87 (0.59-1.29)	0.49
Locus of control	17.9 (17.7-18.0)	16.1 (15.3-16.9)	<0.001	1.16 (0.87-1.55)	0.31
Antidepressant use (%)	17.2	32.0	<0.001	1.43 (0.87-2.37)	0.16
Past BZD use (%)	12.6	44.7	<0.001	3.57 (2.26-5.63)	**<0.001**
Personality Characteristics					
Neuroticism	22.6 (22.2-23.0)	27.1 (25.2-28.9)	<0.001	1.11 (0.79-1.55)	0.56
Extraversion	25.5 (25.2-25.8)	22.7 (21.2-24.3)	<0.001	1.01 (0.76-1.35)	0.92
Openness	26.3 (26.1-26.6)	26.4 (25.1-27.6)	0.98		

Table 1. continued

Agreeableness	31.7 (31.4-31.9)	31.9 (30.7-33.0)	0.78		
Conscientiousness	30.3 (30.0-30.6)	28.8 (27.5-30.1)	0.03	0.97 (0.76-1.24)	0.79
Longitudinal characteristics					
Follow-up time anxiety symptoms (%)			<0.001		
No anxiety symptoms	55.8	29.1			
(Less than) half of time symptoms	18.7	18.4		1.23 (0.64-2.38)	0.53
More than half of time symptoms	25.5	52.4		2.02 (1.14-3.56)	**0.02**
Follow-up time depressive symptoms (%)			0.001		
No depressive symptoms	57.1	37.9			
(Less than) half of time symptoms	4.6	5.8		1.74 (0.66-4.56)	0.26
More than half of time symptoms	38.3	56.3		0.94 (0.55-1.62)	0.83
Life Events					
Number positive life events	2.0 (2.0-2.1)	1.6 (1.3-1.8)	<0.001	0.76 (0.61-0.95)	**0.01**
Number negative life events	2.2 (2.1-2.3)	2.4 (2.1-2.7)	0.15		
Switch of treatment setting (%)			<0.001		
Always primary care	72.8	46.6			
Exit secondary care	7.2	8.7		1.23 (0.53-2.85))	0.64
Entry secondary care	5.0	13.6		2.85 (1.38-5.90)	**0.005**
Always secondary care	15.0	31.1		1.70 (0.92-3.16)	0.09
Change number chronic illnesses	-0.4 (-0.4- -0.3)	-0.5 (-0.7 - -0.3)	0.30		
Change Insomnia Rating scale	-1.4 (-1.6 – 1.2)	-2.4 (-3.3 - -1.5)	0.04	1.02 (0.97-1.07)	0.53

BZD indicates benzodiazepine; IDS indicates Inventory of Depressive Symptomatology; MDD indicates Major Depressive Disorder; OR indicates odds ratio, CI indicates confidence interval. Means (95% confidence intervals) are given for age, personality traits, negative life events, positive life events, change in chronic illnesses, and change in insomnia rating scale. Geometric means (95% CI) based on estimated marginal means and calculated by analysis of variance (ANOVA), are presented for education, medical consumption, chronic illnesses, pain, Insomnia Rating Scale, Beck Anxiety Inventory, and IDS Mood / Cognition Scale as these values are not normally distributed. Percentages are given for categorical variables. *P is derived by ANOVA for quantitative variables or χ^2 statistics for categorical variables. ** P is derived by multivariate logistic regression. All variables with $P < 0.10$ in univariate analyses are entered into the multivariate regression model. The analysis is corrected for sex, age and previous BZD use. Significance is inferred at $P < 0.05$

TABLE 2. Baseline and Longitudinal Characteristics of Users (at Baseline) Who Continued Versus Did Not Continue BZD use (n=369)

	Discontinued Use n= 169	**Continued use n=200**	***P** **	**Multivariate OR (95% CI) for Continued use**	***P** ***
Baseline characteristics					
Sociodemographics					
Sex (% female)	63.3	71.0	0.12	1.28 (0.75-2.18)	0.37
Age (years)	43.2 (41.5-44.9)	49.0 (47.4-50.5)	<0.001	1.03 (1.01-1.06)	**0.02**
Partner status (%)					
Current Partner	66.9	61.0	0.07		
No current partner	23.1	20.5		1.53 (0.81-2.89)	0.19
Widowed/divorced	10.1	18.5		1.76 (0.83-3.69)	0.14
Living status (% alone)	32.0	36.5	0.36		
Employment status (%)			0.03		
Employed	49.1	35.5			
Pension/housewife	4.1	4.5		1.14 (0.33-3.90)	0.83
Unemployed/sick	46.7	60.0		1.45 (0.86-2.45)	0.16
Education level (years)	13.5 (13.0-14.1)	12.5 (12.1-13.0)	0.003	0.62 (0.23-1.67)	0.35
Physical health					
Medical consumption	5.2 (4.8-5.7)	5.5 (5.1-6.0)	0.43		
Chronic illnesses	4.0 (3.7-4.2)	4.3 (4.1-4.6)	0.03	0.70 (0.35-1.39)	0.31
Pain	3.8 (3.7-4.0)	4.0 (3.8-4.1)	0.19		
Smoking (%)	27.8	22.0	0.20		
Alcohol dependence (%)	26.0	28.5	0.60		
Psychological Characteristics					
Six months diagnosis (%)			0.61		
No diagnosis	20.1	18.0			
MDD only	18.9	16.0			
Anxiety only	21.3	19.5			
Comorbid disorder	39.6	46.5			
Insomnia rating scale	11.4 (10.6-12.3)	12.2 (11.4-13.0)	0.21		
Beck Anxiety Inventory	15.2 (13.7-16.8)	19.0 (17.2-20.9)	0.002	1.85 (1.28-2.69)	**0.001**
IDS Mood/Cognition Scale	10.4 (9.4-11.5)	11.5 (10.5-12.6)	0.14		
Locus of control	15.6 (14.9-16.2)	15.0 (14.4-15.6)	0.19		
Antidepressant use (%)	45.0	45.5	0.92		
Personality Characteristics					
Neuroticism	28.0 (26.7-29.2)	28.7 (27.6-29.9)	0.37		
Extraversion	22.1 (21.1-23.2)	21.7 (20.7-22.6)	0.50		
Openness	25.6 (24.6-26.6)	25.0 (24.0-25.9)	0.34		
Agreeableness	31.1 (30.2-31.9)	31.7 (30.9-32.5)	0.31		
Conscientiousness	29.0 (28.0-30.0)	29.0 (28.1-29.9)	0.95		
Characteristics of BZD use					
Long half-life (%)	17.8	20.0	0.58		
Mean daily dose (mg/day)[1]	4.4 (3.9-4.9)	5.6 (5.0-6.2)	0.001	1.04 (0.63-1.71)	0.89
Duration of use (months)	16.3 (13.3-20.1)	40.9 (33.9-49.4)	<0.001	1.54 (1.26-1.87)	**<0.001**

Table 2. continued

Daily BZD use (%)	28.7	44.0	0.001	1.83 (0.89-3.74)	0.10
Number of different types of BZDs used concomitantly	3.1 (3.1-3.2)	3.1 (3.1-3.2)	0.42		
Benzodiazepine Dependence					
Problematic Use	9.0 (8.6-9.4)	9.7 (9.3-10.1)	0.02	1.09 (0.96-1.24)	0.20
Preoccupation	12.0 (11.5-12.6)	13.4 (12.9-13.9)	0.001	1.04 (0.90-1.19)	0.53
Lack of Compliance	8.7 (8.9.0)	9.4 (9.1-9.6)	0.003	1.05 (0.94-1.18)	0.40
Longitudinal characteristics					
Follow-up time anxiety symptoms (%)			0.04		
No anxiety symptoms	42.6	30.0			
(Less than) half of time symptoms	17.8	19.5		1.39 (0.69-2.80)	0.36
More than half of time symptoms	39.6	50.5		1.21 (0.66-2.21)	0.54
Follow-up time depressive symptoms (%)			0.26		
No depressive symptoms	43.2	35.5			
(Less than) half of time symptoms	2.4	4.0			
More than half of time symptoms	54.4	60.5			
Life Events					
Number of positive life events	1.8 (1.7-2.0)	1.7 (1.5-1.8)	0.17		
Number of negative life events	2.4 (2.1-2.6)	2.6 (2.4-2.9)	0.21		
Switch of treatment setting (%)			0.03		
Always primary care	37.9	50.5			
Exit secondary care	16.0	9.0		0.29 (0.13-0.66)	**0.003**
Entry secondary care	5.3	7.0		0.73 (0.26-2.09)	0.56
Always secondary care	40.8	33.5		0.65 (0.34-1.23)	0.19
Change number chronic illnesses	-0.4 (-0.6 - -0.2)	-0.4 (-0.6 - -0.2)	0.82		
Change Insomnia Rating scale	-3.8 (-4.7 - -2.9)	-2.2 (-3.0 - -1.3)	0.009	1.03 (0.99 – 1.08)	0.14

BZD indicates benzodiazepine; IDS indicates Inventory of Depressive Symptomatology; MDD indicates Major Depressive Disorder; OR indicates odds ratio; CI indicates confidence interval. Means (95% CIs) are given for age, personality characteristics chronic illnesses, pain, personality traits, change in number of chronic illnesses, and change in insomnia rating scale, problematic use, and preoccupation. Geometric means (95% confidence intervals) based on estimated marginal means, calculated by analysis of variance, are presented for education, medical consumption, chronic illnesses, pain, Insomnia Rating Scale, Beck Anxiety Inventory, IDS, daily dosage, duration of use, number of different types of BZDs, and lack of compliance as these values are not normally distributed. Percentages are given for categorical variables. **P* is derived by analysis of variance for quantitative variables or χ^2 statistics for categorical variables. ** P is derived by multivariate logistic regression. All variables with $P < 0.10$ in univariate analyses are entered into the multivariate regression model. The analysis is corrected for sex, age and previous BZD use. Significance is inferred at $P < 0.05$.

DISCUSSION

This longitudinal cohort study aimed to identify the most important predictors of initiated and continued BZD use. In the multivariate model, which included the most consistently identified predictors of BZD use from previous research plus a number of not previously investigated determinants, the following variables appeared to be most important. Initiated BZD use (in nonusers at baseline) was more likely in subjects with insomnia, who had enduring anxiety symptoms, who entered secondary care, and who had used BZDs in the past. It was less likely in subjects who experienced a higher number of positive life events. Continued BZD use (among baseline BZD users) was more likely in older subjects with more severe anxiety and a long baseline duration of BZD use, but less likely in subjects who left secondary care during follow-up.

Regarding the initiation of BZD use, we confirmed previous research, which found that subjects with a history of BZD use were more likely to re-start BZD use due to withdrawal symptoms or a new episode of psychopathology.[37] Furthermore, it was consistent with earlier studies[21] that anxiety and insomnia predicted initiated BZD use and were probably the main reasons to issue new BZD prescriptions. However, the following 4 insights were new: 1) Mainly, subjects who were anxious most of the 2-year follow-up time initiated BZD use, indicating that a short duration of anxiety does not necessarily lead to BZD use. 2) Positive life events were associated with less initiation of BZD use, possibly by alleviation of emotional distress both directly and by buffering the adverse consequences of negative life events.[38] 3) Entry of secondary care increased the likelihood that BZDs were initiated. This might be due to the necessity of adding BZDs to the treatment regime in patients who were referred to secondary care because of unsuccessful primary care treatment. 4) Gender, age, marital status, alcohol abuse, antidepressant use, smoking, physical health, and pain were no independent determinants of initiated BZD use in the current model, although they were in previous research.[12-14] As we

corrected for a broad set of important confounders in our multivariate model, it seems that insomnia, enduring anxiety symptoms, entry into secondary care, and BZD use in the past were more important predictors for the initiation of BZD use than these variables were.

Regarding continuation of BZD use, we confirmed previous research that older age,[14] more severe anxiety,[16] and a longer duration of BZD use in the past[17] were important predictors. Yet, the following 2 findings were new: 1) As compared with primary care patients, subjects who left secondary care during follow-up were more likely to discontinue BZD use, possibly because their mental health status had improved. However, secondary care treatment remained an independent predictor in our model even after adjustment for severity of psychopathology. 2) Continued BZD use was not predicted by gender, marital status, health, pain, living status, GP contacts, insomnia, daily BZD use, potency of BZD, duration of use, BZD dosage, and hypnotic use in our multivariate model, although these variables were important determinants in previous research.[14,15,17,20] Again, as we corrected for a broad set of important confounders in our multivariate model, it seems that severe anxiety, a long baseline duration of BZD use and leaving secondary care during follow-up were more important in the explanation of continuation of BZD use than above described variables were.

Our study had several limitations. Because of the medium sized BZD user group and large number of determinants tested, the power of our study was limited and we were not able to investigate subgroups of users. Furthermore, although participants were asked to bring drug containers to the interview, one fourth of the subjects did not do so. This might have introduced recall bias and some error. Finally, we could not include all previously investigated determinants as some of these were not included in the NESDA study (i.e., stress[12] and life satisfaction[21]). This paper is limited to subject characteristics and does not include interactions with prescribers who also may influence BZD use. There were also several strengths to our study. We were able to include the most consistently

identified determinants of BZD use from cross-sectional and longitudinal research as well as a number of never investigated longitudinal variables in a comprehensive multivariate model. That enabled us to identify the most important independent determinants of initiated and continued BZD use.

In conclusion, this study revealed that insomnia and anxiety were the main reasons for initiated BZD use, whereas older age and anxiety were the main reason for continued BZD use. Gender, education, pain, and physical health appeared to be less important.

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Correlates of Benzodiazepine Dependence in the Netherlands Study of Depression and Anxiety

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ABSTRACT

Aims: Benzodiazepines (BZDs) are effective on the short-term against anxiety and insomnia. However, some BZD users develop BZD dependence after a relatively short period of time. Therefore, we aimed to identify the risk factors of BZD dependence.

Design: An observational cohort study.

Setting: The Netherlands.

Participants: Four hundred one BZD users (13.5%) of the 2,981 participants of the Netherlands Study of Depression and Anxiety (NESDA) were included.

Measurements: Sociodemographic, physical, psychological, addiction related, and BZD use related characteristics were investigated as possible correlates of BZD dependence severity. Dependence severity was measured by the three subscales of the Benzodiazepine Self-Report Questionnaire, which are Problematic Use, Preoccupation, and Lack of compliance.

Findings: In multivariate analyses, Problematic Use was associated with more GP contacts in the past six months (β= 0.170, p=0.001) and severity of insomnia (β= 0.145, P=0.004). Preoccupation was related with anxiety severity (β= 0.194, P=0.001), antidepressant use (β= 0.197, P<0.001), alcohol dependence (β= 0.185, P<0.001), and a higher daily dosage of BZD (β= 0.160, P=0.001). Lack of compliance was associated with higher age (β= 0.122, P=0.03), unemployment (β= 0.105, P=0.04), insomnia (β= 0.129, P=0.01), antidepressant use (β= 0.148, P=0.002), and alcohol dependence (β= 0.108, P=0.02).

Conclusions: Insomnia, antidepressant use and alcohol dependence may increase the risk of BZD dependence among individuals who use BZDs.

INTRODUCTION

Benzodiazepines (BZDs) are effective on the short-term against anxiety and insomnia.[1] Long-term use is associated with the development of tolerance[2,3] even at therapeutic dosages.[4] Interestingly, some subjects cease BZD use after a relatively short period of time, while others do not,[5] possibly, due to the development of BZD dependence.[6] The identification of risk factors of dependence severity would allow physicians to prevent BZD dependence in some cases.

BZD dependence was found to be associated with sociodemographic factors (female sex,[7] lower age,[8] non-Dutch cultural origin,[8] lower education,[8] and retirement[8]), psychological and psychiatric factors (depression,[8-11] anxiety,[7-10] antidepressant use,[12] hostility,[8] less difficulties to obtain help for emotional problems,[7] and lower quality of life[9]), physical factors (somatization[11]), addiction related factors (treatment for dependence,[8] drug use[10]), and BZD use related factors (a high daily dosage,[8,12] long-term BZD use,[8,12] short half-life of BZDs,[8] and concomitant use of several BZDs[8]).

However, correlates identified in some studies were not significant in others, possibly due to the following reasons. First, previous studies reporting on BZD dependence used very different patient samples. The included patient samples consisted of community-dwelling seniors with a relatively low percentage of psychiatric diagnoses,[13] long-term BZD users who participated in a BZD reduction trial,[11] patients on buprenorphine maintenance treatment for opiate dependence,[9,14] psychiatric outpatients,[8] club drug users who also abused psychoactive prescription medication,[10] and subjects from addiction centers[13]. While in some studies a large percentage suffered from substance disorder[8] or psychiatric disorders[13], others excluded subjects with a substance abuse disorder or those who received treatment for psychiatric disorders[11]. Second, most studies were restricted to sociodemographic, psychological and BZD use-related correlates and thus did not include all important

variables in one multivariate model.[9,13] Third, the studies applied different definitions of BZD dependence or just investigated aspects of BZD dependence (dependence,[7,8,12] abuse or dependence,[9] addiction, withdrawal, craving[11]).[15] Most of the studies applied dichotomous (yes/no) definitions of dependence,[7,9] while the clinical expression of BZD dependence is better modeled using several subscales[15] and stages of severity[14].

The Benzodiazepine Dependence Self-Report Questionnaire (Bendep-SRQ) has been developed to take severity and subscales into account. The Bendep-SRQ describes severity of BZD dependence by means of three subscales: (awareness of the own) problematic use, preoccupation (with the availability of BZDs), and lack of compliance (with the therapeutic regime).[16] These subscales reflect psychological, physiological, and social aspects of BZD dependence and have been validated by psychiatrists, general practitioners, and self-help patients.[16]

Only one previous study has investigated the correlates of these three subscales of dependence severity.[8] Lower age, depressive disorder, duration and dosage of BZD use were associated with higher scores on problematic use.[8] Anxiety disorder, a short half-life of the BZD and a longer duration of BZD use were associated with more preoccupation.[8] Lower age, retirement, duration of BZD use and a higher dosage were associated with more lack of compliance.[8] Being an outpatient in a substance addiction center was associated with higher scores on all three subscales.[8] However, this study did not examine the impact of some potential physical (chronic illnesses, pain, and GP visits) and addiction-related (alcohol dependence, and tobacco dependence) variables although they might very well be of importance.

This study aimed to determine the independent cross-sectional correlates of BZD dependence severity. We included sociodemographic, psychological, physical, addiction-related, and BZD use-related factors in an extensive multivariate model. We used three subscales of the Bendep-SRQ to measure severity of BZD dependence.[16-18]

MATERIALS AND METHODS

Subjects

Subjects participated in the baseline assessment of the Netherlands Study of Depression and Anxiety (NESDA), a longitudinal cohort study of 2981 adults aged 18-65 years. NESDA was designed to be representative of individuals with depressive and/or anxiety disorders in different health care settings and developmental stages of illness. Subjects were recruited from the community, general practice and specialized mental health care institutions throughout the Netherlands. Primary care patients were recruited from 65 general practitioners by a three-stage screening procedure. A questionnaire was sent to a random sample of 23,750 patients to screen for affective and anxiety disorders. The screen-positives were approached for a phone interview to confirm the diagnoses. Finally, 743 participants with a six months diagnosis, 353 participants with a remitted diagnosis and 141 subjects with subshreshold symptoms were included. Additionally, 373 participants with a screen-negative score participated as control group.[19,20] Regarding specialized mental health care, each newly enrolled patient at the participating outpatient clinics participated in a standardized intake. The clinic staff submitted 1,597 patients with primary depressive or anxiety disorder for inclusion. After exclusion of subjects who did not fulfill inclusion criteria, could not be reached or refused participation, a final sample of 807 subjects remained. At the baseline assessment, all subjects completed a medical exam, an in-person interview, and several self-report questionnaires. The study protocol was approved by the ethical review boards of all participating centers, and all subjects gave written informed consent.[19] A more detailed description can be found in Penninx et al. (2008).[19]

To determine the independent predictors of BZD dependence severity, only BZD users (n=462) were included. As dependence severity was the outcome variable of our analyses, BZD users who had not completed the Bendep-SRQ were excluded (n=61). BZD users who had

filled in the Bendep-SRQ did not differ significantly from those who had not filled in the questionnaire in terms of gender, age, education, and severity of insomnia, anxiety and depression. After exclusion, 401 subjects were available for analysis.

Assessment of BZD Use and BZD Dependence

BZD use in the month prior to the baseline interview was registered by observation of drug-containers brought to the interview (73.6%) or by self-report. Information was collected about name, dose, frequency, number of tablets, and duration of BZD use. The medication was coded according to the Anatomical Therapeutic Code/Defined Daily Dose (ATC/DDD) system developed by the World Health Organization (WHO) collaborating Centre for Drug Statistics Methodology.[21] The Mean Daily Dose was calculated by dividing individual daily doses (in milligrams) of BZDs by the DDD for the particular BZD.[22] For BZDs other than diazepam, an equivalent daily dose was calculated.[23] Dosages were summed when more than one kind of BZD was used. Kinds of BZDs were subdivided into short acting and long acting types of BZDs. Duration of use was recorded in months.[22]

In order to assess the severity of dependence on BZDs, the Bendep-SRQ was used.[18] This questionnaire showed good validity in outpatient settings, and has been used to measure BZD dependence in many previous research studies.[16-18,22] We measured three subscales of the Bendep-SRQ reflecting separate subscales of dependence (5 items each): 1) awareness of problematic use, 2) preoccupation with the availability of BZDs, and 3) lack of compliance with the therapeutic regimen. All subscales showed good reliability and validity and convincingly met the requirements of the Rasch model.[18] Each item of the Bendep-SRQ had 5 possible answers ranging from 1'this is totally not true for me' to 5 'this is totally true for me'. To derive a total score for each 5-item subscale, scores for the individual items per subscale were summed yielding a score ranging from 5 to 25.

Vulnerability Factors of BZD Dependence

Five groups of vulnerability factors were assessed based on previous literature concerning BZD dependence: 1) sociodemographic factors, 2) psychological factors, 3) physical factors, 4) addiction related factors, and 5) factors related to the use of BZDs.[7-9,11-12] Detailed information about these variables and their assessment can be found elsewhere.[19]

In short, sociodemographic factors were reported during the baseline interview and included gender, age, Northern European ancestry (yes, no), education (in years), employment status (employed, unemployed, pension/housewife), and partner status (current partner, no partner, divorced/widowed).

Psychological factors included the severity of the depression and anxiety symptoms, insomnia, personality traits, mastery, and antidepressant use (yes/no). Severity of depressive symptoms was measured by the cognitive/mood scale of the Inventory of Depressive Symptomatology Self Report (IDS-SR), a 30-item self report scale.[24] The severity of generalized anxiety and panic symptoms at baseline was assessed with the Beck Anxiety Inventory (BAI).[25] The presence of insomnia was determined using the Insomnia Rating Scale (IRS).[26] Personality traits were assessed with the Neuroticism Extraversion Openness-Five Factor Inventory (NEO-FFI).[27] Locus of control or mastery was assessed with the 5-item version of the Pearlin Mastery Scale.[28] Antidepressant use was reported during the interview and classified as selective serotonin reuptake inhibitors (SSRIs; ATC codes N06AB02-N06AB10), tricyclic antidepressants (TCAs; ATC codes N06AA01-N06AA23), and other antidepressants including tetracyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and trazodone (ATC codes N06AX05, N06AX11, N06AX16, and N06AX21).

Physical factors included the number of chronic somatic illnesses, medical consumption in the last 6 months and level of pain. An inventory of chronic somatic diseases was made by detailed questions on the presence of chronic illnesses such as chronic lung disease and

heart condition. Medical consumption was defined as the number of GP consultations in the six months prior to the baseline interview, as assessed with the Perceived Need for Care Questionnaire (PNCQ).[29] Pain complaints were measured with the Chronic Graded Pain Scale (consisting of pain intensity and disability).[30]

Addiction related vulnerability factors were the level of dependence on nicotine, a life time diagnosis of alcohol abuse or alcohol dependence, and illicit drug use. Illicit drug use in the month before the baseline interview (cannabis, ecstasy, speed, cocaine, heroin, LSD) was reported during the baseline interview. Nicotine dependence among smoking subjects was measured with the Fagerström questionnaire.[31] Life time diagnoses of alcohol abuse and dependence according to DSM-IV criteria were assessed by the Composite International Diagnostic Interview (CIDI, life time version 2.1).[32]

Statistical Analyses

Sample characteristics and characteristics of BZD use were expressed by percentages, means (and standard deviations) for positively skewed variables or medians (and interquartile ranges) for non-normally distributed variables.

The non-normally distributed Bendep subscale 'lack of compliance' was naturally log transformed for regression analyses. Separate univariate linear regression analyses were carried out to identify the determinants of 1) problematic BZD use 2) preoccupation with availability of BZDs and 3) lack of compliance to the therapeutic regime. All independent variables with $P<0.10$ in univariate analyses were entered into the multivariate regression analyses in order to determine the independent correlates of BZD dependence severity as measured with the three subscales. The above mentioned sociodemographic, psychological, physical, addiction related, and BZD use related vulnerability factors were entered as possible correlates of BZD dependence. All variables with $P<0.05$ in the multivariate models were considered statistically significant. The frequent

BZD users (> 50% of all days in the past month, n=201) were analyzed separately in sensitivity analyses. All analyses were conducted with SPSS 17.0 for Windows.

RESULTS

Characteristics of the Study Group

Of the investigated 401 BZD users, 158 subjects used BZDs on a daily basis (39.4%), 43 (10.7%) used BZDs more than 50% of all days in the past month, 88 subjects (21.9%) used BZDs less than 50% of all days in the past month, and 112 (27.9%) used BZDs when needed. The sociodemographic-, psychological-, physical-, and addiction-related characteristics of the 401 BZD users are shown in Table 1. BZD users were mainly female (69.6%), had a mean age of 46.0 years, and often had a current partner (62.8%). Pure depression disorder (15.5%), pure anxiety disorder (18.7%) or comorbid depression and anxiety disorder (51.4%) were commonly present and 53.4% of the BZD users also used antidepressants. Approximately one fourth of the BZD users had a lifetime diagnosis of either alcohol dependence or abuse. As for the three subscales of BZD dependence severity, the BZD users scored highest on the Bendep-SRQ subscale preoccupation, followed by problematic use and lack of compliance. The mean duration of BZD use was 24.0 months and the average daily dose was 2.8 mg diazepam equivalents per day.

Problematic Use

Univariate and multivariate correlates of problematic use are shown in Table 2. In multivariate analyses, more GP contacts in the past six months (β= 0.170; P=0.001), severity of insomnia (β= 0.145; P=0.004), and antidepressant use (β= 0.108; P=0.02) were associated with more problematic use. There were no independent sociodemographic and addiction related characteristics of problematic use. When analyses were repeated in frequent BZD users only (data not shown), the betas of

GP contacts in the last six months (β=0.266) and more severe insomnia remained comparable (β=0.138). Only the beta of antidepressant use decreased in strength in the frequent user group only.

Preoccupation

In multivariate analyses (Table 3), higher scores on the BAI (β= 0.194; P=0.001), antidepressant use (β= 0.197; P≤0.001), alcohol dependence (β= 0.185; P≤0.001), and a higher daily dosage of BZDs (β= 0.160; P=0.001) were associated with higher scores on preoccupation. No sociodemographic and physical characteristics were associated with preoccupation. When frequent users were analyzed separately, severity of anxiety (β =0.250) and alcohol dependence (β =0.217) remained important correlates. Antidepressant use (β =0.061) and dosage of BZD use (β =0.099) lost relevance in the frequent user group. Severity of depression was negatively associated with preoccupation in the frequent users only (β =-0.272), but not in the whole group (β =-0.054).

Lack of Compliance

In the multivariate model (Table 4), higher age (β= 0.122; P=0.03), unemployment due to sickness or disability (β= 0.105; P=0.04), more severe insomnia (β= 0.129; P=0.01), antidepressant use (β= 0.148; P=0.002), and alcohol dependence (β= 0.108; P=0.02) were associated with more lack of compliance. No physical characteristics were associated with of lack of compliance. When frequent BZD users were analyzed separately, the betas of unemployment (β=0.186), severity of insomnia (β=0.140), alcohol dependence (β=0.118), and antidepressant use (β=0.111) remained comparable while the beta of age decreased. In contrast, mastery (β=-0.240) and pain (β=0.231) had higher betas in the frequent user group only than in the whole group.

TABLE 1. Characteristics of 401 BZD Users and their BZD Use

Sociodemographic characteristics	
Sex (female, %)	69.6
Age in years	46.0 (11.6)
Partner status (%)	
Current partner	62.8
No partner	20.9
Widowed/divorced	16.2
Employment status (%)	
Employed	39.7
Unemployed	56.1
Pension/housewife	4.2
Education level in years	11.0 (9.0 – 15.0)
North European ancestry (%)	95.3
Physical vulnerability factors	
Number medical contacts 6 months	3.3 (2.0 – 5.0)
Number chronic illnesses	2.0 (1.0 – 4.0)
Severity of pain	2.0 (1.0 – 3.0)
Psychological vulnerability factors	
One year diagnosis (%)	
MDD only	15.5
Anxiety only	18.7
Comorbid disorder	51.4
Mastery Scale	15.0 (12.0 – 18.0)
BAI Questionnaire	20.0 (10.0 – 28.0)
Insomnia Rating Scale	10.0 (8.0 – 15.0)
IDS Questionnaire	12.0 (7.0 – 16.0)
Antidepressant use (past month, %)	53.4
Personality Characteristics	
Neuroticism	28.9 (7.8)
Extraversion	21.9 (6.7)
Openness	25.1 (6.1)
Agreeableness	31.4 (5.5)
Conscientiousness	28.6 (6.0)
Addiction related factors	
Fagerström Questionnaire	3.0 (0.0 – 3.9)
Alcohol dependence (%)	19.7
Alcohol abuse (%)	9.0
Drug use past month (%)	6.2
Bendep-SRQ Subscales	
Problematic use	9.6 (3.1)
Preoccupation	13.0 (4.2)
Lack of compliance	7.0 (5.0 – 9.0)
Characteristics of BZD use	
Type of BZD	
Short acting (% t1/2 < 24h)	79.6
Long acting (% t1/2 > 24h)	20.4
Daily BZD use (%)	39.4
Daily dose (mg/day)*	2.8 (0.7 – 6.0)
Duration of use (months)	24.0(5.0 – 96.0)
Most frequently used BZDs (%)	
Diazepam	15.2
Oxazepam	46.6
Alprazolam	6.0
Temazepam	14.2
Lorazepam	4.5
Zopiclone	2.7

BZD indicates benzodiazepine; GP indicates general practitioner; IDS indicates Inventory of Depressive Symptomatology; BAI indicates Beck Anxiety Questionnaire; MDD indicates Major Depressive Disorder. Bendep-SRQ indicates Bendep Self-Report-Questionnaire. Means (standard deviation) are given for age, personality characteristics, Problematic Use and Preoccupation. Medians (interquartile range) are given for education level, medical consumption, number of chronic illnesses, pain, mastery, IRS, BAI, IDS, Fagerström, Lack of Compliance, duration of BZD use, and daily BZD dose as these values are not normally distributed. Percentages are given for categorical variables. *Expressed as diazepam equivalents

TABLE 2. Univariate and multivariate Correlates of Problematic Use in 401 BZD Users

	Univariate associations		**Multivariate associations**	
	β	P*	β	P**
Sociodemographic characteristics				
Sex (female)	0.010	0.84		
Age (years)	-0.046	0.36		
Partner status				
No partner	0.010	0.85		
Widowed/divorced	0.050	0.32		
Employment status				
Unemployed/sickness/disabled	0.201	**<0.001**	0.064	0.21
Pension/housewife	-0.084	0.09	0.026	0.60
Education level (years)	-0.196	**<0.001**	-0.088	0.07
Northern European ancestry	-0.070	0.16		
Physical vulnerability factors				
GP contacts last 6 months	0.294	**<0.001**	0.170	**0.001**
Chronic illnesses	0.145	**0.004**	0.018	0.72
Pain	0.226	**<0.001**	0.006	0.91
Psychological vulnerability factors				
Mastery Scale	-0.199	**<0.001**	-0.081	0.12
BAI Questionnaire	0.315	**<0.001**	0.088	0.14
Insomnia Rating Scale	0.227	**<0.001**	0.145	**0.004**
IDS Questionnaire	0.311	**<0.001**	0.062	0.40
Antidepressant use	0.177	**<0.001**	0.108	**0.02**
Personality Characteristics				
Neuroticism	0.269	**<0.001**	0.074	0.27
Extraversion	-0.096	0.05	0.107	0.06
Openness	-0.105	**0.04**	-0.028	0.56
Agreeableness	-0.106	**0.04**	-0.004	0.94
Conscientiousness	-0.112	**0.03**	0.025	0.64
Addiction related vulnerability factors				
Fagerström Questionnaire	0.123	**0.01**	0.032	0.51
Alcohol dependence	0.108	**0.03**	0.076	0.10
Alcohol abuse	-0.007	0.89		
Drug use past month	0.033	0.51		
Characteristics of BZD use				
Long half life	0.046	0.36		
Duration of use (in months)	0.018	0.72		
Daily Dosage in diazepam equivalents	0.183	**<0.001**	0.082	0.09

BZD indicates benzodiazepine; GP indicates general practitioner; BAI indicates Beck Anxiety Inventory; IDS indicates Inventory of Depressive Symptomatology. All correlates with P<0.10 are included in multivariate analyses. Correlates with P<0.05 in multivariate analyses were considered as statistically significant. *P values are obtained by univariate regression analyses. ** P values are obtained by multivariate regression analyses.

TABLE 3. Univariate and multivariate Correlates of Preoccupation in 401 BZD Users

	Univariate associations		**Multivariate associations**	
	β	P*	β	P**
Sociodemographic characteristics				
Sex (female)	-0.033	0.51		
Age (years)	0.067	0.18		
Partner status				
No partner	-0.030	0.55		
Widowed/divorced	0.016	0.74		
Employment status				
Unemployed/sickness/disabled	0.148	**0.003**	0.041	0.41
Pension/housewife	-0.065	0.20	0.034	0.48
Education level in years	-0.102	**0.04**	-0.045	0.34
Northern European ancestry	-0.009	0.85		
Physical vulnerability factors				
GP contacts last 6 months	0.151	**0.002**	0.069	0.16
Chronic illnesses	0.047	0.35		
Pain	0.103	**0.04**	-0.056	0.28
Psychological vulnerability factors				
Mastery Scale	-0.163	**0.001**	-0.044	0.38
BAI Questionnaire	0.301	**<0.001**	0.194	**0.001**
Insomnia Rating Scale	0.044	0.38		
IDS Questionnaire	0.236	**<0.001**	-0.054	0.45
Antidepressant use	0.272	**<0.001**	0.197	**<0.001**
Personality Characteristics				
Neuroticism	0.245	**<0.001**	0.090	0.17
Extraversion	-0.158	**0.002**	0.004	0.94
Openness	-0.035	0.48		
Agreeableness	-0.054	0.28		
Conscientiousness	-0.116	**0.02**	0.035	0.51
Addiction related vulnerability factors				
Fagerström Questionnaire	0.074	0.14		
Alcohol dependence	0.230	**<0.001**	0.185	**<0.001**
Alcohol abuse	-0.062	0.22		
Drug use past month	-0.036	0.47		
Characteristics of BZD use				
Long half life	-0.001	0.99		
Duration of use (in months)	0.075	0.13		
Daily Dosage in diazepam equivalents	0.267	**<0.001**	0.160	**0.001**

BZD indicates benzodiazepine; GP indicates general practitioner; BAI indicates Beck Anxiety Inventory; IDS indicates Inventory of Depressive Symptomatology. All correlates with P<0.10 are included in multivariate analyses. Correlates with P<0.05 in multivariate analyses were considered as statistically significant. *P values are obtained by univariate regression analyses. ** P values are obtained by multivariate regression analyses.

TABLE 4. Univariate and multivariate Correlates of Lack of Compliance in 401 BZD Users

	Univariate associations		**Multivariate associations**	
	β	P*	β	P**
Sociodemographic characteristics				
Sex (female)	-0.003	0.95		
Age (years)	0.171	**0.001**	0.122	**0.03**
Partner status				
No partner	-0.049	0.32	-0.005	0.92
Widowed/divorced	0.088	0.08	0.023	0.64
Employment status				
Unemployed/sickness/disabled	0.234	**<0.001**	0.105	**0.04**
Pension/housewife	-0.014	0.78	0.042	0.40
Education level in years	-0.204	**<0.001**	-0.078	0.12
Northern European ancestry	0.059	0.24		
Physical vulnerability factors				
GP contacts last 6 months	0.149	**0.003**	0.013	0.80
Chronic illnesses	0.183	**<0.001**	0.022	0.67
Pain	0.222	**0.003**	0.104	0.06
Psychological vulnerability factors				
Mastery Scale	-0.187	**<0.001**	-0.086	0.10
BAI Questionnaire	0.190	**<0.001**	-0.064	0.29
Insomnia Rating Scale	0.229	**<0.001**	0.129	**0.01**
IDS Questionnaire	0.298	**<0.001**	0.136	0.07
Antidepressant use	0.199	**<0.001**	0.148	**0.002**
Personality Characteristics				
Neuroticism	0.205	**<0.001**	0.047	0.50
Extraversion	-0.170	**0.001**	0.052	0.36
Openness	-0.153	**0.002**	-0.077	0.11
Agreeableness	-0.099	**0.048**	0.022	0.66
Conscientiousness	-0.137	**0.006**	0.002	0.97
Addiction related vulnerability factors				
Fagerström Questionnaire	0.108	**0.03**	0.028	0.56
Alcohol dependence	0.143	**0.004**	0.108	**0.02**
Alcohol abuse	-0.057	0.26		
Drug use past month	0.041	0.42		
Characteristics of BZD use				
Long half life	0.120	**0.02**	0.055	0.24
Duration of use (in months)	0.131	**0.009**	0.069	0.17
Daily Dosage in diazepam equivalents	0.205	**<0.001**	0.054	0.28

BZD indicates benzodiazepine; GP indicates general practitioner; BAI indicates Beck Anxiety Inventory; IDS indicates Inventory of Depressive Symptomatology. All correlates with P<0.10 are included in multivariate analyses. Correlates with P<0.05 in multivariate analyses were considered as statistically significant. *P values are obtained by univariate regression analyses. ** P values are obtained by multivariate regression analyses.

DISCUSSION

This study investigated a large set of potential correlates of problematic use, preoccupation, and lack of compliance as indicators of BZD dependence in 401 BZD users. Problematic use was independently associated with more GP contacts, antidepressant use and higher severity of insomnia. Preoccupation was independently associated with anxiety severity, antidepressant use, alcohol dependence, and a higher daily dosage of BZDs. Lack of compliance was independently associated with higher age, unemployment, insomnia, antidepressant use, and alcohol dependence. The following paragraphs will discuss each of the three subscales separately.

High scores on problematic use implied that users were aware of the negative impact of BZDs on their lives, thought about discontinuing, and felt BZDs became less effective in symptom reduction.[16] It is noteworthy that severe insomnia was associated with higher scores on problematic use although BZDs are actually prescribed to lessen insomnia. Further, it is remarkable that subjects were aware of the apparent ineffectiveness of BZDs as well as of their problematic use, but were unable to discontinue BZDs, possibly due to the fear that symptoms might worsen.[4,33-34] GP visits as a correlate of problematic use is in line with previous research reporting a negative association between embarrassment to obtain help and BZD dependence.[13] Subjects who visit their GPs more often may be more likely to become dependent on BZDs (as more BZD prescriptions are issued). With respect to awareness of problematic use, it may also indicate that GPs call their patients' attention on the problems associated with their BZD use. Alternatively, subjects may have been sicker, more in need of GP consultations, and thus more vulnerable to problematic use.

Subjects with high scores on preoccupation with BZDs became nervous when they did not carry their drugs with them and were generally very concerned with BZDs.[16] The association between anxiety and preoccupation was in line with previous research[8,35] and may be due

to a partial conceptual overlap between these constructs. Additionally, subjects with mental disorders were previously shown to self-medicate their problems and subsequently become dependent.[36] The association between preoccupation and antidepressant use is in line with an earlier reported association between depression and BZD craving.[11] It supports the assumption that the presence of negative mood states appears sufficient to elicit the desire for substance (ab)use of e.g. alcohol.[37] Alcohol dependence was also an expected correlate of BZD dependence[8,38] as both substances influence the same gamma-aminobutric acid alpha receptor and cause a dampening of nervous system activity. Subjects may use either substance prior to stressful situations in order to feel calmer. Alternatively, BZDs might have been administered to relieve the withdrawal effects of alcohol and vice versa[39,40] or to increase sedation[41].

Subjects who scored high on lack of compliance with the therapeutic regime took more BZDs than prescribed, tried to renew prescriptions earlier than agreed on, and sometimes even falsified prescriptions.[16] Unemployed and older subjects, who form a vulnerable group in general, had higher scores on lack of compliance. This was roughly in line with previous research.[8,42] It may indicate that for these vulnerable subjects adhering to social norms such as a therapeutic regime become less important. Insomnia being a correlate of lack of compliance possibly pointed toward tolerance development and the resulting perceived need to administer more BZDs (than prescribed) to relieve the insomnia. The concomitant use of antidepressants, BZDs, and alcohol possibly indicated more severe psychopathology and stress vulnerability. Polydrug use might have reduced the threshold to take medication so that prescription constraints were taken less seriously and lack of compliance to therapeutic regimes becomes more likely.[41]

Kan et al. identified a number of correlates of BZD dependence which did not appear to be of importance in the NESDA sample (e.g. duration of BZD use and half-life of BZD).[8] These inconsistencies may be due to the inclusion of different correlates of BZD dependence. Further,

Kan et al. included part of their sample from outpatient addiction centers and the average daily dosage of BZDs in his sample was much higher than in NESDA (10mg vs. 2.8mg of diazepam equivalents, respectively) which might put subjects at increased risk to develop BZD dependence.[8]

In general, it is interesting that mainly psychological, addiction- and BZD use related characteristics predicted BZD dependence. Insomnia, antidepressant use and alcohol dependence predicted BZD dependence severity on two or more severity subscales. Other risk factors which were significant on one subscale (i.e., BAI, alcohol dependence, daily dosage) were borderline significant on other subscales. Therefore, most of the found risk factors seemed to be rather general predictors of BZD dependence. However, there were small disparities across the three subscales. For example, only preoccupation was related to anxiety, only lack of compliance was related to age and unemployment, and only problematic use to GP contacts. Frequency of use by itself seems to be an important predictor of dependence development. This finding is not surprising and in line with previous research reporting that a high daily dosage increases the risk of BZD dependence.[8,12]

Subjects at risk of BZD dependence are in need of close monitoring as they are also vulnerable to the development of concomitant mental disorders and substance abuse. They may benefit from psychotherapy and counseling to make them more resilient and possibly prevent BZD dependence. Further, the therapeutic effectiveness of BZDs should be monitored closely and weighted against the disadvantages, especially in those at risk of BZD dependence. If psychopathology does not improve with treatment, it is recommended to discontinue BZD use and switch to alternative ([non-] pharmacological) treatment options to prevent ineffective long term BZD use.

The present study had some limitations. The observational and cross-sectional design did not allow causal inferences on whether the correlates preceded severity of BZD dependence or vice versa. Our results cannot be generalized to very specific BZD user populations (such as

drug addicts and mentally healthy subjects who only receive BZDs for non-psychiatric disorders such as pain) but only to outpatients using relatively low-dosage of BZDs who mostly suffer from anxiety and insomnia (which are the main indications for BZD use). Further, in the light of the number of correlates tested, multiple testing may have caused type I errors. Despite these limitations, our study had important strengths. We conducted a multivariate analysis across a comprehensive set of possible determinants of BZD dependence so that we were able to identify the independent correlates of BZD dependence severity. In addition, we investigated a large study sample composed of subjects with a wide range of psychopathology representative of the average BZD user. The use of continuous Bendep-SRQ sumscores instead of dichotomous ones allowed us to measure the full variability of the phenotype and detect small differences between subjects and the more subtle associations.

In conclusion, subjects with insomnia, antidepressant use, and alcohol dependence were at highest risk to develop more severe BZD dependence. As concomitant psychopathology and substance dependence may severely compromise these subjects' quality of life, close monitoring and more appropriate symptom treatment is needed.

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Are General Practitioner Attitudes and Characteristics associated with Patient Benzodiazepine Use?

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ABSTRACT

Background: The patient correlates of benzodiazepine (BZD) use have received much attention in the past. Less attention has been paid to the contribution of general practitioners' (GP) attitudes and characteristics to patient BZD use.

Aim: We aimed to investigate GP attitudes and characteristics as possible correlates of patient BZD use and inappropriate use.

Design: Cross-sectional cohort study.

Setting: The Netherlands.

Method: A total of 1433 GP patients of the Netherlands Study of Depression and Anxiety (NESDA) and 62 general practitioners (GPs) participated. Physician- and patient characteristics were measured through questionnaires and interviews. Logistic multilevel regression analyses were used to identify GP characteristics as possible correlates of patient BZD use and inappropriate use.

Results: Patient BZD use and inappropriate use did not vary significantly between GPs and were only associated with few attitudes and characteristics of GPs (after correction for patient correlates of BZD use). Only the GP's perceived 'disability to differentiate unhappiness from depression' was weakly associated with less patient BZD use (OR = 0.98, P = 0.048) and higher 'professional comfort and competence with mental health care' of the GPs correlated with less inappropriate patient BZD use (OR=0.29, P = 0.03).

Conclusions: Our results indicate that the attitudes and characteristics of GPs barely affect patient BZD use. Instead, patient characteristics seem to be decisive in whether BZDs are used (inappropriately) or not. Interventions should target patients at risk of inappropriate use to educate them about the downsides of BZD use, and the prescribing physicians to teach them alternative treatments for their patients.

INTRODUCTION

Benzodiazepines (BZDs) are an effective short-term treatment of anxiety and insomnia,[1,2] but guidelines advise against longer-term use,[3,4] as the risk of side effects[5] and dependence development is high.[1,6] Regardless, (inappropriate) BZD use is common.[7,8] In the past, many studies focused on user characteristics [9-12] and identified old age, severe psychopathology and chronic illnesses as important correlates of (inappropriate) BZD use.[9-13] Less attention has been paid to the contribution of physician characteristics to patient BZD use.[14]

Qualitative research on physician characteristics showed that the majority of physicians were aware of the treatment guidelines.[15-17] Yet, BZDs were inappropriately prescribed due to 1) a presumed lack of time,[18-22] alternatives[16,19,20,23] and skills,[19-22] 2) the idea that BZDs are appropriate for vulnerable patients,[17,19,23] and 3) the wish to maintain a good-doctor patient relationship.[15,20-22]

Quantitative studies identified male gender,[24,25] personal usage of BZDs,[26] being a general practitioner (GP) versus a psychiatrist,[24,26] allowing patients to influence prescription decisions,[25] prolongation of prescriptions without direct doctor-patient contact,[25] and multiple drug prescribing[27] as important correlates of patient BZD use. A substantial number of studies did not identify any significant physician related factors in the fully adjusted model[28,29] or found inconsistent results.[24-27,30] Most of these studies did not correct for patient characteristics[24-26] so that it is unclear if the found differences 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 received little attention in previous research.[24,28,30,31]

This study aims to investigate the GP attitudes and characteristics as possible correlates of (aim 1) patient BZD use and (aim 2) inappropriate patient BZD use.

MATERIALS AND METHODS

Subjects

Subjects participated in the baseline assessment of the Netherlands Study of Depression and Anxiety (NESDA), a longitudinal cohort study of 2981 respondents at different stages of depressive or anxiety disorder.[32] Details on objectives, recruitment, and methods of NESDA have been described elsewhere.[32] The study protocol was approved by the Ethical Review Board of each participating center and all subjects signed an informed consent at the baseline assessment.[32]

Of the 2981 respondents, 1610 were recruited via their 67 general practitioners (GPs).[32,33] GPs who did not return the NESDA self-report questionnaires (n=5), the patients registered with those GPs (n=164) as well as patients with epilepsy (n=13)[34] were excluded. Accordingly, 1433 patients and 62 GPs remained for analyses.

To identify the GP correlates of patient BZD use, (aim [1]), two groups were defined: GP patients who reported BZD use in the month prior to the baseline interview ('BZD users', n=173) and those who reported no use of BZDs during the month before the baseline interview ('non-users', n=1260). For the investigation of GP correlates of inappropriate patient BZD use (aim [2]), non-users were excluded and the BZD user group was defined into appropriate BZD users (n=18) and inappropriate BZD users (n=155).

Patient BZD Use

Two indicators of patient BZD use were investigated:[35] patient BZD use and inappropriate patient BZD use. *Patient BZD use* was registered by self-report or observation of drug containers. It was defined as daily or infrequent BZD use in the month prior to the baseline interview. BZD using patients reported the type and dosage of BZD taken on an average day of use. The daily BZD dose was computed according to the coding system of the Anatomical Therapeutic Code (ATC) and Defined Daily

Dose (DDD) system.[36] The Mean Daily Dose was calculated by division of the individual daily doses (in milligrams) of BZDs by the DDD for the particular BZD.[35] BZDs were classified as ATC-coded groups N05BA, N05CD, and N03AE01. The non-BZD hypnotics zopiclone and zolpidem (ATC code N05CF), were also included.[35] For GP patients who used BZDs other than diazepam, conversion tables were used to calculate equivalent daily doses.[37,35] If more than one BZD was used, dosages were summed. The duration of BZD use was reported in months. The number of different types of BZDs used concomitantly was recorded. *Inappropriate patient BZD use* criteria were derived from Dutch and British treatment guidelines.[4,38,39] The following criteria for appropriate use were derived: 1) mean daily dosage ≤ DDD, 2) duration of benzodiazepine use ≤ 3 months in case of no concomitant antidepressant (AD) use and ≤ 2 months in case of concomitant AD use, and 3) only one type of BZDs is used at a time. Patients who met all 3 appropriateness criteria were categorized as appropriate users and patients who did not meet one or more criteria were categorized as inappropriate users.

Physician Characteristics

Physician characteristics were measured by questionnaires. The first part of the questionnaire contained demographic data including age, gender, clinical experience (in years), employment status of the GP (in full-time equivalents [fte]), the trainer status of the GP (i.e., approved clinical supervisor and mentor of GP registrars yes/no),[33] the type of practice the GP belonged to (i.e., solo vs. group practice), access to health care personnel, and the number of patients per GP. These characteristics were measured by the 'Visit instrument to assess practice management',[40] which was filled in by the practice assistants or practice nurses of the GPs. In part two, the GP's interest and attitudes towards depressive and anxiety disorders were assessed with the Depression Attitude Questionnaire (DAQ)[41] and a questionnaire to measure GPs' attitudes to their role in the management of patients with depression and anxiety.[33,42] In part three,

the collaboration of GPs with professionals and institutions specialized in mental health care was investigated.[33] In part four, the GPs' perceived workload and level of burnout were measured.[33] The Utrecht Burn-Out Scale (UBOS-C) investigated the GPs' perceived level of burn-out.[43] An additional item measured to what extent time limitations were perceived as barriers to the provision of mental health care on a 6 point Likert scale (from 'not at all' to 'very much').[33] The self-report questionnaires of parts two, three and four were filled in by the GPs personally.

Covariates: Patient Characteristics

The patient characteristics older age, singleness, unemployment, severity of anxiety, depression, comorbidity, and insomnia were associated with BZD use in previous research of this study group.[13] Inappropriate patient BZD use was associated with higher age and chronic illnesses.[13] These characteristics were corrected for in the regression analyses in order to identify the GP attitutes and characteristics, which were associated with patient BZD use independent of the characteristics of the patients themselves.

Patients reported gender, age, work status, and partner status in the baseline interview. Depressive and anxiety disorders were measured by the Composite International Diagnostic Interview (CIDI, life time version 2.1).[44] For the present analysis, 1 year CIDI diagnoses of anxiety only, depression only or comorbidity at baseline were established. The severity of generalized anxiety and panic symptoms at baseline was assessed with the Beck Anxiety Inventory (BAI).[45] The severity of insomnia at baseline was determined using the Insomnia Rating Scale (IRS).[46] The presence of chronic illnesses such as chronic lung disease, heart condition, and diabetes mellitus was recorded during the interview and the number of chronic illnesses a person suffered from were counted.

Statistical Analysis

Sample characteristics were expressed by frequencies, means or medians. Because of the hierarchical structure of the study (patients nested within GPs) and the dichotomous outcome variables (BZD use and inappropriate use) univariable and multivariable multilevel logistic models (Proc Glimmix; SAS 9.2; SAS Institute Inc., Cary, NC, USA) were conducted. We started with two separate models that did not contain any GP characteristics yet, but only one of the dependent variables 'BZD use' or 'inappropriate BZD use' and the above mentioned patient characteristics as covariates. As a next step, all above described GP characteristics were considered as potential correlates of BZD use and inappropriate use in separate univariable analyses. Univariable analyses were corrected for the patient characteristics age, sex and employment status. Further, the analyses of BZD use were corrected for the patient characteristics partner status, 1 year diagnosis of depression and/or anxiety, Beck Anxiety Inventory, and Insomnia Rating Scale.[13] The analyses of inappropriate use were additionally corrected for the patient characteristic number of chronic illnesses.[13] GP characteristics with $P < 0.10$ in univariable analyses and above mentioned covariates were entered in the multivariable model. All independent variables were entered as fixed factors. We added a random intercept at the GP level. Two-sided P-values equal or smaller than 0.05 were considered as significant in the multivariable model.

RESULTS

Table 1 shows the characteristics of the 62 GPs. GPs were more often male (54.8%), had an average age of 49.2 years and an average clinical experience of 17.8 years. At least half of the GPs reported good collaboration with social workers, psychologists and social psychiatric nurses, but not with mental health care institutions. Most GPs worked in group practices (93.5%). All GPs had a practice assistant and most GPs had access to mental and non-mental health care professionals. The

GPs were responsible for a median number of 1500 patients, of whom a median of 20 patients were NESDA participants in the current analysis.

GP Correlates of BZD Use

The patient group consisted of 1260 non-users (87.9%) and 173 BZD users. BZD use of patients did not differ between GPs (data not shown, P>0.05). In the multivariable analysis, only the perceived 'disability to differentiate depression from unhappiness' remained a significant correlate of less patient BZD use (Odds ratio [OR]=0.98, P=0.048, Table 2), independent of the included patient characteristics.

GP Correlates of inappropriate BZD Use

Inappropriate BZD use of patients did not differ between GPs (P>0.05, data not shown). In the multivariable analysis, higher 'professional comfort and competence with mental health care' (OR = 0.29, P=0.03) remained the only GP characteristic that was associated with less inappropriate BZD use, independent of the included patient characteristics.

TABLE 1. Characteristics and Attitudes of GPs (n=62)

Sociodemographic characteristics	
Gender (female, %)	45.2
Age (years), mean (sd)	49.2 (8.5)
Clinical experience (in years), mean (sd)	17.8 (10.1)
Employment status (in fte), median (IQR)	0.7 (0.6-0.8)
Approved clinical supervisor of GP registrars (%)	54.8
Employed in a group practice (vs. solo, %)	93.5
Access to health care professionals (%)	
(Non-mental) health care professionals (except practice assistant)	83.9
Mental health care professionals	87.1
Number of patients per GP (per 100), median (IQR)	15.0 (14.6 – 16.3)
GPs interests & attitudes towards depression and anxiety	
Depression Attitude Questionnaire (mean score), mean (sd)	
Preference for drug therapy	44.1 (9.1)
Uncomfortable feeling dealing with depressed patients	44.2 (11.1)
Belief in the inevitability of depression	35.1 (13.2)
Perceived disability to identify depression	39.0 (12.8)
GPs' attitudes on depressive and anxiety disorder management	
Professional comfort and competence with mental health care, mean (sd)	4.5 (1.0)
GPs concerns about difficulties with the health care system, median (IQR)	3.0 (2.6-3.5)
Collaboration with mental health care professionals / institutions	
Good collaboration with social workers (%)	53.2
Good collaboration with primary care psychologists (%)	50.0
Good collaboration with social psychiatrist nurses (%)	67.7
Good collaboration with mental health care institutions (%)	6.5
Perceived workload and level of burn-out	
Perceived time limitations, mean (sd)	3.5 (1.3)
Utrecht Burnout Scale	
Emotional Exhaustion, mean (sd)	1.4 (0.8)
Depersonalisation, mean (sd)	0.9 (0.6)
Personal Accomplishment, median (IQR)	4.5 (4.0 -4.9)

sd indicates standard deviation; IQR indicates interquartile range, BZD indicates benzodiazepine, GP indicates general practitioner, fte indicates full-time equivalent. Mean (sd) is provided for normally distributed variabels. Median (IQR) is provided for skewed variabels.

TABLE 2. GP Characteristics and Attitudes as Correlates of Patient BZD Use

	Univariable OR (95% CI)	P	Multivariable OR OR (95% CI)	P
Sociodemographic characteristics				
Gender (female)	0.91 (0.62 – 1.33)	0.62		
Age (years)	1.00 (1.00 – 1.02)	0.78		
Clinical experience (in years)	1.00 (0.98 – 1.02)	0.94		
Employment status (in fte), median (IQR)	0.88 (0.31 – 2.53)	0.82		
Approved clinical supervisor of GP registrars	0.98 (0.68 – 1.41)	0.90		
Employed in a group practice (vs. solo)	1.06 (0.53 – 2.09)	0.88		
Access to professionals				
(Non-mental) Health care professionals (except practice assistant)	1.45 (0.86 – 2.45)	0.16		
Mental health care professionals	1.28 (0.78 – 2.11)	0.32		
Number of patients per GP (per 100)	1.03 (0.98 – 1.08)	0.23		
GPs interests & attitudes towards depression and anxiety				
Depression Attitude Questionnaire				
Preference for drug therapy	0.99 (0.97 – 1.01)	0.37		
Uncomfortable feeling dealing with depressed patients	1.00 (0.98 – 1.02)	0.81		
Belief in the inevitability of depression	1.00 (0.99 – 1.02)	0.66		
Perceived disability to identify depression	0.99 (0.97 – 1.00)	0.07	0.98 (0.97 – 1.00)	**0.048**
GPs' attitudes on depressive and anxiety disorder management				
Professional comfort and competence with mental health care	1.21 (0.95 – 1.55)	0.13		
GPs concerns about difficulties with the health care system	0.90 (0.74 – 1.08)	0.26		
Collaboration with mental health care professionals				
Good collaboration with social workers	1.30 (0.90 – 1.88)	0.16		
Good collaboration with primary care psychologists	1.37 (0.96 – 1.95)	0.08	0.92 (0.63 – 1.35)	0.67
Good collaboration with social psychiatrist nurses	1.37 (0.92 – 2.05)	0.12		
Good collaboration with mental health care institutions	0.91 (0.46 – 1.78)	0.78		
Perceived workload and level of burn-out				
Perceived time limitations	1.09 (0.95 – 1.26)	0.21		
Utrecht Burnout Scale				
Emotional Exhaustion	1.20 (0.95 – 1.52)	0.12		
Depersonalisation	1.26 (0.97 – 1.64)	0.08	1.25 (0.95 – 1.64)	0.11
Personal Accomplishment	0.80 (0.61 – 1.06)	0.12		

BZD indicates benzodiazepine; GP indicates general practitioner; CI indicates confidence interval. ORs are calculated by univariable and multivariable logistic multilevel regression analyses (SAS glimmix). P Multilevel is derived by univariable and multivariable logistic multilevel analysis with two levels (doctors, patients). Univariable and multivariable analyses were corrected for patient's age, sex and employment status, partner status, 1 year diagnosis of anxiety and / or depression, Beck Anxiety Inventory, Insomnia rating scale. All GP characteristics with $P < 0.1$ in univariable analyses were included into the multivariable model

TABLE 3. GP Characteristics and Attitudes as Correlates of inappropriate Patient BZD Use

	Univariable OR (95% CI)	P	Multivariable OR (95% CI)	P
Sociodemographic characteristics				
Gender (female)	1.81 (0.48-6.75)	0.38		
Age (years)	0.98 (0.91-1.05)	0.50		
Clinical experience (in years)	0.99 (0.93-1.05)	0.67		
Employment status (in fte)	0.32 (0.01-9.26)	0.51		
Approved clinical supervisor of GP registrars	0.84 (0.26-2.72)	0.77		
Employed in a group practice (vs. solo)	0.66 (0.06-7.06)	0.73		
Access to health care professionals				
(Non-mental) Health care professionals (except practice assistant)	0.32 (0.10-1.02)	0.43		
Mental health care professionals	0.87 (0.17-4.45)	0.87		
Number of patients per GP	0.87 (0.17-4.45)	0.49		
GPs interests & attitudes towards depression and anxiety				
Depression Attitude Questionnaire				
Preference for drug therapy	1.03 (0.98-1.09)	0.22		
Uncomfortable feeling dealing with depressed patients	0.93 (0.88-0.97)	**0.003**	0.97 (0.91-1.03)	0.31
Belief in the inevitability of depression	0.97 (0.92-1.02)	0.25		
Perceived disability to identify depression	0.95 (0.90-1.00)	0.07	0.94 (0.88-1.00)	0.07
GPs' attitudes on depressive and anxiety disorder management				
Professional comfort and competence with mental health care	0.41 (0.23-0.76)	**0.005**	0.29 (0.10-0.88)	**0.03**
GPs concerns about difficulties with the health care system	1.73 (1.03-2.90)	**0.04**	0.89 (0.37-2.17)	0.81
Collaboration with mental health care professionals / institutions				
Good collaboration with social workers	0.67 (0.19-2.38)	0.67		
Good collaboration with primary care psychologists	1.17 (0.36-3.76)	0.80		
Good collaboration with social psychiatrist nurses	1.65 (0.45-6.05)	0.45		
Good collaboration with mental health care institutions	0.56 (0.09-3.66)	0.54		
Perceived workload and level of burn-out				
Perceived time limitations	0.76 (0.50-1.17)	0.21		
Utrecht Burnout Scale				
Emotional Exhaustion	0.77 (0.35-1.69)	0.51		
Depersonalisation	0.72 (0.31-1.69)	0.46		
Personal Accomplishment	1.41 (0.53-3.76)	0.50		

BZD indicates benzodiazepine; GP indicates general practitioner; OR indicates odds ratio. Appropriate use was defined as mean daily dosage ≤ DDD, duration of benzodiazepine use ≤ 3 months in case of no concomitant antidepressant (AD) use and ≤ 2 months in case of concomitant AD use and use of only one type of BZDs at a time. Use was defined as inappropriate when at least one of these criteria was not met. ORs were calculated by univariable and multivariable logistic multilevel regression analyses (SAS glimmix). P Multilevel was derived by univariable and multivariable logistic multilevel analysis with two levels (doctors, patients). Univariable and multivariable analyses were corrected for patient's age, sex and employment status, and number of chronic illnesses. All GP characteristics with $p < 0.1$ in univariable analyses were included into the multivariable model.

DISCUSSION

Summary

In this cross-sectional multilevel study amongst 1433 GP patients of 62 GPs, we investigated possible GP correlates of (inappropriate) patient BZD use and corrected for previously identified patient characteristics. Patient BZD use and inappropriate use did not vary significantly among GPs. Most GP characteristics were not associated with patient BZD use and inappropriate BZD use in the multivariable model. Only the GP's perceived 'disability to differentiate unhappiness from depression' was associated with less patient BZD use and the GP's 'professional comfort and competence with the mental health care system' was a correlate of lower inappropriate patient BZD use. This indicates that patient characteristics rather than GP characteristics determine patient BZD use and inappropriate use.

Strengths and Limitations of the Study

Our study had several limitations. In the light of the number of tests conducted, multiple testing may have caused a type I error, indicating that the two significant associations we found might be a chance finding. Further, patient BZD use was established via self-report of the GP patients and might not perfectly reflect GP prescriptions or the actual BZD use. The GP characteristics used in NESDA mainly included attitudes on anxiety and depression and not on the prescription of BZDs. Possibly, more specific GP attitudes towards BZD use need to be investigated in order to be able to detect differences in GPs' BZD prescription behaviour. However, this is unlikely, as there was little variance of BZD use and inappropriate use between GPs. Despite these limitations, we feel that our study is a valuable addition to the existing literature as it is the first study to investigate a large number of potentially important physician characteristics and attitudes in concert as possible correlates of BZD use and inappropriate use. Additionally, we corrected for previously identified

patient characteristics to find out whether GP characteristics could add information on top of already known predicting patient characteristics.

Comparison with existing Literature

The GP's perceived 'disability to differentiate unhappiness from depression' was the only weak correlate of less patient BZD use in the fully corrected model. This was a rather unexpected finding. These GPs had expressed the assumption that depression develops as a consequence of personal misfortune and felt that they could do little to help. Possibly, these GPs were less likely to prescribe BZDs as they felt they could do nothing to improve the mental health of their patients. However, in general, GP characteristics provided little additional information in the prediction of patient BZD use on top of the patient characteristics identified as predictors in previous research. The small number of significant GP characteristics is largely in line with some earlier studies that did not identify any significant GP correlates.[28,29] Other research identified GP correlates of BZD use (e.g. male GP gender[24,25]) which were not significant in our research. These studies differed from our own as they did not correct for patient characteristics.[24,25] Thus, the found differences between GPs in those studies might actually be explained by the variability in patient characteristics (instead of by differences between GPs).

Inappropriate patient BZD use was also hardly associated with the GP characteristics. Only the GPs' comfort with mental health care correlated with less inappropriate patient BZD use. This indicates that GPs who issued less inappropriate BZD prescriptions felt more comfortable in dealing with anxious and depressed patients. This may be in line with earlier qualitative research which reported that BZDs are often prescribed due to a presumed lack of (psychotherapeutic) skills.[19,20] Our findings are also in accord with the earlier finding that subject characteristics are more important for the prediction of long-term BZD use than GP characteristics.[31]

Implications for future Research and clinical Practice

In general, it is striking that GP characteristics added little information on top of the patient characteristics which were shown to be significant correlates of BZD use and inappropriate BZD use in previous research.[13] This refutes the previous notion that some physicians are particularly responsible for the (inappropriate) BZD use of their patients.[16] Interventions to reduce chronic BZD use should target patients at risk and the prescribing physicians alike, with a focus on patient characteristics rather than physician characteristics. Physicians should receive training to improve their knowledge on alternative treatment strategies and interaction skills with subjects at high risk of inappropriate use. Future research will have to show which kind of trainings are most helpful for the GPs to do so. Patients at risk should receive information about the unfavourable consequences of (inappropriate) BZD use, as already minimal intervention was shown to reduce chronic BZD use.[17,47,48]

Conclusion

In conclusion, this study revealed that GP characteristics had little value in the prediction of patient BZD use and inappropriate BZD use on top of the patient characteristics. Apparently, it is primarily dependent on patient characteristics whether BZDs are used (inappropriately) or not.

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Long-term Benzodiazepine Use and salivary Cortisol: the Netherlands Study of Depression and Anxiety (NESDA)

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ABSTRACT

Background: As benzodiazepines (BZDs) have anxiolytic effects, it is expected that they influence the stress system. During short-term treatment, BZD use was found to suppress cortisol levels. However, little research has been done on the effects of long-term BZD administration on the hypothalamic-pituitary-adrenal (HPA) axis.

Methods: The association between long-term BZD use and cortisol levels was investigated in subjects of the Netherlands Study of Depression and Anxiety with a lifetime diagnosis of anxiety or depression (n=1531). Subjects were categorized as "daily BZD users" (n=96), "infrequent BZD users" (n=172) and "nonusers" (n=1263). Possible associations between characteristics of BZD use (dose, duration, and dependence) and salivary cortisol levels were analyzed.

Main outcome measure: Subjects provided 7 saliva samples, from which 4 cortisol indicators were calculated: the cortisol awakening response, diurnal slope, evening cortisol, and cortisol suppression after ingestion of 0.5 mg dexamethasone.

Results: Daily users used BZDs for a median duration of 26.5 months and had a median daily dosage of 6.0 mg as measured in diazepam equivalents. Evening cortisol levels were significantly lower in daily users (P=0.004, effect size: d=0.24) and infrequent users (P=0.04, effect size: d=0.12) as compared to nonusers. We did not find significant differences in the cortisol awakening response, diurnal slope or in the dexamethasone suppression test.

Conclusions: Despite the finding of slightly lower evening cortisol levels in daily and infrequent BZD users as compared to nonusers, results indicate that long-term BZD use is not convincingly associated with HPA axis alterations.

INTRODUCTION

As benzodiazepines (BZDs) have anxiolytic and sedating effects, it is expected that they influence the stress system. Most studies on the effects of short-term BZD treatment (maximum of 3 months) on the hypothalamic-pituitary-adrenal (HPA) axis in human subjects reported a decrease in cortisol levels,[1-11] although some studies reported mixed results.[12,13] These inconsistencies may be explained by differences in dosages and half-lives of the BZDs used[13] and by disparities in the measurement time points used in the assessments (only predrug and postdrug measurements,[13] at certain time intervals,[6,8,10-12,14] or for a full circadian cycle[1,2,5]). Differences in patient groups,[12,13] and measurements of basal versus stress-provoked cortisol levels may also influence the results.[3,13] In general, the studies measured plasma cortisol levels[1-3,5,6,9,11,13] or urinary free cortisol as measures of HPA axis activity.[4] Associations between BZD use and dexamethasone suppression have only been investigated in 1 study and no clear effect of BZD use on dexamethasone suppression was observed.[14] A few studies found that the cortisol decrease in response to BZD treatment was followed by a return to baseline cortisol levels within only a few hours, despite persisting high plasma drug levels,[15-17] suggesting fast development of tolerance to the stress-axis-suppressing effects of BZDs. In contrast, other studies did report significant cortisol reductions in 24h, overnight and daytime means,[1] suggesting that tolerance does not develop as rapidly.

Tolerance to the effects of BZDs as a consequence of chronic use (>3 months) has been extensively discussed in previous studies.[18,19] In related research on the therapeutic effects of BZDs, several authors reported that tolerance was developed to only the cognitive and psychomotor effects and not to the anxiolytic effects of chronic BZD treatment,[19] whereas others found decreasing anxiolytic efficacy as well when treatment exceeded a few weeks.[18] Most studies on the effects of

BZDs on cortisol levels found that cortisol suppression was maintained for up to 3 months of use.[1,2,4,9,12]

There was only 1 small cross-sectional study investigating long-term BZD use (> 3 months).[20] The authors found that long-term users have similar baseline cortisol levels as nonusers, indicating that BZDs do not maintain their cortisol-suppressing effects during longer-term use. In contrast, an additional dosage of BZDs (on top of the BZD dosage that chronic users took daily) still affected the HPA axis after chronic use. However, comparison groups were small, no measurement of the whole circadian rhythm was conducted, and no dexamethasone challenge test was applied.[20]

In this paper, we examine the effects of chronic BZD use on various salivary cortisol measures (cortisol awakening response, diurnal slope, evening cortisol level and suppression after oral dexamethasone administration). In addition, we explore the effects of dosage, duration of use, and level of dependence. The study was carried out on data from 1531 subjects with a lifetime diagnosis of anxiety and / or depression participating in the Netherlands Study of Depression and Anxiety (NESDA).

MATERIALS AND METHODS

Subjects

Subjects participated in the baseline assessment of NESDA, an 8-year longitudinal cohort study of 2981 respondents aged 18 to 65 years.[21] Subjects were recruited from the community, general practice and specialized mental health care institutions throughout the Netherlands. Subjects completed a medical exam, an in-person interview, saliva collection and several questionnaires. The study protocol was approved by the Ethical Review Board of each participating center and all subjects signed an informed consent at the baseline assessment.

To investigate the associations between BZD use and salivary cortisol indicators, 3 groups were defined: subjects who reported daily BZD use in the month prior to the baseline interview ("daily BZD users", n=176), subjects who used BZDs on an infrequent basis in the previous month ("infrequent BZD users", n=264) and those reporting no use of BZDs in the last month ("nonusers", n=1854). All subjects reported a current or past diagnosis of a depressive or anxiety disorder (referred to as a lifetime disorder), defined as an anxiety disorder (panic disorder with or without agoraphobia, generalized anxiety disorder or social phobia) or depressive disorder (dysthymia or Major Depressive Disorder, MDD) as assessed by the Composite International Diagnostic Interview (WHO version 2.1) which classifies diagnoses according to the criteria of the Diagnostic and Statistic Manual of Mental Disorders IV-TR (American Psychiatric Association, 2001). From these 3 groups, 1664 (72.5%) subjects returned saliva samples. Responders on saliva collection did not differ from non-responders in gender (67.7% vs 68.3% women, P = 0.79) but were older (43.6 ± 12.5 years vs 37.9 ± 11.9 years, P<0.001), more educated (12.2 ± 3.3 years vs 11.5 ± 3.2 years, P<0.001) and less likely to have a lifetime diagnosis of comorbid disorder (55.5% vs 64.0%, P<0.001). Furthermore, responders had marginally significantly lower rates of BZD use (18.2% vs 21.7%, P=0.06). Of the responders, 1658 provided sufficient cortisol samples of high quality from which at least one usable salivary cortisol indicator (cortisol awakening response [CAR], diurnal slope, evening cortisol or dexamethasone suppression test [DST], see later section) could be calculated.

Because of known associations with cortisol or use of BZDs, pregnant or breastfeeding women (n=10), subjects using corticosteroids (n=104), and patients with epilepsy (n=13) were excluded, leaving a final sample of 1531 subjects (1263 nonusers, 172 infrequent BZD users and 96 daily BZD users).

MEASURES

Benzodiazepine Use

Four indicators of BZD use were investigated: type of BZD, daily BZD dose, duration of BZD use, and BZD dependence severity. BZD use during the month before the baseline interview was registered by observation of drug containers brought to the interview (73.4%) or self-report (26.6%). Daily and infrequent BZD users reported the type and dosage of BZD taken on an average day of use. Frequency of use for infrequent users was taken into account when calculating the average daily dose. The daily BZD dose was computed according to the coding system of the Anatomical Therapeutic Code (ATC) and Defined Daily Dose (DDD) system.[22] The mean daily dose was calculated by dividing individual daily doses (in milligrams) of BZDs by the DDD for the particular BZD. BZDs were classified as ATC-coded groups N05BA, N05CD, and N03AE01. The non-BZD hypnotics zopiclone and zolpidem (ATC code N05CF), were also included. Similar to BZDs, these hypnotics act on the central omega I gamma aminobutyric acid receptor. For patients using BZDs other than diazepam, an equivalent daily dose was calculated with conversion tables,[23,24] and 10 mg of diazepam were regarded equivalent to 1 mg alprazolam, 10 mg bromazepam, 0.25 mg brotizolam, 20mg clobazam, 20 mg chlordiazepoxide, 13.3 mg clorazepate, 8 mg clonazepam, 30 mg flurazepam, 1 mg loprazolam, 2 mg lorazepam, 1 mg lormetazepam, 7.5 mg midazolam, 10 mg nitrazepam, 33 mg oxazepam, 20 mg prazepam, 20 mg temazepam, 20 mg zolpidem and 13 mg zopiclone. Dosages were summed when more than 1 BZD was used. The duration of BZD use was reported in months. BZD users completed the Benzodiazepine Dependence Self-Report Questionnaire (Bendep-SRQ), a 15-item self-report questionnaire, as a measure of dependence severity. Each item was rated on a 5- point scale. Three dependence dimensions were derived: 1) awareness of problematic use, 2) preoccupation with the availability of BZDs, and 3) lack of compliance with the therapeutic regimen.[25] The Bendep-SRQ has

good scalability, reliability and validity in general practice patients,[26] and psychiatric outpatients.[27]

Salivary Cortisol

The respondents were asked to collect saliva samples at home on a regular, preferably working day, shortly after the baseline interview by using Salivettes (Sarstedt AG und Co, Nürmbrecht, Germany).[28] The median time between the interview and saliva sampling was 9 days (25th – 75th percentile: 4-22). Eating, smoking, drinking tea or coffee, or brushing teeth was prohibited within 15 minutes of sampling. Saliva was measured at seven time points (Ts): upon awakening (T1), 30 minutes (T2), 45 minutes (T3) and 60 minutes (T4) after awakening and in the evening at 10_{PM} (T5) and 11_{PM} (T6). Immediately after saliva sampling at T6, the cortisol suppression test was carried out by oral administration of a 0.5-mg dexamethasone pill and assessed by cortisol sampling the next morning directly after awakening (T7). All samples were refrigerated and returned by mail. During laboratory analysis, Salivettes were centrifuged at 2000g for 10 minutes, aliquoted, and stored at -80°C. Competitive electrochemiluminescence immunoassay (E170 Roche, Basel, Switzerland) was used to measure cortisol levels at a functional detection limit of 2.0 nmol/l.[29] Intraassay and interassay variability coefficients in the measuring range were less than 10%. Assays were repeated if cortisol levels were very high (> 80 nmol/L) or very low (< 1 nmol/L) (n=128). All very high samples remained high in the second measurement, and the mean of the 2 measured values was used in further analyses. In 80% of the very low samples, the repeated cortisol value was within the reference range and was used for analysis. In cases where the second measurement was also very low, the mean of the samples was used. Data cleaning was performed by excluding cortisol values more than 2 SDs above the mean.[28]

Four cortisol measures were derived: the CAR, diurnal slope, evening cortisol and cortisol suppression on the DST.[28]

Cortisol Awakening Response (CAR)

The CAR was calculated from 4 sampling points: T1, T2, T3, and T4. In our study, it was calculated by analysis of T1 to T4 with Linear Mixed Models (LMM) and 2 aggregate indicators: area under the curve with respect to the ground (AUCg) and with respect to the increase (AUCi) according to Pruessner's formulas.[30] The AUCg is an estimate of the total cortisol secretion and predicts mean cortisol levels throughout the day, and the AUCi is a measure of the dynamics of the CAR, related to the sensitivity of the system and emphasizing changes over time.[28,30] For the AUC analyses, a minimum of 3 samples were required. For those with 1 missing cortisol value (n=84), the fourth was imputed using linear regression analyses with information on the other available 3 cortisol values, gender, age, awakening time and smoking status.

Diurnal Slope and Evening Cortisol

As cortisol levels at 10_{PM} (T5) and 11_{PM} (T6) were correlated ($r=0.73$, $P < 0.01$), evening cortisol was defined as the average of the 2 values (T5 and T6) or by one of the 2 if only one was available. Diurnal slope was calculated by subtracting the evening cortisol level (as calculated earlier) from the cortisol level at T1 and dividing it by the time in hours between the 2 samples, resulting in the change over time of cortisol throughout the day, calculated per hour.[28,31]

Dexamethasone Suppression Test (DST)

In addition to the cortisol level at awakening after dexamethasone ingestion (T7), a cortisol suppression ratio was calculated by dividing the cortisol value at awakening on day 1 (T1) by the post-dexamethasone cortisol value at awakening on day 2 (T7). Lower post-dexamethasone cortisol levels (T7) and higher DST ratios (ie, a larger difference between T1 and T7) indicate a greater cortisol-suppressing effect of dexamethasone.

Covariates

As associations between sociodemographics (gender, age, education, and North-European ancestry), sampling factors (awakening time, work status, weekday, season, and sleep duration) and health indicators (smoking, physical activity) on salivary cortisol variables have been described previously,[32] these identified determinants were considered as covariates.

Comorbidity of anxiety and depression as well as antidepressant use have been found to be associated with salivary cortisol levels in previous research in this study sample,[28] and numbers of antidepressant use and comorbidity differed between BZD groups (Table 1). Therefore, comorbidity and antidepressant use were also included as covariates. Depression and anxiety disorders were established with the Composite International Diagnostic Interview (WHO version 2.1) which classifies diagnoses according to the criteria of the *Diagnostic and Statistic Manual of Mental Disorders Fourth Edition-Text Revision* (American Psychiatric Association, 2001). The use of antidepressants in the past month was determined by observation of drug containers brought to the baseline interview. Antidepressants were subdivided into selective serotonin re-uptake inhibitors (SSRI, ATC code N06AB), tricyclic antidepressants (TCA, ATC code N06AA), and other antidepressants (monoamine oxidase inhibitors N06AG, non-selective N06AF, and antidepressants classified as N06AX).

Respondents were asked to report time of awakening, and working status on the sampling day. Sampling date information was used to categorize weekday versus weekend day and season categorized in less daylight (October through February) and more daylight (March through September) months. Average sleep duration during the last week was dichotomized as ≤6 or >6 hours/night, and smoking status as current versus non-smoker. Physical activity was assessed using the International Physical Activity Questionnaire and expressed as activity

per 1000 MET-minutes (metabolic equivalent of number of calories spent by a person per minute) a week.[28]

Statistical Analyses

Characteristics of study groups were expressed by frequencies, means or medians, and compared using $\chi 2$ statistics (categorical variables), analysis of variance (continuous variables, normally distributed), and the Kruskal-Wallis-test (continuous variables, non-normally distributed). Area under the curve with respect to the increase and diurnal slope were normally distributed, which allowed data analysis with nontransformed values. T1-T4, AUCg, evening cortisol, T7, and DST were naturally log transformed because of their positively skewed distributions. Back-transformed values are given in Table 2.

Differences in AUCg, AUCi, diurnal slope, evening cortisol, T7, and DST across groups were analyzed using analysis of covariance (ANCOVA), adjusting for basic sociodemographic variables, sampling factors, health indicators, comorbidity, and antidepressant use. Cohen's *d* (the difference in group means, divided by their pooled SD) was calculated as a measure of effect size. Further analysis of the CAR was carried out with random coefficient analysis of the 4 morning cortisol data points by using LMM. This analysis keeps original values on all 4 data points, accommodates for missing data, and takes correlations between repeated measurements within subjects into account.[33]

Linear regression analyses were used to assess associations between characteristics of BZD use (ie, duration, dose and dependence as separate independent variables) and salivary cortisol indicators as continuous dependent variables after full adjustment in daily and infrequent BZD users.

Differences across the 4 most commonly used BZD types, that is, oxazepam (n=115), diazepam (n=33), alprazolam (n=16), and temazepam (n=45) on salivary cortisol indicators were analyzed in pairwise comparisons using ANCOVA, adjusting for aforementioned

covariates. The other BZDs were not included in these analyses as group numbers were to small (n<15). Oxazepam was used as reference group. Statistical significance was inferred at P < 0.05. All statistical analyses were conducted using SPSS for Windows, version 16.0 (SPSS, Chicago, Ill).

RESULTS

Characteristics of the 3 BZD user groups are presented in Table 1. BZD users were older, less educated, more often diagnosed with a comorbid disorder, and more likely to use antidepressants as compared to nonusers. Only 17.9% of subjects were short-term users (≤3 months), and the remaining 82.1% were long-term users (> 3 months). The median duration of use was 35.5 months (25th – 75th percentile: 5-96). Although the group of short-term users was too small (n = 48) to be analyzed separately, exclusion of these subjects did not affect our main results (data not shown). The median daily dosage of BZDs used was 1.0 mg (25th – 75th percentile: 0.2 – 2.0) of diazepam equivalents for infrequent users and 6.0 mg (25th – 75th percentile: 3.2 – 13.9) of diazepam equivalents for daily users. Crude saliva levels (T1-T4 and T7) did not differ between groups (Table 2).

Cortisol Awakening Response

Overall, 71.5 % of respondents showed an increase in cortisol in the first hour after awakening, with a mean increase of 6.6 nmol/L (or 53.5%). No significant effects were found for any of the crude CAR analyses (Table 2). Adjusted CAR results showed that daily users and infrequent users did not differ on overall cortisol levels from nonusers, reflected by analysis of AUCg (P=0.09 for daily users vs nonusers and P=0.74 or infrequent users vs nonusers; Table 2) and LMM analysis (daily users vs non-users, $F_{(1329, .097)}$=3,07, P=0.08; and infrequent users vs nonusers, $F_{(1413, 642)}$=0.11, P=0.74). A nonsignificant effect on AUCi (daily users vs nonusers, P=0.99

and infrequent users vs nonusers, *P*=0.99, Table 2) and no significant group by time interaction in the LMM analysis (daily users vs nonusers, $F_{(3947, 327)}$=0.49, *P*=0.69 and infrequent users vs nonusers, $F_{(4171, 422)}$=0.92, *P*=0.43) were found, indicating a similar time course between groups.

Diurnal Slope

No significant effects were found for crude or adjusted diurnal slope analyses (daily users vs non users: *P*=0.79).

Evening Cortisol Level

Unadjusted evening cortisol levels did not differ between groups (Table 2). After adjustment, evening cortisol was significantly lower in daily BZD users (*P*=0.004, effect size [Cohen's *d*], 0.24) and infrequent users (*P*=0.04, effect size, 0.12) compared to nonusers. Age and SSRI use were the most important confounders in the fully adjusted model.

Dexamethasone Suppression Test

The unadjusted cortisol suppression ratio was significantly lower in daily users as compared to nonusers (*P*=0.049, effect size, 0.08, Table 2) which indicates increased nonsuppression after dexamethasone ingestion in the daily user group. After adjustment, however, cortisol suppression ratios (*P*=0.71) and T7 levels (*P*=0.46) did not differ between groups. Infrequent users also did not differ from nonusers on either of the cortisol indicators (*P*=0.46 for cortisol suppression ratio and *P*=0.31 for T7).

Characteristics of BZD Use

Table 3 reports the results of additional analyses on specific associations between salivary cortisol levels and characteristics of BZD use (duration, dose and severity of BZD dependence as measured by the Bendep-SRQ) among the combined BZD user groups (infrequent and daily). For the duration of use, no effect on any cortisol indicator was found except

for a weak negative association with adjusted T7 cortisol levels after dexamethasone ingestion (β=-0.15, *P*=0.03), indicating that a longer duration of BZD use was associated with a somewhat lower cortisol level after dexamethasone ingestion, that is stronger suppression. The daily BZD dose and the 3 subscales of the Bendep-SRQ (problematic use, preoccupation and lack of compliance) were not associated with any salivary cortisol indicator.

Pairwise comparisons of the most common BZD types showed that the temazepam group did not differ from the oxazepam group on any of the cortisol indicators. However, the diazepam group had lower diurnal slope levels (*P*=0.01) and a decreased dexamethasone suppression ratio (*P*=0.01) as compared to oxazepam users. The alprazolam group had a lower AUCg than the oxazepam group (*P*=0.007, data not shown).

TABLE 1. Characteristics of Study Groups

	N	Nonusers n=1263	Infrequent Users n=172	Daily Users n=96	*P*
Sociodemographics					
Gender, % female	1531	67.2	71.5	58.3	0.09
Age, years	1531	42.5 (41.9-43.2)	46.0 (44.2-47.9)	48.6 (46.2-51.1)	<0.001
Education, years	1531	12.3 (12.1-12.5)	12.0 (11.5-12.5)	11.3 (10.6-11.9)	0.009
North European ancestry, %	1531	95.1	93.0	96.9	0.34
Sampling Characteristics					
Time of awakening	1531	7.27h (7.23-7.31h)	7.40h(7.28-7.52h)	7.39h(7.24-7.53h)	0.05
Working on day of sampling, %	1531	63.2	50.6	33.3	<0.001
Sampling on a weekday, %	1531	92.8	86.0	86.5	0.002
Sampling in month with more daylight hours, %	1531	56.4	64.0	47.9	0.03
≤6 hours of sleep, %	1531	27.6	41.3	41.7	<0.001
Health Indicators					
Smoking , %	1531	36.1	35.5	40.6	0.65
Physical activity (1000 MET-min/week)	1531	3.7 (3.5-3.9)	3.5 (3.1-4.0)	3.1 (2.5-3.7)	0.13
Psychiatric indicators					
Lifetime Diagnosis, %					
MDD only	1531	31.0	23.8	24.0	0.07
Anxiety only	1531	15.4	12.2	9.4	0.18
Comorbid disorder	1531	53.7	64.0	66.7	0.003
Benzodiazepine (BZD) use					
Duration of BZD use, months	268	N/A	36.0 (5.0-99.0)	26.5 (5.3-96.0)	0.29
Daily dosage of diazepam equivalents, mg*	268	N/A	1.0 (0.2-2.0)	6.0 (3.2-13.9)	<0.001
Type of BZD, %					
Oxazepam	1531	N/A	48.8	36.5	<0.001
Temazepam	1531	N/A	24.4	14.6	<0.001
Diazepam	1531	N/A	13.4	10.4	<0.001
Alprazolam	1531	N/A	2.3	14.6	<0.001
Others	1531	N/A	19.2	45.8	<0.001

Bendep SRQ					
Highly problematic use	232	N/A	8.0 (6.0-11.0)	10.0 (8.0-12.0)	<0.001
High preoccupation	232	N/A	12.0 (9.0-14.0)	15.0 (13.0-17.0)	<0.001
High lack of compliance	232	N/A	6.0 (5.0-8.0)	8.0(6.0-10.0)	<0.001
Antidepressant Use, %					
SSRI	1525	17.6	29.1	44.8	<0.001
TCA	1530	2.7	5.2	7.3	0.02
Others	1528	6.0	10.5	16.7	<0.001

Means (95% confidence intervals[CI]) are given for age, education, time of awakening, physical activity. Median (interquartile range) is given for duration of BZD use, daily dosage of BZD use, and BENDEP-SRQ as these values are not normally distributed. Percentages are given for categorical variables. *P* is derived by analysis of variance (ANOVA) for quantitative, normally distributed variables, Kruskal-Wallis test for continuous, non-normally distributed variables, or χ^2 statistics for categorical variables. Significance is inferred at $P < 0.05$. ˚Users reported the dosage of BZPs taken on an average day of use. Frequency of use has been taken into account for infrequent users.

BENDEP-SRQ indicates Benzodiazepine Dependence Self Report Questionnaire; MDD, Major Depressive Disorder; SSRI, Selective Serotonin Reuptake Inhibitor; T, Timepoint; TCA, Tricyclic Antidepressant; N/A, not applicable.

TABLE 2. Associations Between Benzodiazepine Use and Various Salivary Cortisol Indicators

Cortisol Characteristics	N	Nonusers n=1263	Infrequent Users n=172	Daily Users n=96	Nonusers vs Daily Users	Nonusers vs Infrequent Users
		Mean	Mean	Mean	P	P
Unadjusted Cortisol Characteristics		(95% CI)	(95% CI)	(95% CI)		
Cortisol Awakening Response						
Cortisol T1, at awakening, nmol/L	1517	15.6 (15.3 - 16.0)	15.8 (14.8 – 16.8)	15.2 (14.0 – 16.5)	0.53	0.77
Cortisol T2, + 30 min, nmol/L	1509	19.3 (18.8 – 19.8)	19.7 (18.4 – 21.1)	18.3 (16.8 – 20.1)	0.29	0.54
Cortisol T3, + 45 min, nmol/L	1508	17.9 (17.4 – 18.4)	18.3 (17.0 – 19.7)	16.5 (14.9 – 18.2)	0.12	0.57
Cortisol T4, + 60 min, nmol/L	1511	15.7 (15.3 – 16.2)	15.3 (14.2 – 16.5)	14.9 (13.5 – 16.4)	0.29	0.48
AUCg, nmol/L per hour	1490	18.1 (17.7 - 18.4)	18.3 (17.2 - 19.3)	17.2 (16.0 - 18.6)	0.25	0.73
AUCi, nmol/L per hour	1490	2.5 (2.1 – 2.9)	2.3 (1.3 – 3.3)	2.3 (1.0 – 3.6)	0.75	0.73
Evening Cortisol, nmol/L	1525	4.8 (4.7 – 5.0)	4.6 (4.2 – 5.0)	4.6 (4.2 – 5.2)	0.50	0.26
Dexamethasone suppression test						
Cortisol suppression ratio[1]	1452	2.4 (2.3 – 2.5)	2.4 (2.2 – 2.6)	2.2 (1.9 – 2.4)	0.049	0.91
Cortisol T7, after dexamethasone, nmol/L	1476	6.6 (6.4 – 6.8)	6.6 (6.1 – 7.1)	7.1 (6.4 – 7.9)	0.16	0.98
Diurnal Slope , nmol/L per hour	1510	0.8 (0.7 – 0.8)	0.8 (0.8 – 0.9)	0.8 (0.7 – 0.9)	0.55	0.06
Adjusted Cortisol Characteristics[2]						
Cortisol Awakening Response						
AUCg, nmol/L per hour	1490	18.1 (17.7 – 18.4)	18.3 (17.3– 19.3)	16.8 (15.6 – 18.1)	0.09	0.74
AUCi, nmol/L per hour	1490	2.5 (2.1 – 2.8)	2.5 (1.5 – 3.4)	2.5 (1.2 – 3.8)	0.99	0.99
Evening Cortisol, nmol/L	1525	4.9 (4.7 – 5.0)	4.5 (4.1 – 4.8)	4.2 (3.8 – 4.7)	0.004	0.04
Dexamethasone suppression test						
Cortisol suppression ratio	1452	2.4 (2.3 – 2.4)	2.5 (2.3 – 2.7)	2.3 (2.1 – 2.6)	0.71	0.46
Cortisol T7, after dexamthesone, nmol/L	1476	6.6 (6.5 - 6.8)	6.4 (5.9 – 6.9)	6.4 (5.8 – 7.1)	0.46	0.31
Diurnal Slope, nmol/L per hour	1510	0.8 (0.7 – 0.8)	0.8 (0.8 – 0.9)	0.8 (0.7 – 0.9)	0.79	0.17

For all cortisol indicators except of AUCi geometric means (95% CIs) are presented based on estimated marginal means calculated by analysis of covariance (ANCOVA). For AUCi, estimated marginal means (95% CIs) are presented. P-values are calculated by ANCOVA comparing two groups at a time. Significance is inferred at P<0.05 Nonusers are the reference group.

[1] Cortisol suppression ratio= salivary cortisol T1/salivary cortisol T7, after 0.5 mg dexamethasone. [2]Adjusted for sociodemographics (gender, age, education, North-European ancestry), sampling factors (working, weekday, time of awakening, sleep and month with more day light), comorbidity, antidepressant use (None / SSRI / TCA / other) and health indicators (smoking and physical activity).

AUCg indicates Area under the morning curve with respect to the ground; AUCi, Area under the morning curve with respect to the increase; T, timepoint; CI, Confidence Interval.

TABLE 3. Associations Between Dose and Duration of Benzodiazepine (BZD) Use as Well as Severity of BZD Dependence and Various Cortisol Indicators in a Sample of 285 BZD Users

Cortisol Indicators – Adjusted[1]	Characteristics of BZD Use					BZD Dependence (BENDEP-SRQ)						
	N	Duration of BZD Use		Daily BZD Dose		N	Problematic Use		Preoccu-pation		Lack of Compliance	
		β	*P*	β	*P*		β	*P*	β	*P*	β	*P*
Cortisol Awakening Response												
AUCg, nmol/L per hour	261	-0.031	0.64	-0.013	0.84	225	-0.005	0.95	0.057	0.39	0.048	0.49
AUCi, nmol/L per hour	261	0.010	0.88	0.048	0.47	225	-0.054	0.46	0.042	0.55	0.097	0.19
Evening cortisol												
Evening cortisol, nmol/L	267	-0.097	0.11	-0.046	0.46	231	0.037	0.58	-0.003	0.96	0.034	0.62
Dexamethasone suppression test												
Cortisol suppression ratio[2]	249	0.089	0.20	-0.084	0.22	216	0.112	0.13	0.048	0.50	-0.016	0.83
Cortisol T7, after dexamethasone, nmol/L	254	-0.147	0.03	0.028	0.68	221	-0.076	0.30	-0.011	0.87	-0.018	0.81
Diurnal Slope												
Diurnal Slope, nmol/L per hour	262	-0.036	0.59	-0.040	0.57	226	0.034	0.65	0.019	0.78	-0.064	0.39

Duration of BZD Use ranges from 1-512 months. Daily BZD dose is calculated as diazepam equivalents; mean daily doses are given, ranging from 0.05 to 105 mg (in diazepam equivalents).[1] Adjusted for sociodemographics (gender, age, education, North-European ancestry), sampling factors (working, weekday, time of awakening, sleep and month).[2] Cortisol suppression ratio= salivary cortisol T1/salivary cortisol T7, after ingestion of 0.5 mg dexamethasone.

BENDEP-SRQ indicates Benzodiazepine Dependence Self Report Questionnaire; AUCg, Area under the morning curve with respect to the ground; AUCi, Area under the morning curve with respect to the increase; β, the standardised beta coefficient by linear regression analyses

AUCg, Basal Cortisol, Cortisol Suppression Ratio and Cortisol T7 were naturally log-transformed before regression analyses.

BZD nonusers are excluded from these regression analyses.

DISCUSSION

In this study, the relationship between BZD use and various salivary cortisol measures was studied in NESDA subjects with a lifetime diagnosis of depression and/or anxiety. With the exception of slightly lower evening cortisol levels in daily and infrequent BZD users compared with non-users, the user groups did not differ on any cortisol indicators after adjustment for covariates. Dose, frequency of use, and dependence were not associated with salivary cortisol levels except of a correlation of longer duration of use with stronger cortisol suppression after dexamethasone ingestion. As the found effect sizes were small, the clinical relevance of the statistically significant findings is limited. Further, in the light of the number of tests conducted, multiple testing may have caused a type 1 error for evening cortisol in BZD users.

An explanation for the lack of consistent associations could be that BZDs inhibit the HPA axis during short-term use and that tolerance to the cortisol-suppressing effect of BZDs develops after long-term BZD treatment. Correspondingly, intervention studies that found lower cortisol levels in response to BZD administration mainly looked at short-term effects during a time period ranging from 1 day to 1 month,[3,5,6,9,13,34-37] except for a few studies with a duration of 2-3 months.[1,2,4] In contrast, chronic users were found to have similar baseline cortisol levels as nonusers, also indicating that BZDs do not maintain their cortisol-suppressing effects in long-term use.[20] As our study mainly consists of chronic users (3-year median duration of use), the lack of association between BZD use and baseline cortisol levels agrees with results from the latter study.[20]

Although tolerance is likely to develop during long-term use, an additional dosage of BZDs (on top of a regular daily dosage) still induces HPA axis inhibition. Indeed, Cowley et al.[20] found that long-term users showed similar decreases in plasma cortisol after an extra dosage of BZDs as treatment-naïve patients.[20] In related research on the therapeutic

effects of BZDs, an increased dosage of BZDs was found to increase anxiolytic effects even after more than 10 years of daily use.[38]

Along with the hypothesis of tolerance development to the cortisol suppressing effects of long-term BZD use, there are several alternative explanations that may account for discrepancies in findings. First, BZD users may have had enhanced HPA axis activity prior to the start of BZD treatment which was subsequently normalized by long-term BZD treatment. Indeed, a significantly higher percentage of daily users compared to nonusers had comorbid disorder, which has been found to be associated with increased cortisol levels in this study population.[28] Second, it might be that the joint investigation of a number of different types of BZDs with possibly opposing effects on the HPA axis has covered effects on cortisol levels.[39] We found lower diurnal slope levels and a decreased dexamethasone suppression ratio in the diazepam group and a lower AUCg in the alprazolam group compared to the oxazepam group. This may be evidence for the possibly opposing effects of the different BZDs. This corresponds to a former study that reported BZDs to have either a stimulating or an inhibiting effect on the HPA axis conditional on the alpha subunit of the GABA receptor modulated by the drugs.[39] However, as comparison groups were small in NESDA, results have to be replicated in future research. Third, stronger effects on cortisol levels may be due to higher dosages. In intervention studies higher average dosages were used than in the current study (ie, 12 mg of diazepam equivalents in intervention studies versus 6 mg in NESDA). Another explanation for basal cortisol being the only cortisol measurement differing significantly between BZD user groups might be that hippocampal mineralocorticoid receptors (MRs) are more affected by central acting BZDs than glucocorticoid receptors (GRs). Because MRs are more occupied at intermediate cortisol concentrations while GRs are not,[40] basal evening cortisol might be a probe of MR activity.[41] However, because research on GR, MR and BZDs is still limited, this assumption deserves further confirmation in future research.

Our study has some limitations. A cross-sectional analysis was done, which precludes causal inferences or differentiation between the potential explanations of the lack of group differences in salivary cortisol. Because we had to rely on subjects' self-report on BZD intake, we cannot be completely sure whether subjects were actually using the medications as prescribed and as they themselves indicated. Noncompliance with instructions of saliva collection due to the ambulatory setting could have resulted in measurement error. In addition, because time of drug intake was not recorded, acute effects of BZD use could not be assessed. Despite these limitations, our study had many strong aspects, including a large sample size with clearly distinct BZD groups primarily composed of long-term users, the inclusion of multiple cortisol measures indicative of different aspects of HPA axis activity, the investigation of various characteristics of use and the adjustment for various potential confounders.

In conclusion, we found no consistent associations between BZD use and salivary cortisol indicators within a sample primarily composed of long-term users. This finding is in line with the hypothesis that the HPA axis develops tolerance to the cortisol-suppressing effect of BZDs during chronic BZD use.

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Initiated and discontinued Benzodiazepine Use in Relation to Autonomic Nervous System Activity

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ABSTRACT

Background: As benzodiazepines (BZDs) are used for the treatment of stress, they may affect the autonomic nervous system (ANS) which is aroused in stressful situations. Studies on the short-term effects of BZDs on the ANS are inconsistent and the effects of long-term use have hardly been studied.

Materials and Methods: In 2838 participants of the Netherlands Study of Depression and Anxiety, we examined the associations between baseline characteristics of BZD use (frequency, type, dosage, duration) and ANS measures. BZD initiators (n=85), BZD discontinuers (n=145), and chronic users (n=158) were also compared to non-users (n=1726) on absolute changes of the following ANS measures over a two-year period: heart rate [HR], respiratory sinus arrhythmia [RSA, as an indicator of PNS], and pre-ejection period [PEP, as an indicator of SNS].

Results: BZDs were used–for a median duration of two years by 442 (15.6%) of NESDA participants at baseline. At follow-up, 243 (11.5%) used BZDs. In adjusted cross-sectional analyses no associations between BZD use and ANS measures were found. During follow-up, PEP increased in BZD initiators (Cohen's d=0.23; P=0.04), but decreased in chronic users (d=0.19; P=0.03) versus non-users. No association between HR (P=0.21) and RSA (P=0.99) with BZD use was found.

Conclusion: In general, long-term BZD use does not seem to negatively affect ANS activity. The only observations were slightly increased sympathetic activity in chronic BZD users and slightly decreased sympathetic activity in new BZD users. The clinical relevance of these findings needs to be established in future research.

INTRODUCTION

The autonomic nervous system (ANS) is part of the peripheral nervous system and controls functions that are engaged in physiological homeostasis. It consists of the sympathetic (SNS) and the parasympathetic nervous system (PNS). The SNS mobilizes the fight-or-flight response; it enhances energy release and increases heart rate to prepare the body for action. The PNS stimulates "rest-and-digest" activities that occur when the body is at rest, such as digestion and salivation. In research, SNS activity can be measured through the pre-ejection period (PEP) which is a widely used, valid index of sympathetic effects on cardiac contractility.[1] PNS activity is often measured through respiratory sinus arrhythmia (RSA) which is an index of heart rate variability (HRV). Heart rate (HR) reflects both the inhibitory and augmenting control of PNS and SNS on the heart.[2]

It was recently described with cross-sectional and longitudinal data of the Netherlands Study of Depression and Anxiety (NESDA) that antidepressant medication use is associated with unfavourable effects on SNS and PNS activity.[2-4] The use of tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRI) and serotonin–norepinephrine reuptake inhibitors (SNRI) was associated with decreased HRV, the use of SNRI and TCAs was associated with decreased PEP, and the use of SSRIs was associated with increased PEP.[2-4] Consequently, it raises the important question, whether BZDs could have similar effects.

Based on animal research, two theories about the effects of BZDs on the ANS were put forward. BZDs were suggested to suppress (stress-induced) sympathetic activation by enhancing the sympathoinhibitory effects of GABA on presympathetic neurons in the paraventricular nucleus (PVN) of the hypothalamus.[5,6] These neurons are critically involved in the forebrain regulation of sympathetic outflow[5] and project to the rostral ventrolateral medulla and the spinal cord to modulate the excitability of sympathetic preganglionic neurons.[7] As GABA is localized in

discrete autonomic centers of the brain, BZDs might enhance GABAergic inhibition of sympathetic outflow by other brain structures than the PVN as well (such as nucleus ambiguous,[8] caudal ventrolateral medulla,[8] rostral ventrolateral medulla, [8] medullary raphe nuclei[9]). BZDs were also hypothesized to have vagolytic effects, meaning that they enhance the direct GABAergic inhibition of cardiac vagal neurons and the GABAergic inhibition in the nucleus tractus solitarii.[10]

Both hypotheses have been investigated in short-term intervention studies in humans with the following results. In line with the hypothesis that BZDs affect SNS activity, BZDs were generally found to suppress stress-induced increases of sympathetic activity, [11-13] except for one study where BZDs seemed to heighten sympathetic outflow[10] and another one which did not detect any SNS related effects of BZDs.[14] During rest, BZDs were either reported to decrease sympathetic tone[15-17] or not to have any effect at all. [14,18-20] Corresponding to the hypothesis that BZDs have a vagolytic effect, BZDs were commonly found to attenuate heart rate variability[10,19,21-25] and to increase HR[10,19,21,24-26]. In contrast, two studies reported heightened heart rate variability[17,27] and HR[14] after BZD administration. Thus, based on these results of experimental studies, the effects of BZDs remained unclear.

Opposite to intervention studies, observational research on the effects of BZDs on the ANS is less common. While BZDs' effects on SNS activity have not been investigated yet, cross-sectional research of our own group did not find significant differences in HRV and HR between BZD users and non-users.[2] There are several possible explanations for the discrepancy of this finding with previous experimental research that reported an attenuation of HRV caused by BZDs. As dissimilar effects of lorazepam and alprazolam on the ANS have been reported,[17] the joint investigation of different types of BZDs with possibly opposing effects might have cancelled each other out, resulting in no overall effects of BZDs on the ANS in long-term users. An alternative explanation is that only frequent BZD use and/or high BZD dosages lead to alterations of

ANS activity. Consistently, several intervention studies only found ANS alternating effects at higher dosages of BZDs[22,28] and a dose-response effect of BZDs was reported.[21,27] Finally, long-term users might develop tolerance to the effects of BZDs on the ANS so that they no longer differ from non-users. As most studies were limited to one day of testing, little can be said about this hypothesis. Only one study reported that BZDs still increases HR after seven nights of use,[28] indicating that at least for this duration of use no tolerance develops.

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. The current study examined the associations between several characteristics of BZD use (frequency, type of BZD, daily dosage, duration of use) and SNS and PNS measures at baseline in 2838 subjects participating in the Netherlands Study of Depression and Anxiety (NESDA). Additionally, we compared BZD initiators, BZD discontinuers and chronic users to non-users (n=2114) over a two-year period on changes in several SNS and PNS functioning parameters in order to confirm or refute our previous cross-sectional results.[2]

MATERIALS AND METHODS

Subjects

Subjects participated in the baseline assessment of the Netherlands Study of Depression and Anxiety (NESDA), a longitudinal cohort study of 2981 respondents aged 18 to 65 years.[29] Subjects were recruited from the community, general practice and specialized mental health care institutions throughout the Netherlands. The baseline interview consisted of a blood draw, a medical examination, supine rest with blood pressure recordings, psychiatric interviews, a cognitive computer task, and saliva sampling. The study protocol was approved by the Ethical Review Board of each participating center and all subjects signed an informed consent at the baseline assessment.

For the cross-sectional analyses, we excluded subjects with lacking data on ANS measures (n=143). For prospective analyses, additionally, subjects who did not participate in the follow-up assessment (n=385) or those with lacking follow-up data on BZD or ANS measures were excluded (n=482). Consequently, our final sample consisted of 2838 subjects at baseline and 2114 subjects at follow-up. At baseline and follow-up subjects who reported daily or less regular BZD use in the month prior to the baseline interview were defined as "BZD users" (baseline: n=442, follow-up: n=243) and those reporting no use of BZDs in the month before the baseline interview were defined as "non-users" (baseline: n=2396, follow-up: n=1871). For the follow-up measurement, we divided subjects into "non-users" (subjects who did not use BZDs during the whole follow-up period, n=1726), "BZD initiators" (subjects who did not use BZDs at baseline, but initiated use during follow-up, n=85), "chronic users" (subjects who used BZDs at baseline and follow-up, n=158), and "BZD discontinuers" (subjects who used at baseline, but discontinued during follow-up, n=145) independent of dose and frequency of use in order to maximize group sizes.

BZD Use

As characteristics of BZD use might be associated with ANS function,[27] four indicators of BZD use were investigated at baseline: frequency of BZD use, type of BZD, daily BZD dose, and duration of BZD use. BZD use during the month prior to baseline interview was registered by observation of drug containers brought to the interview (approximately 70% of cases) or self-report. Daily and infrequent BZD users reported the type and dosage of BZD taken on an average day of use.[30] The daily BZD dose was computed according to the coding system of the Anatomical Therapeutic Code (ATC) and Defined Daily Dose (DDD) system.[31] The Mean Daily Dose was calculated by dividing individual daily doses (in milligrams) of BZDs by the DDD for the particular BZD. Frequency of use for infrequent users was taken into account when calculating the

average daily dose.[30] BZDs were classified as ATC-coded groups N05BA, N05CD, and N03AE01. The non-BZD hypnotics zopiclone and zolpidem (ATC code N05CF), were also included. For patients using BZDs other than diazepam, equivalent daily doses were calculated with conversion tables.[30,32,33] Dosages were summed when more than one BZD was used. The duration of BZD use was reported in months.

Physiological Measurements of the Autonomic Nervous System

Physiological recording was performed using the Vrije Universiteit Ambulatory Monitoring System (VU-AMS; Vrije Universiteit, Amsterdam, the Netherlands). The VU-AMS is a lightweight portable device that records electrocardiograms (ECG) and the impedance cardiogram (ICG) from 6 electrodes placed on the chests and backs of participants.[34,35] Recording was unobtrusive, and participants, who maintained full freedom of movement, tended to adjust very rapidly to this type of recording. Details on the VU-AMS recording can be found elsewhere.[2,36] In short, NESDA participants wore the VU-AMS device during most of the baseline assessments. The start of the various assessments was indicated by an event marker to divide the total recording into fixed periods (resting baseline, breaks, and test periods [interview 1, computer task, and interview 2]). Movement registration by a vertical accelerometer was used to excise periods in which participants were not stationary. Removal of breaks and non-stationary moments (about 15 minutes) left an average registration of 99.9 minutes (standard deviation [SD], 23.0 minutes). The ANS controls several aspects of cardiac function, and is therefore reflected by the following indices: HR (controlled by the balance between the PNS and SNS), respiratory sinus arrhythmia (RSA, an indicator for heart rate variability [HRV], solely controlled by the PNS), and pre-ejection period (PEP, as a measure of sympathetic control).[2] From the ECG and the ICG, interbeat interval time series and respiration signal were extracted as described elsewhere.[34,35,37] HR was derived from the interval between R-R waves in the ECG. RSA was obtained

by directly combining the electrocardiogram data with the respiration signal to obtain the variation in the interbeat intervals restricted to the typical respiratory frequency range (0.15-0.40 Hz), as described in detail elsewhere.[38] High RSA reflects high parasympathetic activity. From the ICG PEP was derived, as described in detail elsewhere.[39] Under conditions of unchanged preload and after load, the PEP is a pure measure of SNS control on the contractility of the heart, with high PEP signaling low SNS activity.[36] The mean HR, PEP, and RSA were computed for rest and test conditions at baseline and follow-up separately. As rest and test scores for HR and RSA were not significantly different, they were collapsed to a single 'test' condition for each ANS indicator to simplify analyses.[40] As PEP data during the computer task and the two interview conditions was also found to be very comparable, these data were combined to create one single PEP value per subject.[3]

Covariates

As respiration rate has often been identified as possible confounder of HRV,[41] we adjusted RSA analyses for respiration rate. Further important covariates in analyses of ANS have been identified in previous research in our study group.[47,48] Those relevant for analyses on BZDs were sociodemographic characteristics (age, gender, education), health indicators (body mass index (BMI), physical activity, alcohol use, smoking, presence of a heart disease, number of chronic illnesses, and medication (use of heart medication, frequent use of antidepressant medication including selective serotonin reuptake inhibitors [SSRIs, ATC code N06AB], tricyclic antidepressants [TCAs, ATC code N06AA], and selective serotonin and noradrenalin reuptake inhibitors [including monoamine oxidase inhibitors, nonselective N06AF, and antidepressants classified as N06AX].

Sociodemographic characteristics included age, gender, and education in years and were reported during the baseline interview. Health indicators were measured at baseline and follow-up. BMI was

calculated as weight in kilograms divided by the square of height in meters. Physical activity was measured using the International Physical Activity Questionnaire[42] and expressed as MET-minutes per week (the multiple of one's resting metabolic rate times minutes of physical activity per week). Smoking was categorized as non-smoker versus smoker. For regular alcohol use, a continuous variable was computed as mean number of alcoholic consumptions per day. Self reports were used to ascertain the presence of heart disease (including coronary disease, cardiac arrhythmia, angina pectoris, heart failure, and myocardial infarction). The number of other chronic conditions such as diabetes, stroke, and cancer was ascertained by self-report and summed into a count variable. The presence of insomnia was determined using the Insomnia Rating Scale (IRS).[43] Medication use was recorded at baseline and follow-up. Dichotomous variables for the use of heart medication were computed at both time points, scoring 'yes' if subjects frequently (daily or>50% of the time) used a medication with the following ATC codes: cardiac therapy, C01; antihypertensive drugs, C02; diuretic drugs, C03; peripheral vasodilator drugs, C04; vasoprotective drugs, C05; β-blocking agents, C07; and calcium channel blockers, C08. In addition, frequent use (daily or >50% of the time) of selective serotonin reuptake inhibitors (SSRIs, ATC code N06AB), tricyclic antidepressants (TCAs, ATC code N06AA), and serotonin and noradrenalin reuptake inhibitors (SNRI; including monoamine oxidase inhibitors, nonselective N06AF, and antidepressants classified as N06AX) was defined at either of the time points.

Statistical Analyses

Characteristics of study groups at baseline and follow-up were expressed by frequencies, means or medians, and compared using $\chi 2$ statistics (categorical variables), analyses of variance (continuous variables, normal distribution), and Kruskal-Wallis tests (continuous variables, non-Gaussian distribution).

Analyses of variance (ANOVAs) were conducted to compare non-users, infrequent users and daily users as well as the different types of BZDs at baseline on RSA, PEP, and HR. Linear regression analyses were used to assess associations between baseline characteristics of BZD use (i.e., duration of BZD use and BZD dose) and ANS indicators as continuous dependent variables. All analyses were conducted unadjusted as well as after adjustment for sociodemographic characteristics in model 1 and additional adjustment for health indicators and used medication in model 2. We did not adjust for diagnosis and severity of depression and/ or anxiety, as these diagnoses were not associated with ANS variables in previous research of our study group. Analyses of variance (ANOVAs) were conducted to compare BZD initiators, BZD discontinuers and chronic users to non users on absolute changes of RSA, PEP, and HR between baseline and follow-up in order to confirm or refute cross-sectional results by prospective data. In order to investigate changes of ANS indices between the baseline and the follow-up measurement, a change score was calculated by subtracting the baseline RSA, PEP and HR value from the follow-up value. A higher score indicated higher values at follow-up, as compared to baseline. These analyses were adjusted for above mentioned covariates in model 1 as well as for health indicators and medication use as measured at follow-up in model 2. We additionally performed sensitivity analyses after separate exclusion of the different antidepressant groups (TCA, SSRI, and SNRI users at baseline and / or follow-up), in order to make sure that our findings would not be confounded by the strong effects of antidepressant use on the ANS. Cohen's *d* (i.e., the difference in group means, divided by their pooled standard deviation) was calculated as a measure of effect size. Post-hoc tests on individual group differences were performed using the Fisher's Least Significant Difference test. Statistical significance was inferred at $P < 0.05$. All statistical analyses were conducted using SPSS version 16.0 for Windows.

RESULTS

Characteristics of the three user groups as defined at baseline are presented in Table 1. Daily and infrequent users were older than non-users (P<0.001) and had a lower education level (P<0.001). They had a higher BMI (P<0.001), more often suffered from heart disease (P<0.001) and more often had comorbid anxiety and depression (P<0.001). They also used more antidepressants (P<0.001). Daily BZD users used a higher daily BZD dosage than infrequent users (P<0.001).

Baseline Associations between BZD Use and ANS Measures

Table 2 presents group differences between daily users, infrequent users, and non-users on the PNS measure RSA, the SNS measure PEP, and HR. In the fully adjusted models, daily and infrequent users did not differ from non-users on HR (P=0.27), RSA (P=0.96), and PEP (P=0.08).

Table 3 shows associations between the ANS variables and the duration as well as the daily dosage of BZD use. In the fully adjusted models, neither duration nor dosage of BZD use was associated with any of the SNS and PNS measures. Further, we compared oxazepam, diazepam, alprazolam, temazepam, lorazepam and zopiclone users on the different ANS measures. Neither in unadjusted nor in adjusted analyses groups differed on HR, HRV and PEP (data not shown).

TABLE 1. Characteristics of the Study Groups (n=2838)

	Non-Users n=2396	Infrequent Users n=266	Daily Users n=176	*P*
Sociodemographic characteristics				
Gender, % female	66.4	70.7	64.8	0.32
Age, years	40.9 (40.4 – 41.4)	45.0 (43.4 – 46.5)	48.3 (46.4 – 46.5)	<0.001
Education level, years	12.0 (10.0 – 15.0)	11.0 (9.0 – 15.0)	10.0 (9.0 – 15.0)	<0.001
Lifestyle factors				
Body Mass Index, kg/m^2	25.4 (25.2 – 25.6)	26.2 (25.7 – 26.8)	26.7 (26.0 – 27.4)	<0.001
Physical Actvity, 1000 MET-min/week	3.1 (1.4 – 5.0)	2.8 (1.4 – 4.6)	2.6 (0.7 – 4.8)	0.01
Current smoker, %	28.9	26.7	21.6	0.10
Alcohol use, # drinks/day	0.4 (0.02 – 1.2)	0.3 (0.02 – 1.2)	0.02 (0.0 – 0.8)	<0.001
Physical and psychological health				
Heart disease, %	5.1	7.1	12.5	<0.001
Respiration rate, breaths/min	17.1 (17.0 – 17.1)	16.9 (16.8 – 17.1)	17.0 (16.8 – 17.2)	0.07
Number of chronic illnesses	1.0 (0.0 – 1.0)	1.0 (0.0 – 2.0)	1.0 (0.0 – 2.0)	<0.001
One year diagnosis, %				<0.001
Anxiety disorder only	14.7	20.3	15.9	
Depressive disorder only	15.2	18.0	16.5	
Comorbid disorder	23.3	44.4	55.1	
BAI Questionnaire	8.0 (3.0 – 16.0)	19.0 (9.0 – 25.0)	22.0 (11.0 – 31.0)	<0.001
IDS-SR Mood/Cognition Scale	6.0 (2.0 – 11.0)	10.5 (5.0 – 15.0)	13.0 (7.6 – 19.0)	<0.001
Medication Use				
Use of heart medication, %	3.3	5.6	9.7	<0.001
Frequent antidepressant use, %				<0.001
TCA	2.0	4.5	8.5	
SSRI	13.6	30.5	40.9	
SNRI	4.0	9.4	16.5	
Characteristics of BZD Use				
Duration of Use, months	NA	24.0 (5.0 – 84.0)	24.0 (5.0 – 96.0)	0.84
Dosage of BZD, mg	NA	1.0 (0.3 – 2.0)	6.3 (5.0 – 13.1)	<0.001
Long half-life, %	NA	17.3	19.9	0.49

MDD indicates Major Depressive Disorder; SSRI indicates Selective Serotonin Reuptake Inhibitor; TCA indicates Tricyclic Antidepressant; NA indicates not applicable. Means (95% confidence intervals) are given for continuous, normally distributed variables. Medians (interquartile ranges) are given for continuous, non-normally distributed variables (education, physical activity, alcohol use, number of chronic illnesses, BAI, IDS-SR, duration of BZD use, and daily dosage of BZD use). Percentages are given for categorical variables. *P* is derived by analysis of variance (ANOVA) for quantitative, normally distributed variables, Kruskal Wallis test for continuous, non-normally distributed variables, or χ^2 statistics for categorical variables.

TABLE 2. Association Between ANS Measures and Frequency of BZD Use (n=2838)

	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	*P*
Characteristic	**Non-users (n=2396)**	**Infrequent Users (n=266)**	**Daily Users (n=176)**	
HR, beats/min				
Unadjusted	72.0 (71.6 – 72.4)	71.2 (70.1 – 72.4)	72.7 (71.3 – 74.1)	0.35
Model 1	71.9 (71.6 – 72.3)	71.4 (70.3 – 72.5)	73.3 (71.9 – 74.7)	0.07
Model 2	72.0 (71.6 – 72.4)	71.2 (70.1 – 72.4)	72.8 (71.4 – 74.3)	0.27
RSA, ms				
Unadjusted	45.8 (44.8 – 46.9)	39.7 (36.6 – 42.8)*	33.5 (29.7 – 37.3)*	<0.001
Model 1	45.0 (44.2 – 45.9)	42.4 (39.9 – 45.0)	40.5 (37.3 – 43.7)*	0.007
Model 2	44.5 (43.7 – 45.4)	44.3 (41.7 – 46.8)	44.6 (41.4 – 47.8)	0.96
PEP, ms				
Unadjusted	119.3 (118.6 – 120.0)	121.4 (119.2 – 123.6)	122.8 (120.1 – 125.5)*	0.02
Model 1	119.3 (118.5 – 120.0)	121.6 (119.4 – 123.8)*	123.2 (120.5 – 126.0)*	0.007
Model 2	119.4 (118.7 – 120.1)	120.9 (118.8 – 123.1)	122.0 (119.2 – 124.7)	0.08

HR indicates heart rate; RSA indicates respiratory sinus arrhythmia; PEP indicates pre-ejection period; BZD indicates benzodiazepine; CI indicates confidence interval. Model 1 was adjusted for age, gender, and education. Model 2 was additionally adjusted for physical activity, BMI, smoking, alcohol/day, number of chronic diseases, presence of heart disease, TCA, SSRI, SNRI, heart medication. The analyses of RSA were additionally adjusted for respiration rate. P-value was calculated by analysis of variance (ANOVA, P for linear trend). Significance was inferred at $P<0.05$. * indicates that the group differs significantly from the non-user group (post-hoc test, $P<0.05$).

TABLE 3. Associations Between BZD Dose and Duration of BZD Use and Various ANS Indicators in 442 BZD Users

ANS measures	Duration of Use			Daily BZD Dose		
	N	β	*P*	N	β	*P*
HR, beats/min						
Unadjusted	439	-0.075	0.12	436	0.025	0.60
Model 1	439	-0.062	0.22	436	0.046	0.34
Model 2	439	-0.077	0.14	436	0.047	0.35
RSA, ms						
Unadjusted	439	-0.119	0.01	436	-0.141	0.003
Model 1	439	0.028	0.54	436	-0.086	0.04
Model 2	439	0.053	0.22	436	-0.026	0.53
PEP, ms						
Unadjusted	439	-0.054	0.26	436	0.044	0.36
Model 1	439	-0.053	0.30	436	0.041	0.41
Model 2	439	-0.051	0.32	436	0.012	0.80

HR indicates heart rate; RSA indicates respiratory sinus arrhythmia; PEP indicates pre-ejection period; BZD indicates benzodiazepine;. Model 1 was adjusted for age, gender, and education. Model 2 was additionally adjusted for physical activity, BMI, smoking, alcohol/day, number of chronic diseases, presence of heart disease, TCA, SSRI, SNRI, heart medication. The analyses of RSA were additionally adjusted for respiration rate. *P* was calculated by linear regression analysis. Significance was inferred at P<0.05.

Prospective Associations between BZD Use and ANS Measures

Chronic users were older (*P*<0.001) and had more chronic diseases (*P*<0.001) than non-users, BZD initiators and BZD discontinuers. Chronic users had more severe anxiety than all other groups (*P*<0.001) and more severe depression than non-users and initiated users, but not than discontinued users. Further they had a lower education (*P*<0.001) than non- users and BZD discontinuers. All BZD user groups more often used antidepressants than non-users (*P*<0.001). At follow-up, the average HR across the whole sample was 72.7 beats/minute, the mean RSA 41.7 milliseconds and the mean PEP 119.2 milliseconds. Paired sampled t-tests showed a significant mean increase in HR (*P*<0.001) and a significant decrease in RSA (*P*<0.001), but no significant changes in

PEP (P = 0.88) over time within participants. The Spearman's correlation coefficients between baseline and follow-up measurements were 0.72 for HR, 0.81 for RSA, and 0.59 for PEP (all Ps<0.001). The mean HR was 72.6 for non-users, 73.8 for BZD initiators, 71.7 for BZD discontinuers and 73.5 for chronic users. The mean RSA was 41.7 for non-users, 41.7 for BZD initiators, 42.3 for BZD discontinuers and 41.3 for chronic users. Mean PEP was 119.1 for non-users, 121.8 for BZD initiators, 120.6 for BZD discontinuers and 117.4 for chronic users.

In fully adjusted analyses, BZD user groups did not differ on HR (P=0.21) and RSA (P=0.99). However, groups showed significant differences on PEP, even after adjustment for all covariates (P=0.009). BZD initiators displayed a higher increase of PEP between baseline and follow-up than non-users (Cohen's d=0.23; P=0.04). As higher PEP represents lower SNS activity, this indicates that BZD initiators have a higher decrease in SNS activity than non-users. Chronic users displayed a higher decrease in PEP than non-users (d=0.19: P=0.03), indicating that chronic users had higher increase in SNS activity than non-users. When TCA users (n=74) and SNRI users (n=168) were excluded in separate sensitivity analyses, these results did not change. When the SSRI users were excluded (n=441), group differences on PEP were not significant anymore (P=0.13) while the effect sizes of the difference between initiated users and non-users decreased (d=0.18) and the effect size of chronic users vs. non-users increased (d=0.20).

Figure 1 shows the prospective group differences of BZD initiators, BZD discontinuers, and chronic users compared to non-users on HR, RSA, and PEP after adjustment for all covariates at baseline and follow-up. Over the follow-up period, BZD initiators displayed a significantly higher increase in PEP while chronic users showed a significantly higher decrease in PEP versus non-users in post-hoc analyses.

TABLE 4. Prospective Associations Between Transitions in BZD Use and Changes in ANS Measures

	Non-Use (n=1726)	**Initiated use (n=85)**	**Discontinued use (n=145)**	**Continued use (n=158)**	
	Δ (95% CI)	Δ (95% CI)	Δ (95% CI)	Δ (95% CI)	*P*
HR, beats/min					
Unadjusted	0.5 (0.1 – 0.8)	1.1 (-0.5 – 2.7)	1.2 (-0.0 – 2.4)	2.6 (1.5 – 3.8)*	**0.005**
Model 1	0.5 (0.2 – 0.9)	0.8 (-0.8 –2.4)	1.0 (-0.2 –2.3)	2.4 (1.2 –3.6)*	**0.04**
Model 2	0.6 (0.3 – 1.0)	0.3 (-1.2 –1.9)	1.0 (-0.2 – 2.2)	1.9 (0.7 – 3.1)	0.21
RSA, ms					
Unadjusted	-2.1 (-2.8 – -1.3)	-4.0 (-7.3 – -0.6)	-1.4 (-3.9 – 1.2)	-2.3 (-4.7 – 0.1)	0.67
Model 1	-1.9 (-2.6 – -1.2)	-3.9 (-7.1 – -0.6)	-2.6 (-5.1 – - 0.0)	-3.2 (-5.7 – - 0.8)	0.52
Model 2	-2.1 (-2.8 – -1.4)	-2.7 (-5.9 – -0.6)	-2.2 (-4.7 – -0.3)	-2.3 (-4.7 – 0.2)	0.99
PEP, ms					
Unadjusted	0.7 (-0.1 – 1.4)	2.0 (-1.5 – 5.5)	-2.9 (-5.5 – -0.2)*	-5.0 (-7.5 – -2.4)*	**<0.001**
Model 1	0.4 (-0.4 – 1.1)	2.8 (-0.6 – 6.3)	-1.3 (-4.0 – 1.4)	-3.6 (-6.2 – -1.0)*	**0.008**
Model 2	0.3 (-0.5 – 1.0)	3.8 (0.5 – 7.1)*	-1.6 (-4.2 –1.0)	-2.7 (-5.2 – -0.2)*	**0.009**

HR indicates heart rate; RSA indicates respiratory sinus arrhythmia; PEP indicates pre-ejection period; BZD indicates benzodiazepine.
Model 1 was adjusted for baseline age, gender, education, physical activity, BMI, smoking, alcohol/day, number of chronic diseases, presence of heart disease, TCA, SSRI, SNRI, and heart medication. The analyses of RSA were additionally adjusted for respiration rate. Model 2 was additionally adjusted for physical activity, BMI, smoking, alcohol/day, number of chronic diseases, presence of heart disease, TCA, SSRI, SNRI, and heart medication at follow-up.
P was calculated by analysis of variance (ANOVA). Significance was inferred at P<0.05. * indicates that the group differs significantly from the non-user group (post-hoc test, *P* <0.05)

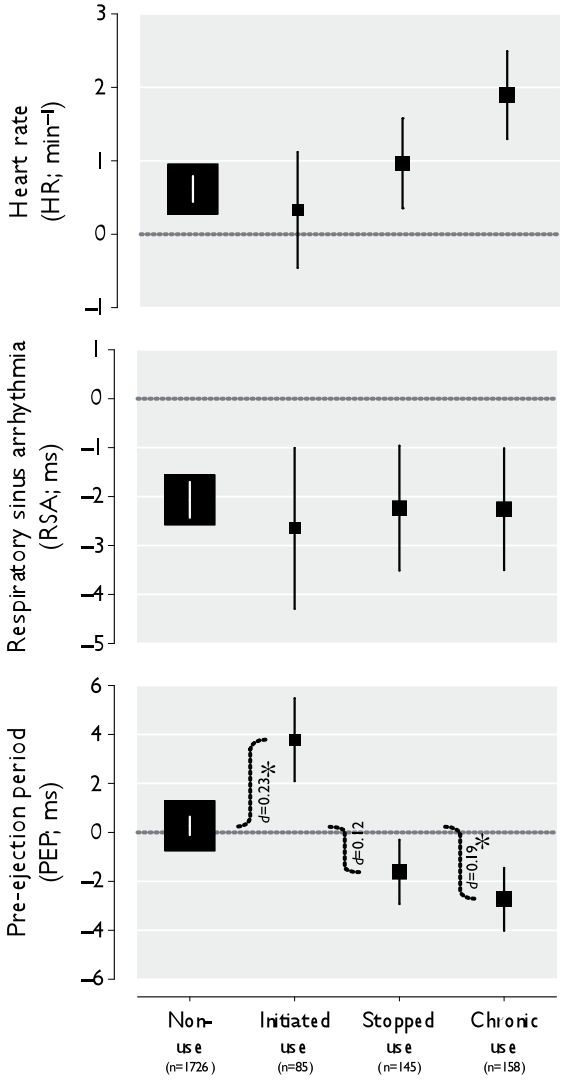

FIGURE 1. Prospective Associations Between Transitions in BZD Use and Changes in ANS Measures

DISCUSSION

In this study, possible associations between BZD use and various measures of the autonomic nervous system (ANS) were studied over a two-year follow-up period. In cross-sectional analyses, BZD use in general and characteristics of use (type, dose, frequency, and duration of use) were not associated with any of the ANS indicators. In contrast to previous research,[17] alprazolam did not have different effects on the ANS than other BZDs. In prospective analyses, BZD initiators displayed slightly lower SNS activity while BZD chronic users displayed slightly higher SNS activity. No associations between BZD use and PNS function were found. As effect sizes of the found group differences were relatively small, the clinical relevance of these findings is questionable. As the increase in PEP in BZD initiators opposed that of the decrease found in chronic users, the significant results might be chance findings considering the number of tests conducted in this study. The absence of strong effects on the ANS by BZDs is in contrast with our earlier observations for antidepressants, for which we found unfavourable effects on SNS and PNS activity.

In our cross-sectional analyses, we did not detect associations between SNS functioning and BZD use. In prospective analyses, BZD initiators showed a decrease in SNS activity versus non-users, indicating that BZD use may slightly suppress SNS functioning. This finding is in line with a number of studies that found a suppression of SNS activity (as measured by spectral power analysis,[11,12,15] norepinephrine,[16] and muscle sympathetic nerve activity[15]) after BZD administration,[11-13,15-17] but in contrast with those that reported heightened SNS activity[10] or HR[10,19,21,24-26] upon BZD intake. As in NESDA most subjects initiated BZD use longer than two months ago, the slight, sustained reduction in SNS activity in BZD initiators suggests that tolerance to BZDs SNS decreasing effect has not developed, at least not within several months. However, a suppression of SNS activity should also be reflected in a decrease of HR which was not present in our study. This complicates the interpretation of our results.

Further, chronic users displayed a higher increase in SNS activity between baseline and follow-up than non-users and also had higher absolute SNS activity values than the non-user group. This might be explained by the development of tolerance to the SNS decreasing effects of BZDs in chronic use. However, as the majority of chronic BZD users were already using for a long duration of time when the baseline measurement took place, tolerance development would have been expected much earlier. Therefore, these explanations are unlikely. As the cross-sectional and longitudinal results of the PEP analyses were quite inconsistent and the decrease of PEP was not accompanied by a decrease in HR, the group differences are difficult to explain and further research is needed to clarify the clinical relevance of our findings. When the sizeable group of SSRI users was excluded in a sensitivity analysis, the effect size of the difference between BZD initiators and non-users decreased by 20%, but the effect size of the difference between chronic users and non-users increased by 5%. As SSRIs were found to decrease sympathetic activity in previous research,[3] a small part of the SNS decrease found in BZD initiators may have been driven by concomitant SSRI use.

The absence of group differences on PNS activity in our cross-sectional and prospective analyses contrasts with the BZD induced lowered HRV and elevated HR values found in experimental research.[10,19,21-26] There are several possible explanations for these discrepancies. Tolerance may have developed to the effects of BZDs on the ANS, so that BZDs do not affect PNS activity in chronic BZD users as they do in short-term users.[21,22,24] This hypothesis is not supported by previous research which did not report tolerance development to BZDs effects on HR after a duration of seven days.[28] However, other research indicated that BZD induced HR increases went back to baseline after approximately 30 minutes, suggesting that this effect might be transient in nature.[10,24] Alternatively, NESDA mainly consists of participants using relatively low dosages of BZDs (median daily dosage of 6.0 mg diazepam equivalents) and previous research mainly found alternated ANS activity

with higher dosages.[22,28] However, some studies also found ANS effects with comparably low dosages of BZDs.[27] Further, low dosage BZD use presents the daily treatment practice so that the NESDA BZD user sample is representative of the average BZD user.

A dysregulation of the ANS can manifest itself as a reduction in HRV, an increase in HR, and heightened SNS activity. These alterations of the ANS are established risk factors for cardiovascular disease (CVD) such as coronary heart disease and acute myocardial infarction.[44-46] As BZDs are often used for long periods of time, adverse effects on the ANS may put users at a higher risk to develop CVD. This is especially true when BZDs are used in the treatment of anxiety caused by chest pain and myocardial ischemia.[47] Therefore it is reassuring that BZDs - unlike antidepressants - do not seem to affect PNS functioning in long-term users.[2] Furthermore, BZDs may even modestly decrease SNS activity. In contrast, chronic BZD use was associated with a slight increase in SNS activity and might thus be harmful, especially for patients with established CVD.

Our study has some limitations. We were not able to investigate the effects of high dosages of BZDs as the median daily dosage in NESDA was relatively low. As we had to rely on subjects' self-report on BZD intake, we cannot be sure whether subjects were actually using the medications as prescribed and as they themselves indicated. In addition, as the time of the most recent drug intake was not recorded we could not know if and how long ago the most recent BZD intake had taken place. This might have reduced the reported effects. Despite these limitations, our study had also several strengths. We were the first study to investigate the potential effects of type of BZD, dosage, duration and frequency of BZD use on the ANS. Further, we were able to investigate the effects of transitions of BZD use on the ANS over a two-year follow-up while correcting for the most important confounders. Finally, we included several aspects of ANS activity and investigated a user group representative of the average BZD

user. Therefore, our results may reflect the actual effects of BZDs on the ANS in the average BZD user.

In conclusion, long-term BZD use does not appear to have strong adverse effects on SNS or PNS activity as earlier described for some antidepressants.[2,3] Longitudinal analyses seem to suggest that relatively recent BZD initiation might slightly suppress SNS activity while chronic BZD use might slightly increase SNS activity. Whether this finding has clinical relevance needs to be established.

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High-Dose Benzodiazepines prolong Reaction Times in chronic Users

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ABSTRACT

Aim: Short-term administration of benzodiazepines (BZD) was found to prolong reaction time (RT) in experimental studies. However, studies on long-term BZD use did not always adjust for important confounders and showed inconsistent results. We aimed to identify a possible relationship between long-term BZD use and RT in BZD users of this large cross-sectional, observational study.

Methods: The RT of non-users (n=2404) were compared to low- (n=288), intermediate- (n=74), and high dose BZD users (n=57) of the Netherlands Study of Depression and Anxiety. RTs were obtained from the Implicit Association Test. Analyses were adjusted for sociodemographic characteristics, health indicators, severity of psychopathology, and antidepressant use.

Results: Of the NESDA participants, 419 subjects (14.8%) used BZDs. A higher dose of BZDs was associated with prolonged RTs (P=0.01). When comparing the different dose groups, the high dose group, but not the low and medium dose groups, had significantly longer RTs than the non-users.

Conclusions: Tolerance for the RT prolonging effect of relatively high doses of BZDs does not seem to develop. As prolonged RTs can have severe consequences in daily life, BZDs should be prescribed conservatively at the lowest possible dose.

INTRODUCTION

As the prevalence of long-term benzodiazepine (BZD) use is high,[1] the accompanying side effects are an important research topic. Reaction time (RT) impairments are common in short-term BZD use[2] and even seem to remain in chronic use[3]. Choice RT tasks (CRTTs), where different responses are to be sorted to one of several stimuli as fast as possible, are an objective means to detect RT impairments due to the use of BZDs.[4,5]

Previous research on the association between BZD use and RT (as measured by CRTTs) mainly consisted of small randomized trials, which compared the effects of short term BZD administration to placebo. In most of these studies, BZD administration prolonged RTs for a duration up to six weeks.[6-11] Only two small studies did not find prolonged RTs after BZD intake.[12,13]

The few studies on the association between longer-term BZD use and RTs reported inconsistent results. One cross-sectional, observational study found longer RTs in chronic users than in non-users, but did not investigate if this effect was confounded by psychopathology.[14] Two studies did not report differential RTs among BZD users and non-users.[15,16] When an extra dose of 20mg oxazepam was administered, RT increased in 18 BZD-naive participants, but not in 18 long-term BZD users, suggesting that tolerance to BZDs effects on RT may have developed.[16]

The inconsistent results regarding chronic BZD use may be caused by the lack of correction for established confounders such as psychopathology,[14,16] physical health,[14,15] and antidepressant use[14]. Further, differences in sample selection (healthy subjects versus subjects with psychopathology) may have led to the discrepancies. In order to determine whether the effects of BZD on RT remain in long term BZD use, we analyzed the association between BZD use and RT as measured by the Implicit Association Test (IAT) in 2823 participants of the NESDA study and corrected for important confounders.

METHODS

Subjects

Subjects participated in the baseline assessment of the Netherlands Study of Depression and Anxiety (NESDA).[17] NESDA recruited 2981 individuals aged 18-65 with and without symptoms of depressive and/or anxiety disorders from different health care settings.[17] Lifetime diagnoses were defined as current or past diagnosis of a depressive or anxiety disorder as assessed by the DSM-IV Composite International Diagnostic Interview (CIDI, WHO version 2.1). The baseline assessment included written questionnaires, an oral interview and the IAT computer task.[17] The study protocol was approved by the ethical review board of each participating center, and all subjects signed an informed consent.

Subjects without IAT data (n=129), those with unusual long RTs (>10seconds, n=5) or missing values on BZD dose (n=6) or BZD users without a lifetime diagnosis of depression or anxiety (n=18) were excluded. After exclusion, 2823 subjects (94.7%) remained for our analyses. Of this group, 419 (14.8%) subjects used BZDs. Subjects who conducted the IAT were not statistically different from those who did not in terms of BZD use in general, used dose of BZDs, gender, education, and severity of depression and anxiety. However, subjects without IAT data were significantly older (P=0.002).

MEASURES

BZD Use

BZD use was registered by observation of drug containers brought to the interview (73.4%) or self-reports. BZDs were classified as ATC-coded groups N05BA, N05CD, and N03AE01 and the non BZD hypnotics zopiclone and zolpidem (ATC code N05CF).[18] The daily BZD dose was computed according to the coding system of the Anatomical Therapeutic Code (ATC) and defined daily dose (DDD) system.[19] The mean daily

dose was calculated by dividing individual daily doses of BZDs by the corresponding DDD. For subjects using BZDs other than diazepam, an equivalent dose was calculated.[20] The DDD was categorized into three groups: 1) daily dose below 0.5 DDD (low dose), 2) daily dose between 0.5 and 1 DDD (intermediate dose), and 3) daily dose > 1 DDD (high dose). BZD users completed the BZD Dependence Self-Report Questionnaire (Bendep-SRQ) as a measure of dependence severity.[21,22]

Implicit Association Test

The Implicit Association Test (IAT) is a computerized RT task which measures the strength of implicit associations.[23] However, we did not use the IAT to measure implicit associations, but solely to measure RTs in a CRTT. To avoid the interference of implicit associations, we only used four single concept blocks of the IAT (Supplement 1). Stimulus words from two categories (e.g., anxious or calm) appeared in mixed order in the middle of a computer screen. Participants were instructed to sort the stimulus words as fast as possible to one of the two categories by pressing either a left response key ('Q') or a right response key ('P') on the keyboard. The RT of a trial was defined as the time from the appearance of a stimulus word until the correct response key was pressed.[24] In the NESDA study, two IATs were included, a 'depression IAT' and an 'anxiety IAT'.[25] In the anxiety IAT, subjects needed to sort words (such as nervous or relaxed) into the categories 'anxious' and 'calm'. In the depression IAT, subjects needed to sort words (such as meaningless or valuable) in the categories 'depressed' and 'elated'.[25]

Covariates

As sociodemographic characteristics (sex, age, education), health indicators (alcohol use, chronic disease), psychopathology (severity of anxiety and depression), and antidepressant use were found to be associated with RTs and BZD use,[5,26,27] these variables were included as

covariates in our analyses. Additionally, the total number of mistakes made during the analyzed IAT blocks was taken into account.

Sociodemographic characteristics were reported during the baseline interview. For regular alcohol use, the mean number of alcoholic consumptions per day was computed. The number of chronic somatic conditions was ascertained by self-report and dichotomized into presence of one or more chronic somatic conditions (yes/no). The severity of generalized anxiety and panic symptoms was assessed with the Beck Anxiety Inventory (BAI).[28] The severity of depressive symptoms was measured by the cognitive/mood scale of the Inventory of Depressive Symptomatology Self Report (IDS-SR).[29] Antidepressant use was subdivided into selective serotonin reuptake inhibitors (SSRIs, ATC code N06AB), tricyclic antidepressants (TCAs, N06AA), and selective serotonin and noradrenalin reuptake inhibitors (N06AF, N06AX). The mean daily dose of antidepressant use was calculated and categorized into three groups.

Statistical Analyses

Sample characteristics were expressed by percentages for categorical variables, by means for continuous, normally-distributed variables and by medians for continuous, non-normally distributed variables. RTs were transformed into their negative inverse (-1/RT) due to their positively skewed distributions, yielding a normal distribution.[30] The negative inverse of the blocks 2, 5, 8, and 11 of the IAT were averaged to diminish the influence of a preference for responses with the dominant hand. To correct for the learning effect, *z*-scores were calculated for each block (using -1/RTs transformed values). These were averaged into one single score per subject. A higher *z*-score indicates a longer RT, thus a prolonged response. Group differences between non-users, low dose users, intermediate dose users and high dose users on RTs were analyzed by analysis of covariance. Post-hoc tests on individual group differences were performed using the Fisher Least Significant Difference test. The

analysis was corrected for sociodemographic characteristics, duration of BZD use, health indicators, severity of psychopathology, duration of BZD use, daily dose of antidepressant use, and number of mistakes made in the IAT. Analysis for trend was conducted. Linear regression analyses were used to examine associations between characteristics of BZD use as separate independent variables and RT in BZD users only after adjustment for all covariates.

RESULTS

Characteristics of the Study Population

Table 1 shows the sample characteristics of the 2823 included participants, of which 419 subjects (14.8%) had used BZDs in the past month. Subjects with a low daily dose were more often female (72.2%) than the non users, intermediate-, and high dose groups. The average age was lower in the non-users (40.9 years) and increased with each BZD dose. Non-users had lower BAI (median=8.0) and IDS (median=6.0) scores than all BZD user groups. The mean RT for the group as a whole was 0.96 seconds (s). It was shortest in the non users group and increased with each dose group. All groups had a median number of three mistakes in the four included blocks.

Associations Between BZD use and RT

Table 2 shows group differences between non-users and low-, intermediate- and high dose users on RT. In unadjusted (P for linear trend <0.001) and adjusted analyses (P=0.01) groups differed significantly on RT. Gender (F=16.69), age (F=521.32), education (F=108.03), number of alcoholic drinks consumed (F=5.27), severity of depression (F=15.88) and anxiety (F=14.38) had much higher F values than dose of BZD use (F=2.35). In contrast, daily dose of TCA (F=0.008), SSRI (F=0.05), and other antidepressants (F=0.13) had much lower F values than daily dose of BZDs. In post-hoc tests, high dose BZD users had significantly

longer RTs than non-users, while the other dose groups did not differ significantly from non-users. Figure 1 shows the adjusted mean RTs per user group as obtained by multivariate regression analysis. Higher BZD doses were significantly associated with longer RTs (*P*=0.01).

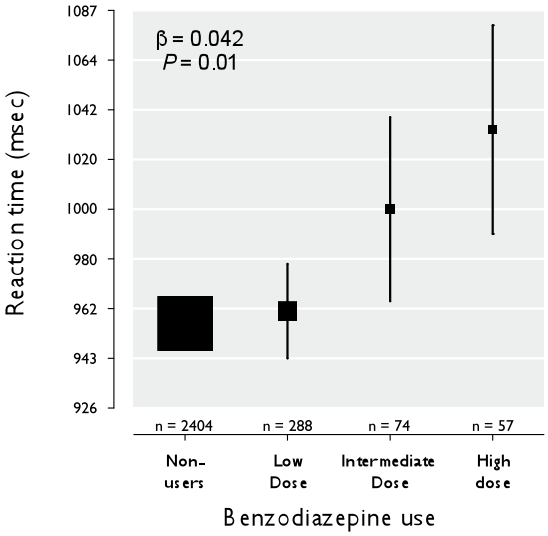

FIGURE 1. The adjusted mean values of reaction time (in milliseconds) obtained from the Implicit Association Test (IAT) according to the dose of BZDs used in 2823 NESDA participants. The size of each square is proportional to the number of participants. Vertical lines indicate standard errors. Analyses were adjusted for sociodemographic variables (i.e., gender, age, education), health indicators (i.e., daily alcohol use, presence of somatic disease), psychopathology (i.e., IDS-mc, BAI), and antidepressant use (in 4 categories). Low dose was defined as <5 mg diazepam equivalents/day, intermediate dose as 5-10 mg/day, and high dose as > 10 mg/day. Beta-coefficients and *P*-values by multivariate linear regression analysis.

TABLE 1. Characteristics of the Study Group according to BZD Dose Category (n=2823)

	No BZD	BZD Low Dose <½ DDD	BZD Intermediate Dose ½ - 1 DDD	BZD High Dose > 1 DDD	
	n=2404	n=288	n=74	n=57	*P*
Sociodemographics					
Female gender, n (%)	1584 (65.9)	208 (72.2)	42 (56.8)	32 (56.1)	0.02
Age, years, mean (sd)	40.9 (13.3)	45.1 (11.9)	46.6 (11.1)	48.8 (9.1)	<0.001
Education level, years, median (IQR)	12.0 (10.0 – 15.0)	11.0 (10.0 – 15.0)	10.0 (9.0 – 15.0)	10.0 (9.0 – 11.5)	<0.001
Health indicators					
Non/mild drinker, n (%)	1470 (61.1)	189 (65.6)	55 (74.3)	41 (71.9)	0.09
Moderate drinker, n (%)	534 (22.2)	52 (18.1)	11 (14.9)	7 (12.3)	
Heavy drinker, n (%)	400 (16.6)	47 (16.3)	8 (10.8)	9 (15.8)	
Somatic disease, n (%)	1259 (52.4)	186 (64.6)	50 (67.6)	44 (77.2)	<0.001
Psychopathology					
BAI, median (IQR)	8.0 (3.0 – 16.0)	19.0 (9.0 – 27.0)	24.0 (13.8 – 30.5)	21.0 (12.1 – 31.5)	<0.001
IDS-SR mc, median (IQR)	6.0 (2.0 – 9.0)	9.0 (5.0 – 12.0)	10.0 (8.0 – 13.0)	11.0 (8.5 – 14.0)	<0.001
Antidepressant use					
No AD use, n (%)	1920 (79.9)	159 (55.2)	24 (32.4)	16 (28.1)	<0.001
AD low dose, n (%)	58 (2.4)	18 (6.3)	3 (4.1)	2 (3.5)	
AD intermediate dose,n (%)	251 (10.4)	50 (17.4)	22 (29.7)	15 (26.3)	
AD high dose n (%)	175 (7.3)	61 (21.2)	25 (33.8)	24 (42.1)	
Reaction time					
RT (s), mean (95% CI)	0.94 (0.93 – 0.96)	1.02 (0.98 – 1.06)	1.11 (1.05 – 1.18)	1.19 (1.12 – 1.28)	<0.001
BZD use					
Duration, months, median (IQR)	N/A	24.0 (5.0 – 93.0)	12.0 (3.0 – 60.0)[a]	36.0 (8.5 – 96.0)	0.04
Half-life of BZD, n (%)					0.24
Short acting	N/A	238 (82.6)	60 (81.1)	40 (70.2)	0.093
Long acting	N/A	50 (17.4)	14 (18.9)	17 (29.8)	
BENDEP-SRQ, median (IQR)					
Problematic use	N/A	9.1 (8.8 – 9.5)	10.5 (9.7 – 11.2)	11.3 (10.4 – 12.2)	<0.001
Preoccupation	N/A	12.3 (11.8 –12.8)	14.4 (13.3 – 15.4)	15.6 (14.5 – 16.6)	<0.001
Lack of Compliance	N/A	6.0 (5.0 – 9.0)	7.5 (5.3 – 10.0)	10.0 (7.8 – 11.0)	<0.001

BZD, benzodiazepines; BENDEP-SRQ, Benzodiazepine Dependence Self Report Questionnaire; BAI, Beck anxiety Index; IDS-SR mc, Mood cognition scale of the Inventory of Depressive Symptomatology; AD, antidepressant; RT, Reaction time; s, seconds; DDD, defined daily dose; sd, standard deviation; IQR, interquartile range. RT is the mean RT of 80 trials. 1 DDD is defined as 10 mg diazepam equivalents per day. P is derived by analysis of variance (ANOVA) for quantitative, normally distributed variables, Kruskal-Wallis test for continuous, non-normally distributed variables and $\chi 2$ statistics for categorical variables. Significance is inferred at $p < 0.05$.

TABLE 2. Differences of Non-users, Low Dose Users, Intermediate Dose Users, and High Dose Users on RT as Analyzed in 2823 NESDA Participants

	No Use	Low Dose	Intermediate Dose	High Dose	
	n=2404	n=288	n=74	n=57	
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	*P*
Unadjusted	0.95 (0.94–0.96)	1.03 (1.00-1.06)	1.11 (1.04-1.18)	1.19 (1.11-1.29)	<0.001
Adjusted	0.96 (0.95-0.97)	0.97 (0.95-0.99)	0.99 (0.95-1.05)	1.03 (0.97-1.10)	0.01

RT, reaction time; BZD, benzodiazepines; DDD, defined daily dose; CI, confidence interval. 1 DDD was defined as 10 mg diazepam equivalents per day. The adjusted analysis was adjusted for sociodemographic characteristics (gender, age, education level), health indicators (alcohol intake and presence of a somatic disease), severity of psychopathology (BAI and IDS-mc), daily dose of used antidepressants, and number of mistakes made in the IAT. Low dose was defined as <5 mg diazepam equivalents/day, intermediate dose as 5-10 mg/day, and high dose as > 10 mg/day. *P* was obtained by ANCOVA (analysis for linear trend). Significance was inferred at $P < 0.05$.

Associations Between Characteristics of BZD use and RT

Table 3 reports the results of additional regression analyses on specific associations between the characteristics of BZD use and RT among the BZD users only. After adjustment, a higher daily dose of BZDs was associated with longer RTs (β=0.096, *P*=0.03). This indicates a possible dose-response effect of BZDs on RTs. Further, problematic use showed a positive association (β=0.118, *P*=0.02) with RT. Figure 2 shows the adjusted mean values of reaction time according to problematic use on the Bendep-SRQ in BZD users only (n=366). Beta-coefficients and P-values were obtained by multivariate linear regression analysis. A higher score on the Bendep-SRQ subscale Problematic Use was significantly associated with longer RTs (*P*=0.02).

TABLE 3. Associations between Characteristics of BZD use and RT in 419 BZD Users

		Univariate analysis		Adjusted model[§]	
Characteristics of BZD use	**n**	**β**	***P***	**β**	***P***
Dose[$]	419	0.167	0.001	0.096	0.03
Duration of BZD use	419	0.114	0.02	0.036	0.40
Type of BZD	419	0.115	0.02	-0.013	0.77
Problematic use[#]	366	0.190	<0.001	0.118	0.02
Preoccupation[#]	366	0.110	0.04	0.023	0.64
Lack of Compliance[#]	366	0.210	<0.001	0.070	0.17

BZD; benzodiazepines, β; standardized beta coefficient by linear regression analyses. $ Daily dose is entered as a continuous variable. # Subscales of the Benzodiazepine Dependence Self Report Questionnaire. § The adjusted models were adjusted for sociodemographics (gender, age, education), health indicators (daily alcohol use, presence of somatic disease), severity of psychopathology (IDS-mc, BAI), and antidepressant use (SSRI, TCA, other antidepressants).

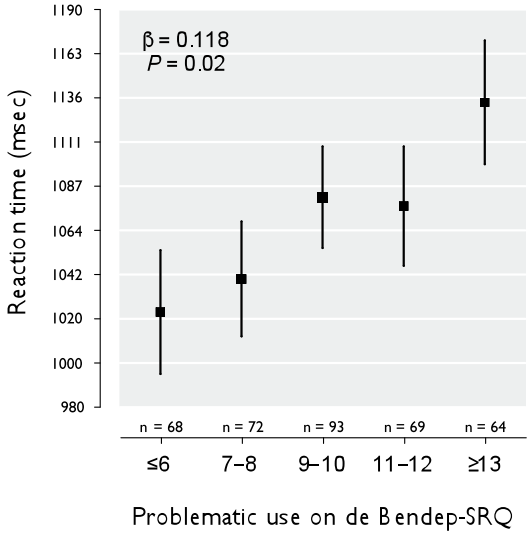

FIGURE 2. The adjusted mean values of reaction time (in milliseconds) obtained from the Implicit Association Test (IAT) according to problematic use on the Bendep-SRQ in BZD users only (n=366). The size of each square is proportional to the number of participants. Vertical lines indicate standard errors. Analyses were adjusted for sociodemographic variables (i.e., gender, age, education), health indicators (i.e., daily alcohol use, presence of somatic disease), psychopathology (i.e., IDS-mc, BAI), and antidepressant use. Beta-coefficients and *P*-values by multivariate linear regression analysis.

DISCUSSION

In this cross-sectional, observational cohort study, we investigated the putative association between long-term BZD use and RT. High doses of BZDs (>1DDD), but not lower doses, were associated with prolonged RTs. This indicates that tolerance to the RT prolonging effect of BZDs does not (completely) develop at higher doses of BZDs.

The finding of longer RTs in high dose BZD users was in line with experimental research on short-term BZD use and RT[6-11] as well as with an observational study which found longer RTs in anxious, high dose BZD users (1.2 - 4 DDD) than in healthy non-users[14]. However, in the latter study it was unclear, whether prolonged RTs were due to BZD intake or psychopathology.

Still, several studies did not find associations between BZD use and RT in chronic users.[15,16] Possibly, BZDs still affect RTs in chronic use, but study design issues led to a lack of significant group differences in these studies (small sample size, absence of adequate statistical transformations).[15,16] Alternatively, the lack of significant associations between BZD use and RT may indicate that tolerance to BZDs' RT prolonging effect develops in long-term BZD use so that only relatively high doses affect RT.

Our study has some limitations. The data are limited by representing only one outcome composed of six individual RT trials. The highest doses in NESDA were still rather moderate doses, so that effects of very high doses could not be investigated. The IAT may not be the most optimal task to measure RT, because the stimulus words were not neutral but related to depression and anxiety and may therefore influence subjects suffering from these illnesses. However, as the effects on RT remained after adjustment for severity of anxiety and depression, this is unlikely. Further, the validity of a CRTT for real life situations such as driving or working at a machine is lower than the validity of a simulation task. Despite these limitations, our study makes an important contribution to

the literature on BZDs and RT due to the following strengths. NESDA is a large observational, cohort study and includes a large sample of average BZD users with a long duration of use and comorbid psychopathology, so that our findings can be generalized to outpatient BZD users in primary and secondary care. The study size enabled us to adjust for important confounders such as psychopathology. The investigation of various characteristics of BZD use enabled us to determine the aspects of long-term BZD use which are associated with RT.

In conclusion, we found increased RTs in high dose BZD users even after adjustment for severity of psychopathology and antidepressant use. This indicates that no complete tolerance to the RT prolonging effect of high BZD doses develops in long-term BZD users. Medical doctors should alert their patients of the prolonged RTs associated with high doses of BZDs and possible consequences for everyday tasks where fast reaction is required. This study also underlines the directive to prescribe and use BZDs conservatively, and at the lowest dose possible.[31]

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SUPPLEMENT 1. Arrangement of the Different Implicit Association Test Blocks

Block	*Left Label (s)*	*Right Label(s)*	*No. of trials*
1 Single concept	Me	Other	20
2 Single concept*	Anxious	Calm	20
3 & 4 Combined concepts	Me/Anxious	Other/Calm	80
5 Single concept*	Calm	Anxious	20
6 & 7 Combined concepts	Me/Calm	Other/Anxious	80
8 Single concept*	Depressed	Elated	20
9 & 10 Combined concepts	Me/Depressed	Other/Elated	80
11 Single concept*	Elated	Depressed	20
12 & 13 Combined concepts	Me/Elated	Other/Depressed	80

*Single concept trials used to measure the average RT.

General Discussion

SUMMARY OF RESULTS

This thesis had three aims. Our first aim was to identify the independent correlates of BZD use in general, inappropriate BZD use, and BZD dependence. As the prescribers may affect the BZD use of their patients, we also established the GP characteristics of patient BZD use. Our second aim was to examine whether there is evidence that (chronic) BZD use has an impact on the functioning of two human stress systems, the hypothalamic-pituitary-adrenal axis (HPA axis) and the autonomic nervous system (ANS). Third, we aimed to investigate whether the relationship between BZD use and prolonged reaction time (RT) would persist in long-term BZD use or whether tolerance to this side effect of the BZDs would develop. We conducted these analyses on data from the Netherlands Study of Depression and Anxiety (NESDA). NESDA is a prospective cohort study on the course of depressive and anxiety disorders that comprises a large number of BZD users.

As the prevalence of BZD use and inappropriate use is high, we investigated the correlates of BZD use and inappropriate BZD use in cross-sectional regression analyses (**chapter two**). Of the NESDA sample, 15.0% (n=429) used BZDs. Of these BZD users, only 15.2% used BZDs according to international prescription guidelines. Most users (82.5%) exceeded the recommended duration of safe use, but some also surpassed the recommended dosages or had prescriptions for more than one type of BZD at a time. Older age, being single, unemployment, treatment in secondary care, more GP visits in the past six months, (more severe) anxiety, depression, comorbidity, insomnia, and use of antidepressants were independently associated with BZD use. Older age and chronic illnesses were independently associated with inappropriate BZD use. We concluded that mentally or physically vulnerable subjects were most likely to use BZDs. The most vulnerable (i.e. old and physically ill) BZD users were at highest risk of inappropriate BZD use.

In **chapter three**, we investigated the prospective determinants of initiated and continued BZD use. During follow-up, BZD use was initiated by 4.9% of BZD non-users at baseline. Initiated use was predicted by insomnia, enduring anxiety symptoms, entering secondary care during follow-up and past BZD use. Positive life events during follow-up reduced the likelihood of BZD initiation. Of the BZD users at baseline, 54.2% continued use during the entire follow-up period. Continuation of BZD use was predicted by higher age, severe anxiety, and a long duration of BZD use. Leaving secondary care was associated with less continued BZD use. We concluded that insomnia and anxiety were the main risk factors of initiated use, while advanced age and anxiety severity were the main risk factors of continued use.

As BZD dependence is experienced by many BZD users, but regularly remains unrecognized, we investigated the cross-sectional correlates of BZD dependence in **chapter four**. Problematic use was independently associated with more GP contacts in the past six months and severity of insomnia. Preoccupation was related to anxiety severity, antidepressant use, alcohol dependence, and a higher daily dosage of BZDs. Lack of compliance was associated with higher age, unemployment, insomnia, antidepressant use, and alcohol dependence. We concluded that BZD users with insomnia, antidepressant use and alcohol dependence were at the highest risk to develop BZD dependence.

The patient correlates of BZD use have received much attention in the past. Less attention has been paid to the contribution of general practitioner (GP) characteristics to patient BZD use. Therefore, we investigated GP characteristics as possible correlates of patient BZD use and inappropriate BZD use in **chapter five**. Patient BZD use and inappropriate use did not vary significantly between GPs. Only few GP characteristics were associated with patient BZD use (after correction for patient correlates of BZD use). Only the GP's perceived disability to

differentiate unhappiness from depression was weakly associated with less patient BZD use. Higher professional comfort and competence with mental health care of the GPs correlated with less inappropriate patient BZD use. Our results indicate that GP characteristics barely affect patient BZD use. Instead, patient characteristics seem to be decisive in whether BZDs are used (inappropriately) or not.

As BZDs are used for the symptomatic treatment of anxiety and stress, they may influence the human stress system. Short-term BZD use was found to suppress cortisol levels. However, little research has been done on the effects of long-term BZD administration on the hypothalamic-pituitary-adrenal (HPA) axis. The relationship between BZD use and various salivary cortisol measures was studied in **chapter six**. Daily and infrequent BZD users displayed slightly lower evening cortisol levels as compared to non-users, but did not differ on any other cortisol indicator. As BZDs are often taken at night time, the reduced cortisol levels in the evening may reflect a transient suppressive effect of BZDs on the HPA axis (which could not be detected anymore in the morning). Alternatively, tolerance to BZDs cortisol suppressant effects may develop in long-term BZD use.

Short-term BZD use was repeatedly found to suppress sympathetic nervous system activity and heart rate variability. However, findings between studies were inconsistent. Further, it was unclear if BZDs maintain their effects on the autonomic nervous system (ANS) in chronic use. Therefore, we investigated the prospective association between transitions in BZD use and ANS alterations in **chapter seven**. After adjustment of covariates, subjects who had initiated BZD use during the follow-up period displayed a decrease in sympathetic activity while chronic users showed an increase in sympathetic activity. No effects of BZDs on parasympathetic activity were detected. This finding suggests that BZDs suppress sympathetic activity in short-term use, and that

these effects remain, but become smaller, in longer term users, potentially due to tolerance development.

Short-term administration of benzodiazepines (BZD) was found to prolong reaction time (RT) in experimental studies. However, studies on long-term BZD use did not always adjust for important confounders and showed inconsistent results. In **chapter eight**, we investigated the relationship between BZD use and RT in mainly chronic BZD users of NESDA. We found that high dosage chronic BZD users, but not lower dosage users, had longer RTs than non-users. This indicates that tolerance to this side effect of the BZDs did not develop (completely). Further, BZD users with higher scores on problematic use, a dimension of BZD dependence severity, had longer RTs than those who scored lower on problematic use.

GENERAL DISCUSSION

In this discussion, these findings are discussed. Further, clinical implications, methodological considerations, and topics for future research will be outlined.

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

Despite the narrow indication range for BZDs and the growing public awareness of the drawbacks of BZD use, many patients use BZDs, also for invalid indications.[1-4] Against international prescription guidelines, high daily dosages are used, though these may increase the risk of side effects, dependence, and suicidal ideations.[5,6] BZDs are also used inappropriately for long periods of time, even though the therapeutic effectiveness may decrease.[7] Therefore, we aimed to identify patients at risk of new BZD use, chronic use, inappropriate use, and dependence. Our findings are summarized in Table 1.

TABLE 1. Risk and Protective Factors in Relation to BZD Use

New BZD use	Chronic BZD use	Inappropriate use	BZD dependence	BZD prescribers
Risk factors: Insomnia Chronic anxiety Entry into secondary care Past BZD use	Risk factors: Higher age Severe anxiety Long duration of BZD use Past BZD use	Risk factors: Higher age Chronic illnesses	Risk factors: Unemployment Many GP contacts Insomnia Severe anxiety Antidepressant use Alcohol dependence High BZD dose	Risk factors: None
Protective factors: Positive life events	Protective factors: Returning to primary care	Protective factors: Agreeableness	Protective factors: None	Protective factors: Comfort in dealing with anxious and depressed patients Disability to differentiate unhappiness from depression

The Initiation of BZD Use

During the two year follow-up period, BZD use was initiated by 4.9% of the subjects who did not use BZDs at baseline.[8] We investigated the risk factors of the initiation of BZD use in prospective analyses in the NESDA sample.[8] Beyond the studies already discussed in chapters two and three of this thesis, no other prospective cohort studies have been published on this specific topic, so we will restrict this argumentation to our own results and the scarce previous literature on new BZD use.

We found that insomnia, enduring anxiety, and entry of secondary care were the strongest predictive factors of the initiation of BZD use.[8] This finding is in line with previous research[9,10] and suggests that BZDs are primarily prescribed for their main indications. We discovered that BZD use

was initiated for longer rather than shorter episodes of psychopathology.[8] Possibly, GPs and patients try different treatment alternatives before they decide to initiate BZDs. This suggests that guidelines[11,12] for BZD initiation are followed relatively well by most patients and prescribers. Albeit, BZDs only suppress symptoms of anxiety and insomnia for the duration of use and do not cure the underlying disorder. Consequently, relapse rates after BZD discontinuation are high.[13] BZD use may even interfere with cognitive behavioural therapy due to its impairing effects on cognitive functions.[14] For these reasons and reasons related to other side effects, namely decreasing effectiveness, dependence, and tolerance development, BZDs are never the first treatment option.[15] Before prescribing BZDs, GPs should try the alternative treatment approaches suggested by Dutch and international guidelines as summarized in Table 2.[11,12] The mentioned pharmacological alternatives are mostly better suited as first choice treatments of anxiety and insomnia. The non-pharmacological treatment options may additionally help to treat these disorders, and reduce the need for long-term drug prescriptions. As current insomnia treatment guidelines do not include pharmacological treatment alternatives to BZDs and so-called z drugs, we have also added empirical research evidence regarding psychopharmacological insomnia treatment to Table 2.[16]

TABLE 2. Alternative Treatment Approaches for Anxiety and Insomnia[11,12]

Disorder	Panic Disorder	Social Phobia	GAD	PTSD	Insomnia
Pharmacological treatment	SSRIs TCAs	SSRIs Venlaflaxine	SSRIs Venlaflaxine TCAs Buspiron	SSRIs TCAs Venlaflaxine Anticonvulsives	Tradozon Mirtazapine (Quetiapine)
Non-pharmacological treatment	Exposure therapy Panic management	Social skills training Exposure therapy Cognitive therapy Task concentration training	Exposure therapy Applied relaxation Anxiety management therapy	Exposure therapy Stress management Cognitive therapy Eye movement desensitization and reprocessing	Information about sleep physiology Advice on sleep hygiene Muscle relaxation

Female gender,[17] older age,[17] divorce,[17] alcohol problems,[9] antidepressant use,[9] smoking,[10] and poor physical health[10] were identified as important risk factors for BZD initiation in previous research, but not confirmed in our study.[8] As we corrected for these confounders in one large multivariate model, these factors may be less important in the prediction of new BZD use than insomnia, anxiety and entry of secondary care. However, as older age, divorce, alcohol problems, and physical health problems are often accompanied by anxiety and insomnia, it is possible that BZDs were prescribed for symptom reduction, (although it would have been better to treat the cause of the anxiety and insomnia). Alternatively, the discrepancies may be caused by differences in sample selection or the inclusion of a different subset of BZD predictors.

An interesting observation was that the risk for BZD initiation was reduced by the occurrence of positive life events.[8] This indicates that patients at risk of BZD use may benefit from the active search for more positive life situations, such as making new friends and participating in

recreational activities. They may be taught how to do so in counselling or psychotherapy.

Chronic BZD Use

At baseline, 82.5% of the 429 BZD users in NESDA were chronic users.[18] Of all BZD users at baseline, 54.2% continued use during the entire follow-up period of two years.[8] As most of the BZD users in NESDA were already long-term users at baseline, we combined the results of our own cross-sectional and prospective analyses in this discussion.[8,18] Older age, severe anxiety and treatment in secondary care were associated with chronic BZD use in both analyses and thus formed the most important risk factors.[8,18] These results are in line with other prospective research studies.[19,10]

Old patients with severe anxiety seem to form a vulnerable group who suffer from the troubles of aging in combination with psychopathology. As these patients often have a low quality of life, it is important to reduce their symptoms, but even more favourable to treat the underlying disorders. Only when other treatment alternatives (see Table 2) have been tried without success, long-term BZD use may be considered. Yet, BZDs should only be prescribed for the duration of time that they actually reduce symptoms of anxiety and insomnia. As there is little evidence for BZDs effectiveness in daily, long-term use,[20] intermittent use may be a pragmatic alternative in order to delay tolerance development.[21] However, intermittent use is also no optimal solution, as it may also lead to (or even be an expression of) BZD dependence.[22]

The association between BZD use and secondary care treatment[18,8] indicates that BZDs are often initiated at entry of and discontinued at exit of specialized mental health care treatment. This finding is not surprising as oftentimes all other treatment options are exhausted when subjects enter secondary care and immediate symptom reduction is necessary. However, it does seem positive that BZD treatment is also discontinued, when subjects leave secondary care. Apparently, specialized health care

personnel largely adhere to treatment guidelines. Further, subjects seem to benefit from secondary care treatment, so that they are no longer in need of BZDs when they leave the mental health care institutions.

Female gender,[23] divorce,[23] pain,[10] general practitioner contacts[23] and several characteristics of BZD use[24] were established as important risk factors of chronic use in previous research, but not confirmed by the thesis on hand. Possible explanations are again the differences in sample selection or the inclusion of different putative risk factors in multivariate models. However, as mentioned above, insomnia and anxiety may also be a consequence of pain complaints and divorce. Thus, GPs may have treated symptoms of anxiety and insomnia, although it would have been better to treat the cause of these two disorders.

Inappropriate BZD Use

Inappropriate BZD use was defined as using a mean daily dose higher than the DDD as defined by the World Health Organisation, using BZDs for longer than three months, and using more than one type of BZDs at a time.[18] In NESDA, the prevalence of inappropriate use was high, with 84.8% of the 429 BZD users meeting at least one of the mentioned criteria.[18] In order to find out who was at highest risk, we investigated the correlates of inappropriate BZD use in the NESDA sample. In our study, older patients who also had chronic, physical illnesses were at highest risk of inappropriate BZD use. These patients may insist to receive or refuse to discontinue their BZD prescriptions. Alternatively, GPs may view BZDs as the only treatment option for the vulnerable patients and therefore issue prescriptions despite the treatment guidelines.[25-28] Of the inappropriate users, the majority exceeded the recommended duration of BZD use of three months,[18] while only a relatively small percentage surpassed the recommended dose or used more than one type of BZDs at a time.[18] Thus, chronic long-term use presents the most common problem. Although the prevalence of exceeded doses was relatively low (14.0%), high dose use may have substantial impact on public health due to the

increased risk of adverse outcomes such as hip fractures[29] and motor vehicle accidents.[30] Patients using antidepressants were at highest risk of inappropriately high BZD doses, possibly due to co-prescription of BZDs to reduce the most severe symptoms in the first weeks of antidepressant treatment. Even after full effectiveness of the antidepressant treatment enfolded, subsequent BZD use was found to be frequent.[31] Therefore, it is important to ensure that BZD tapering is initiated as soon as patients respond to antidepressants.

High scores on agreeableness protected against inappropriate BZD use. This is in line with an earlier found association between agreeableness and treatment adherence in hypertensive subjects.[32] As agreeable subjects are generally characterized as empathetic, harmony seeking, and trusting,[33] they may be more likely to listen to the GPs advices when short-term BZD treatment or BZD tapering is recommended. They may also trust their GPs more easily on the drawbacks of BZD use. This emphasizes the importance of developing a trusting doctor-patient relationship, so that the patient believes in the competence of the GP and is willing to take his/her advice. GPs should also learn how to convince less trustful patients of the most appropriate treatment options and to refrain from prescribing when they do not consider BZDs justified. Future research needs to investigate whether GPs with these skills issue less inappropriate prescriptions. If that is the case, more emphasis needs to be put on training these skills to GPs.

BZD Dependence

Patients dependent on BZDs commonly initiate use due to anxiety or insomnia and continue their prescriptions longer than recommended or at doses outside the recommended range.[20] As they are partly maintained on this inappropriate use by their prescribers, this is occasionally called ‘involuntary’ dependence. The prevalence of patients seeking BZDs for intentional abuse is much lower, and those who do, usually have a comorbid diagnosis of substance-abuse and derive their drugs from

more than one prescriber or other additional sources such as illicit sales and internet sites.[34] Nevertheless, dependence development is relatively common, even in low-dose BZD users, and especially in subjects with comorbid psychopathology.[20] As BZD dependence impairs the quality of life of the affected subjects and interferes with the treatment of the primary disorder,[35] its development should be prevented.

In order to prevent BZD dependence, GPs may identify patients at risk with empirically validated correlates of BZD dependence. In the thesis on hand, severity of insomnia, antidepressant use and alcohol dependence were identified as the most important correlates of the three scales of BZD dependence severity. These correlates were significantly associated with more than one subscale of dependence severity. Higher age, unemployment, more GP contacts, severity of anxiety and a daily dosage of BZD use were associated with one subscale of BZD dependence.

As alcohol dependence increases the risk of BZD dependence and vice versa, caution is essential in patients with alcohol problems. It has been shown that polydrug users often combine high doses of BZDs and alcohol in order to increase sedation.[20] This can be very dangerous as memory impairments are enhanced and the risk of accidents and injuries becomes even more pronounced. Therefore, BZDs should not be prescribed for mild alcohol withdrawal where supportive care may be sufficient.[36] Instead, it should be reserved for severe alcohol withdrawal and delirium tremens, where short-term BZD administration is considered as treatment of choice.[36] Regarding insomnia, the above stated may also hold true. Subjects often initiate BZD use for the treatment of insomnia and continue longer than indicated due to enduring symptoms. Finally, they become dependent. This has also been shown for antidepressant use, where subjects initiate BZD treatment during the first weeks of antidepressant treatment and continue their BZD use thereafter.

Previous research identified a number of correlates (e.g. female gender,[37] retirement,[38] depressive disorder,[38] drug use,[39] longer duration of BZD use[38]) which we did not confirm in our own research. However,

as most studies on BZD dependence used dichotomous definitions of dependence[37,40] instead of severity dimensions, results are difficult to compare. Additionally, BZD users in previous research were on higher dosages of BZDs[37] and had more severe alcohol problems, which may increase the risk of BZD dependence.

General Practitioner Characteristics, Patient Characteristics and BZD Use

General practitioners (GP)s have often been blamed for the inappropriate BZD use of their patients as they bear at least part of the responsibility by maintaining patients on the prescription drug. Therefore, we aimed to investigate whether certain physician characteristics were associated with an increased risk of inappropriate patient BZD use, even after the correction for patient characteristics. Previous research has identified a number of independent physician determinants of patient BZD use including male gender,[41,42] personal usage of BZDs,[43] allowing patients to influence prescription decisions,[42] prolongation of prescriptions without direct doctor-patient contact,[42] and multiple drug prescribing[44]. However, these studies did not adjust for patient characteristics, so that it was unclear if the found differences were due to variation in the physicians or in the treated patients.[41-43] The only study which adjusted for patient characteristics reported that patient and practice characteristics were more important in the prediction of patient BZD use than GP characteristics.[45]

Our results were very consistent with the latter findings.[45] When analyses were adjusted for patient characteristics, the majority of GP characteristics were no longer associated with patient BZD use. This indicates that GP characteristic are not decisive to the inappropriate BZD use of patients. Instead, it seems that most GPs prescribe BZDs (inappropriately) to a specific group of vulnerable patients (independent of their own GP characteristics). This assumption was supported by numerous qualitative studies which reported that GPs are commonly

aware of the BZD treatment guidelines, but still prescribe BZDs, because of the idea that BZD treatment is appropriate for subjects with severe mental problems or as they feel incapable of helping these patients by any other means.[25-28] Less inappropriate BZD prescriptions were issued by GPs who reported feeling comfortable in dealing with anxious and depressed patients. Possibly, these GPs are more confident to inform patients about the risks of BZD use and the need of discontinuation after short-term treatment.

Summary and Discussion Part A: BZD use, Inappropriate Use and the Influence of BZD Prescribers

BZD use was mostly initiated by patients with a diagnosis of insomnia or anxiety and those who entered secondary care; while the experience of positive life events protected from the initiation of BZD use.[8] The most vulnerable patients, i.e. the old and psychologically or physically ill, were at highest risk of inappropriate (and in particular chronic) BZD use.[18] Patients with a diagnosis of insomnia or alcohol dependence or those also using antidepressants were at highest risk of BZD dependence. Patient characteristics rather than GP characteristics were associated with the different modalities of patient BZD use. Therefore, patients as well as GPs should receive education and training on responsible BZD use. Since GPs who felt more comfortable in dealing with anxious and depressed patients issued less inappropriate BZD prescriptions, GPs need to be trained on how to manage this patient group[25,46] and acquire good knowledge on alternative treatment options.[25,28] For example, the *Dutch Institute for Responsible Drug Use (Instituut voor Verantwoord Medicijngebruik)* offers education, trainings and improvement trajectories to support health care organisations with responsible drug prescriptions.[47]

PART B) THE PHYSIOLOGICAL CONSEQUENCES OF BZD USE

In short-term intervention studies, BZDs were found to acutely suppress the HPA axis (stress-induced activation) and SNS activity.[48-50] The underlying mechanism of action may be as follows. BZDs bind to $GABA_A$ receptors, enhance the inhibitory effect of these receptors in the paraventricular nucleus (PVN) of the hypothalamus and thereby suppress the HPA axis and the SNS. As SNS arousal was found in stressful situations[51] and HPA axis hyperactivity was detected in anxious subjects, these suppressant effects of the BZDs may contribute to their anxiolytic and stress reducing actions. Consistent with this hypothesis, BZD induced cortisol reductions were found to be accompanied by an improvement of anxiety.[52,53] Additionally, the alpha 2 subunit of the $GABA_A$ receptor, which mediates BZDs' anxiolytic effects, was found to be most abundant in the hypothalamus,[54,55] which is involved in the regulation of ANS and HPA axis effects.[48,49] However, findings were inconsistent, in particular for the ANS, so that no firm conclusions can yet be drawn.

It is also not known whether BZDs effects on the HPA axis and the ANS remain in chronic BZD users or if tolerance develops. Possibly, the BZD concentration needed to suppress the HPA axis becomes higher with tolerance development so that the daily dose of BZDs does not affect the HPA axis activity anymore after a certain period of use. Alternatively, BZDs may only suppress the HPA axis activity briefly, so that the activity returns to baseline shortly (in a couple of hours) after BZD administration. It was oftentimes reported that BZDs lose their anxiolytic and especially hypnotic effectiveness in chronic BZD use.[56,57] Possibly, once BZDs effects on ANS and HPA axis decrease, their anxiolytic and hypnotic effectiveness also diminish.

If BZDs constantly suppressed the SNS and the HPA axis in chronic BZD users, a deregulation of these two stress systems was to be expected. Constant hyperarousal of the HPA axis was found to be

associated with psychiatric and somatic conditions, such as depressive and anxiety disorders, osteoporosis, atherosclerosis, and certain infectious diseases.[58-60] Hypoarousal of the HPA axis was found to be associated with fibromyalgia, hypothyroidism, chronic fatigue syndrome, and post-traumatic stress disorder.[58] Altered ANS activity was found to be associated with angina pectoris, myocardial infarction, coronary heart disease death, or congestive heart failure.[61,62] If these conditions were likely to develop, even more caution regarding the (long-term) use of BZDs would be warranted.

To find out whether the effects of BZDs on the ANS and the HPA axis remain in long-term users, we investigated the cross-sectional association between BZD use, the HPA axis and the ANS in mainly long-term BZD users of the NESDA sample. Additionally, we investigated prospective data on BZD use and the ANS.

The Association Between BZD use and the HPA Axis

In the past, the effects of short-term BZD administration on serum, urine and salivary cortisol levels as a measure of the HPA axis were studied during a time period ranging from one day to one month. In most of these studies, BZDs suppressed (stress-induced increases of) cortisol levels.[50,53,63-68] It was concluded that the suppression of the HPA axis may be involved in BZDs' mechanism of action.[53]

Research on the effects of chronic BZD use on the HPA axis has been scarce. In one study, chronic BZD users had similar baseline plasma cortisol levels as non-users, indicating that these subjects' daily BZD use did not (lastingly) affect the HPA axis.[57] In NESDA, long-term BZD users did not differ from non-users on most cortisol indicators, confirming these findings.[69] This suggests tolerance development for the HPA axis suppressant effects of BZDs. Only evening cortisol levels of BZD users were lower than those of non-users in the NESDA sample.[69] As BZDs are usually taken at night time, this may indicate the existence of an acute, transient, cortisol suppressant effect of BZDs in long-term

users. In line with the finding of transient cortisol reductions, a short-term intervention study reported that a BZD-induced suppression of the HPA axis was followed by a rapid return to baseline cortisol levels, despite persisting high plasma BZD levels.[70,71] Consistently, the morning cortisol samples of BZD users in NESDA were only non-significantly lower than those of non-users with smaller effect sizes.[69] This suggests that cortisol levels went back to baseline as the BZD suppressant effect wore off.

Nonetheless, the lack of strong effects of BZD use on cortisol in NESDA does not prove the absence of these effects on the HPA axis. Earlier research found significantly decreased ACTH levels, but non-significantly reduced cortisol levels upon BZD administration. The authors concluded that ACTH and cortisol reductions might be unassociated.[72] This illustrates the biological complexity of the human stress system which we tried to capture by the measurement of salivary cortisol as the single biological indicator.

In summary, BZDs still seem to slightly suppress the HPA axis in chronic BZD users. This cortisol suppression seems to occur only transiently directly after BZD ingestion. However, the BZD induced cortisol reductions are much smaller than in short-term use, probably due to the development of tolerance.

The Association Between BZD use and the ANS

The current body of literature on the effects of BZDs on the ANS is inconsistent and largely comprises short-term intervention studies that measured the effects of relatively high doses of BZDs on the ANS. The majority of studies on SNS activity reported a suppression of (stress-induced increases of) sympathetic activity.[51,73-77] However, one study reported that BZDs increased sympathetic outflow[78] and a few other studies did not detect any SNS related effects of BZDs.[79-82] Research on PNS activity found that BZD administration attenuated HRV,[78,80,83-87] and heightened HR,[78,80,83,86-88] aside from two studies which announced

heightened HRV after BZD administration.[77,89] Based on these short-term results, the effects of BZDs on the ANS remain unclear.

Less research has been conducted on the effects of chronic BZD use on the ANS. Cross-sectional analyses of the NESDA study reported similar HRV in chronic BZD users and non-users.[90] In prospective research, this finding was confirmed. On the one hand, this may imply that BZDs do not affect PNS activity in chronic use due to tolerance development. On the other hand, it may indicate that BZDs have an acute, transient effect on the ANS (which could not be detected hours after BZD intake when NESDA interviews took place).

In contrast, the SNS activity of BZD initiators in NESDA was lower at the two year measurement than it was at baseline. This may suggest that initiating BZDs slightly decreased SNS activity. Yet, a BZD induced decrease in SNS activity would also be reflected in a decrease of HR, which was not found in NESDA. Further, chronic users displayed an increase in SNS activity between the baseline and the follow-up measurement, which is difficult to explain. As different group and ANS measure comparisons gave conflicting results, we need to be cautious when drawing firm conclusions. At this point, is seems that BZDs suppress SNS activity in short-term use, and that these effects remain, but become smaller, in longer term users due to tolerance development. It is also very likely that the effect of BZDs on the ANS is transient in nature so that it can be measured directly after BZD intake and decreases with time. As we did not record the time of BZD intake, it is very likely that the effect of the BZDs on the SNS had already worn off in some subjects, while it was still present in others and again others may have shown rebound SNS increases (between doses elevations).

Summary and Discussion Part B: The Physiological Consequences of BZD Use

We neither detected strong effects of BZDs on the HPA axis nor on the ANS in long-term BZD users. This is in contrast with intervention studies

which reported a suppression of the HPA axis and either decreased SNS or HRV levels directly after the administration of BZDs. The absent or weak influences of BZDs on the ANS and the HPA axis in long-term users have several implications. On the one hand, it suggests that patients, who suffer from anxiety and/or depression, may use BZDs without strong adverse effects on these two stress systems. While in the first weeks of BZD use minor respiratory and cardiovascular changes may occur, these effects should wane relatively fast with the development of tolerance. Most importantly, no chronic hypo- or hyperarousal of the two stress systems is expected. In this respect, BZDs may be safer than antidepressants which were shown to have adverse effects on the ANS and the HPA axis. The use of tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) was associated with decreased HRV, the use of SNRIs and TCAs was associated with decreased PEP, and the use of SSRIs was associated with increased PEP.[90-92] Further, the use of antidepressants was associated with less cortisol suppression after dexamethasone,[59] which may increase the risk to develop hypercortisolemia.

The absence of strong physiological consequences of BZD use in long-term users may also explain why BZDs do not maintain their anxiolytic and hypnotic effectiveness in chronic BZD use.[56,57] As decreases in cortisol levels were found to be associated with decreases in anxiety,[53] tolerance development to the cortisol-suppressant effect might also indicate tolerance development to BZDs anxiolytic and hypnotic effects.

Cautiousness in drawing final conclusions is recommended. As GABA is widely spread throughout the human brain, BZDs may affect several different brain structures via their direct and indirect effects on GABA. The lack of strong alterations of the HPA axis and the ANS indicators associated with BZD use reported in this study, are no proof for the absence of stress system effects in chronic BZD use. Future research needs to confirm if tolerance to BZDs' suppressant effects on the HPA axis and the ANS develops in chronic use. Further, it needs to

be established, if tolerance development to these physiological effects of BZDs is the reason for the decreasing anxiolytic and hypnotic effects of BZDs in long-term use.

PART C) SEDATIVE AND ATTENTION IMPAIRING EFFECTS OF BZDS

Until the 1970s it was assumed that BZDs did not have any cognitive side effects.[93] However, it is now common knowledge that clinical doses of BZDs induce high levels of sedation, attention impairments, and memory deficits in short-term use.[93] In long-term use, only some of these effects seem to remain, while others are subject to tolerance. Memory deficits were found to persist in long-term use (even after five years)[94] indicating that tolerance to these effects never fully develops. While some research studies suggested that sedation and attention impairments improve with time,[93] others found sustained attention impairments in chronic BZD users,[95] but no impairments of simple reaction time.[95] Another research study reported no effect of diazepam on psychomotor speed in a group of subjects using BZDs for 5-20 years, pointing to the persistence of tolerance.[94] From these research studies, it did not become clear, whether sedation and attention impairments remain in chronic BZD use. Therefore, we aimed to investigate whether BZDs' effects on attention and sedation would persist in chronic BZD use. Daytime sedation (including psychomotor speed impairments) and attention deficits can objectively be measured by reaction time (RT) tasks such as choice reaction time tasks (CRTTs).

The Association between BZD use and Reaction Time

Previous research on the association between BZD use and RT mainly consisted of small randomized trials which compared the effect of short term administration of BZDs to the effect of placebo in CRTTs. In these studies, the administration of BZDs was generally found to prolong

RTs in healthy, BZD-naive subjects.[96,97] This increase was reported to last for the time measured, which ranged from 0,5 to 36 hours.[96,97] One intervention study investigated the effects of BZD use on RT during a longer period of time and found that six weeks of daily BZD intake still increased RTs.[98] This finding indicates that at least for this duration of time limited or no tolerance for the RT prolonging effect had developed. Two small studies did not find prolonged RTs after BZD intake, possibly due to a lack of power related to small sample sizes.[99,100]

Only a few observational studies investigated the association between long-term BZD use and RT with inconsistent results. One cross-sectional, observational study did not detect longer RTs in chronic BZD users as compared to healthy controls.[101] In contrast, another study found longer RTs in chronic BZD users with anxiety than in healthy non-users,[102] but did not investigate whether the increased RTs were due to psychopathology or the use of BZDs.[102] 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.[103] When analyses were repeated in the depressed group only, RTs did not differ between BZD-users and non-users.[103] This suggests that the increased RTs were due to psychopathology rather than BZD use.

We wanted to investigate if BZD use prolongs RT independent of psychopathology. Therefore, we examined BZDs' effects on RT (as measured by a CRTT) in chronic BZD users. We found a positive association between the daily dose of BZDs and RTs. This significant effect remained after adjustment for psychopathology, indicating that the harmful effects of BZDs on RT are independent of psychopathology and remain in chronic BZD use. The found dose-response relationship in this thesis was in line with previous short-term research which reported that impairments of psychomotor speed and attention increased with the administered dose.[96]

In this thesis, the awareness of problematic BZD use was associated with prolonged RTs, independent of the used dose. High scores on problematic use probably reflect the experienced strength of side effects. The experienced side effects may differ between individuals, as they are influenced by the individual drug metabolism and pharmacokinetics. Studies on BZD pharmacokinetics have shown that alterations in distribution and elimination of certain compounds occur in old age.[104] In older subjects, half a dosage is sufficient to achieve a comparable therapeutic effect to the effect the whole DDD causes in younger patients. If the common DDD is used in older patients, side effects become much stronger and the risk of accidents, falls, and other consequences of cognitive impairments increases.[105,106] Yet, younger subjects may also show differential reactions to the same dose of BZDs. This may be related to the individual genetics. Alternatively, the concomitant use of other drugs or substances (cigarettes, certain food, alcohol, opioids, lithium, antipsychotics) may enhance or suppress the effects of BZDs.[107] For example, diazepam and chlordiazepoxide plasma concentrations increase in combination with drugs that inhibit cytochrome P (CYP) enzymes CYP450 and CYP 343/4, including cimetidine, disulfiram, and isoniazid and result in much stronger side effects.[107,108] Therefore, GPs should closely monitor the drug regime of their patients, consider possible drug interactions and regularly ask them about the experienced side effects.

Summary and Discussion Part C: Sedative and Attention Impairing Effects of BZDs

We found a dose response relationship between the daily BZD dose and RT. This result underlines the importance of limiting BZD use to the defined daily dose. Medical doctors should repetitively alert BZD users of the prolonged RTs associated with high doses of BZDs and the possible consequences for everyday tasks where good concentration, attention, and psychomotor speed are required, (such as driving or working with machinery), even when they are already using for a long duration of time.

Interestingly, we did not find strong associations between BZD use and the two stress systems, but did detect associations between BZD use and RT. A possible explanation for this finding may be that sedation and anxiolysis are mediated via two different receptor subunits of the $GABA_A$ receptor.[109] Possibly, BZDs effects on the stress system are related to their anxiolytic effects while RT impairments rather reflect daytime sedation (including psychomotor slowing) and attention deficits. Anxiolytic effects are mediated via the alpha 2 subunit of the $GABA_A$ receptor[110,111] which is dominant in the PVN of the hypothalamus. In contrast, sedation was found to be mediated via the alpha 1 subunit of the $GABA_A$ receptor[110,112] which is present in most parts of the adult brain, including the PVN (although not dominant in this area). Tolerance to BZDs' anxiolytic effects on the alpha 2 subunit may develop earlier than tolerance to the sedative effects on the alpha 1 subunit does. This hypothesis contradicts previous research which reported fast (2 weeks) tolerance development to the sedative effects of BZDs,[113,114] and slower tolerance development to the anxiolytic effects of BZDs. Yet, the association between dose of BZDs and RT indicates that there is no complete tolerance development to BZDs sedative effects in chronic BZD use. Most likely, the dose needed to impair RT is lower than the dose needed to put a patient to sleep. This would explain why studies found decreasing sedative effectiveness in insomniac patients with a longer duration of use and why we still detected prolonged RT in long-term users (indicating that the sedative effects have not yet completely disappeared).

PART D) METHODOLOGICAL CONSIDERATIONS

Specific limitations of the studies presented in this thesis have already been addressed in the corresponding chapters. In this part of the thesis, only the general methodological considerations will be discussed. One of the overarching limitations was the limited ability to determine causality due to the observational nature of our studies. Therefore, we

do not know for sure, if the identified correlates are actually risk factors of the modalities of BZD use or otherwise related (due to confounding). However, The Medical Ethical Committee (in Dutch: Medisch Ethische Toetsingsingscommissie or METc) does not allow long-term trials on BZD use to be conducted due to the high risk of BZD dependence.

Due to attrition and the recruitment of patients in outpatient (and not in inpatient) settings, the most severely depressed and anxious subjects were not optimally represented within the NESDA study, especially at the follow-up measurement. As a result, the findings of this thesis cannot be generalized to the most severely ill psychiatric patients. Furthermore, the NESDA sample mainly consisted of low-dose BZD users, while high dose and severely dependent subjects were not included in this study. Therefore, our results cannot be generalized to these patients. As NESDA mainly consists of outpatients with previous or current psychopathology or a family history of psychopathology, subjects who use BZDs (inappropriately) for other than psychiatric indications are less present in our studies. A related restriction is that only adults aged 18 through 65 were included in NESDA, so we cannot be sure if our findings can be generalized to the elderly above 65. This is unfortunate as the age of 65 and older is a major part of the BZD user population. Additional restrictions were related to the group sizes for the subgroups of BZD users. Since the group sizes of most of the different BZD types were relatively small (for some analyses the groups were smaller than n=20), small group differences could have been missed due to the restricted power of these analyses. Moreover, the BZD user sample did not comprise many short-term users with less than one month of use. Consequently, the correlates of short-term versus long-term use and the respective consequences could not be compared. The same problem also applied for high dose and low dose BZD use and high and low severity of BZD dependence.

Furthermore, certain analyses could not be conducted as the necessary variables had not been included in the NESDA study. For

example, we could not analyse the attitudes and ideas of GPs regarding BZD use (but only more general attitudes regarding depression and anxiety) and did not know the reasons for BZD initiation. Other limitations of this thesis are related to non-compliance or memory bias. BZD use, which was registered by self-report and observation of drug containers, may not always represent the actual use. Our studies were also limited by the fact that patients took their daily dose of BZDs at home and we did not ask them for the most recent time of intake. Therefore, we could not be sure whether all patients actually took BZDs on the days of the RT, ANS and HPA axis measurements, nor did we know how much time had passed since the last administration of BZDs. Several NESDA subjects may have used short-acting BZDs at night so that the plasma BZD concentration was very low at time of RT, HPA and ANS measurements and no acute effects could be established.

PART E) IMPLICATIONS FOR FUTURE STUDIES AND CLINICAL PRACTICE

Effort should be made for the inclusion of high dose, BZD-dependent patients in observational studies to confirm present findings in that patient group. Strategies to motivate this group to participate need to be developed, as these patients are not only most difficult to motivate, but also most in need of professional care. In addition, research should focus on old patients (and also include subjects older than 65) with comorbid physical and mental diseases, in order to define detailed treatment strategies for this patient group who is at high risk of inappropriate BZD use. These subjects are often excluded from trials as they suffer from more than one disorder. As a consequence, participants of trials commonly do not represent the average BZD user and thus the findings of these studies might not apply to the actual BZD user group. Therefore, research studies with these subjects are needed in order to define BZD prevention and reduction strategies for the people most in need.

Furthermore, available treatment options should be compared in terms of clinical outcome so that the optimal strategies for this high risk group can be defined.

ANS, HPA axis and RT measurements should be taken several times prior to and after BZD administration in order to define time-dependent changes and distinguish between transient and relatively lasting effects of BZDs. Different levels of BZD dependence severity, different BZD types, high and low doses users as well as short-term and long-term users should be compared on these measurements. Perceived anxiety, sedation, and side effect levels should be measured prior and post BZD intake with validated self-report questionnaires in order to assess whether the found stress system effects are associated with their therapeutic (anxiolytic and sedative) and their adverse effects. Cortisol in hair may be a good opportunity to assess the effects of chronic BZD use on the HPA axis, as changes can be detected relatively easily.[116] The time of the last BZD intake as well as the reason for BZD use should be reported. Ideally, psychomotor speed and attention impairments should not only be measured by RT tasks, but also by other tasks that are more similar to real life activities (i.e., driving simulation, working at a machine simulation).

Implications for Clinical Practice

As BZDs are an effective short-term, symptomatic treatment for stress, anxiety and insomnia,[11] they should be prescribed for rapid symptom relief when needed. More effort should be put into restricting prescriptions to the licensed durations of use (typically: 4 weeks anxiolytics, 2 weeks hypnotics) by preparing patients beforehand that their BZD use will only be short-term.[20] Generally, GPs have three options regarding BZD prescriptions: 1) Prevent the use of BZDs, 2) Prescribe BZDs for short-term use only and already invest in discontinuation strategies at the start, or 3) Accept BZD use when benefits outweigh risks.

Option 1: BZD use can be prevented by informing patients about the drawbacks of BZDs and offering them a (non-) pharmacological

alternative treatment (see table 2). As GPs who felt more comfortable in dealing with anxious and depressed patients issued less inappropriate BZD prescriptions, GPs need to be trained in how to refuse BZD prescriptions when inappropriate [25,46] and acquire good knowledge on alternative treatment options.[25,28] Trainings are for example offered by the *Dutch Institute for Responsible Drug Use (Instituut voor Verantwoord Medicijngebruik).*[47]

Option 2: If patients suffer from acute severe stress, anxiety or insomnia, prevention of short-term BZD treatment for fast symptom relief may not always be possible. In these cases, short-term use needs to be prevented from becoming long-term use. GPs can use the risk factors for inappropriate BZD use (older age, physical and psychological comorbidity) to identify patients at risk. All patients and the 'high risk' group in particular, should be informed right at the start of BZD treatment that their BZD treatment will only be short–term, so that expectations are clear. If anxiety or insomnia is mild or transient (e.g. related to a specific situation), symptoms may improve so that no other treatment is needed and BZDs can be discontinued. For subjects who are in need of longer-term treatment for anxiety and insomnia, alternative treatments should be used from the start. For anxiety disorders, pharmacological treatment with SSRIs and TCAs (for patients who do not suffer from ANS related comorbidities) should be accompanied by non-pharmacological treatment options (i.e., exposure therapy, cognitive therapy, relaxation, etc.) so that not only symptom reduction, but also a cure of the underlying disorder is targeted. For insomnia, non-pharmacological treatments such as information about sleep physiology and hygiene should be attempted first. When insomnia is severe and disabling, cognitive therapy directed at sleep, as well as tradozon or mitrazapine may be prescribed instead of BZDs. As soon as this treatment has built up its full effectiveness, BZD discontinuation can be initiated and actively be supported by the GP. Minimal intervention such as a discontinuation letter with the advice to taper BZD use off gradually is a common strategy to end BZD

treatment.[22] If this intervention is unsuccessful, the GP should commence and actively support gradual dose reduction.[20,117,118] For patients, who experience severe distress during the discontinuation of BZDs, low-dose flumazenil infusion may be a potent aid to reduce the severity of withdrawal symptoms.[20,119]

Option 3: In treatment resistant patients with physical and psychological comorbidities and little problem-solving as well as coping abilities,[120] long-term BZD treatment may not always be avoidable. However, research showed that a lack of response to antidepressants is often caused by suboptimal prescribing practices (such as prescriptions of insufficiently low doses or for too short durations of use).[121,122] As a consequence, subjects are declared as treatment resistant and longer-term BZD use is justified according to the treatment protocol, although these patients possibly could have been helped by antidepressant treatment if the regime had been followed well. This calls for more accurate prescribing practices in general and more cautiousness before issuing a BZD prescription. For those patients who have been proven to be treatment resistant and chronic BZD treatment is indicated, treatment must be monitored closely to observe if symptom reduction is actually achieved by the use of BZDs as there is little evidence for BZDs effectiveness during chronic use. This constitutes a difficult task since patients insist on BZDs enduring effectiveness (probably due to memory impairments, the fear of symptom recurrence and experienced withdrawal effects), although the limited research on this topic does not support this view. As use of a high daily dose of BZDs was found to be associated with prolonged RTs, this small subgroup of high dose BZD users should enter a BZD discontinuation (or at least reduction) program. This goes especially for older subjects who are more sensitive to the adverse effects of BZDs due to altered drug metabolism and pharmacodynamics. Further, GPs should closely monitor the drug regime of their patients to avoid aversive drug interactions and question their patients about the perceived side effects. Prospective observational studies in long-term BZD users and

clinical trials on BZD discontinuation will have to investigate associations between biological indicators, clinical symptoms and side effects, to shed more light on this important matter. In the meantime, intermittent use may help to maintain the anxiolytic and hypnotic effectiveness of BZDs longer than in daily use.[21] With these action alternatives, the GP is put in the position of a risk manager who weighs the advantages and disadvantages of BZD use for certain patients.

PART F) CONCLUSIONS AND FINAL REMARKS

In this large research cohort, BZD use was mainly initiated by patients with a diagnosis of insomnia or anxiety. The most vulnerable patients, i.e. the old and psychologically or physically ill, were at highest risk of inappropriate (and especially chronic) BZD use. Patients with a diagnosis of insomnia and alcohol dependence or those who used antidepressants were at highest risk of BZD dependence. BZD users did not differ from non-users on most HPA axis and ANS measures, indicating tolerance development. However, a higher dose of BZD use was associated with prolonged RTs, suggesting that tolerance to this psychomotor effect of BZDs does not seem to develop completely.

Many chronic BZD users seem to believe in the maintained effectiveness of the BZDs, although supportive research evidence is missing. Additionally, chronic BZD users are usually those who suffer from the most severe anxiety and insomnia. This raises the question, if BZDs are actually still effective in reducing symptoms of anxiety and insomnia, and if not, if subjects should continue taking BZDs for such a long time. Future research should focus on long-term therapeutic and side effects of BZDs use, so that a clear risk benefit ratio can be established for long-term BZD users. Despite continuing attempts to do so, no such risk-benefit ratio could be established yet. A wise man once said: “Men love to wonder, and that is the seed of science.”[123] So there is still hope.

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Summary in Dutch, German and English
List of Abbreviations
List of Publications
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ENGLISH SUMMARY

Benzodiazepines are a class of psychotropic drugs with anxiolytic, sedative, muscle-relaxant and hypnotic properties. In clinical practice, they are mainly used to manage the symptoms of anxiety and insomnia. There is a broad evidence-based knowledge foundation which showed benzodiazepines' therapeutical effectiveness in short-term use. However, as benzodiazepine use is associated with a high risk of side effects, tolerance, and dependence development, prescription guidelines recommend to limit benzodiazepine prescriptions to short-term treatment of two to three months. Still, benzodiazepine users and prescribers do not always adhere to these guidelines and long-term benzodiazepine use – oftentimes over many years- is a common phenomenon. Furthermore, many benzodiazepine users use very high dosages or receive prescriptions for more than one type of benzodiazepine, which can easily and unnecessarily lead to dose escalation. As many benzodiazepine users are long-term users, prescribing decisions for these patients should be based on clinical research. Nevertheless, studies in long-term users are scarce. This thesis therefore investigated the determinants and consequences of long-term BZD use on the data of the Netherlands Study of Depression and Anxiety (NESDA), which is a longitudinal, observational cohort study of 2981 adults aged 18-65 years.

Our first aim was to identify the independent correlates of benzodiazepine use in general, as well as of new, inappropriate and chronic benzodiazepine use and of benzodiazepine dependence. Of the NESDA sample, 429 subjects (15.0%) used benzodiazepines. Of these benzodiazepine users, only 15.2% used benzodiazepines according to international prescription guidelines. Most users (82.5%) exceeded the recommended duration of safe use, but some also surpassed the recommended dosages or had prescriptions for more than one type of benzodiazepine at a time. Older age, being single, unemployment, treatment in secondary care, more general practitioner contacts in

the past six months, (more severe) anxiety, depression, comorbidity, insomnia, and use of antidepressants were independently associated with benzodiazepine use (chapter two). Older age and chronic illnesses were independently associated with inappropriate benzodiazepine use. We concluded that mentally or physically vulnerable subjects were most likely to use benzodiazepines. The most vulnerable (i.e. old and physically ill) benzodiazepine users were at highest risk of inappropriate benzodiazepine use and are thus in need of close monitoring, support and possibly benzodiazepine reduction programs.

During the two year follow-up period, benzodiazepine use was initiated by 4.9% of the benzodiazepine non-users at baseline (chapter three). Initiated use was predicted by insomnia, enduring anxiety symptoms, entering secondary care during follow-up and past benzodiazepine use. Positive life events during follow-up reduced the likelihood of benzodiazepine initiation. Of the BZD users at baseline, 54.2% continued use during the entire follow-up period. Continuation of benzodiazepine use was predicted by higher age, severe anxiety, and a long duration of BZD use. Subjects who were discharged from specialized health care centres, were more likely to discontinue their benzodiazepine use. We concluded that insomnia and anxiety were the main risk factors of initiated use, while advanced age and anxiety severity were the main risk factors of continued use.

Benzodiazepine dependence was measured by the three following dimensions: awareness of the own problematic benzodiazepine use, preoccupation with the use of benzodiazepines and lack of compliance with the therapeutic regimen (chapter four). Problematic use was independently associated with more general practitioner contacts in the past six months and severity of insomnia. Preoccupation was related to anxiety severity, antidepressant use, alcohol dependence, and a higher daily dosage of BZDs. Lack of compliance was associated with higher age, unemployment, insomnia, antidepressant use, and alcohol dependence. As benzodiazepine users with insomnia, antidepressant use and alcohol

dependence scored high on two out of three benzodiazepine dependence dimensions, they were the highest risk group. The concomitant psychopathology and substance dependence may severely compromise these subjects' quality of life. Therefore, close monitoring and more appropriate symptom treatment is needed.

As the prescribers may affect the benzodiazepine use of their patients, we also established the general practitioner characteristics of patient benzodiazepine use (chapter five). Not much research has been conducted on this topic and usually the patient characteristics formed the focus of previous research, so that there was not much literature available which our findings could have been compared to. In the NESDA study, patient benzodiazepine use and inappropriate use did not vary significantly between general practitioners. Furthermore, patient benzodiazepine use and inappropriate use were only associated with a minor fraction of the general practitioner characteristics. The general practitioners' perceived disability to differentiate unhappiness from depression was weakly associated with less patient benzodiazepine use and higher professional comfort and competence with mental health care of the general practitioners correlated with less inappropriate patient benzodiazepine use. Our results indicate that general practitioner characteristics are barely associated with patient benzodiazepine use. Instead, patient characteristics seem to be more decisive in whether benzodiazepines are used (inappropriately) or not.

Our second aim was to examine whether there is evidence that (chronic) benzodiazepine use affects the functioning of two human stress systems, the hypothalamic-pituitary-adrenal axis and the autonomic nervous system. Most of the previous research on the hypothalamic-pituitary-adrenal axis was of experimental nature and investigated the short-term effects of benzodiazepines on the stress hormone cortisol as the end product of the stress axis. Short-term benzodiazepine use was found to suppress cortisol levels in these studies. Research on the effects of long-term benzodiazepine administration on the hypothalamic-pituitary-

adrenal axis was hardly existent. In the NESDA study, benzodiazepine users displayed slightly lower evening cortisol levels as compared to non-users, but did not differ on any other cortisol indicator (chapter six). As BZDs are often taken at night time before going to bed, the reduced cortisol levels in the evening may reflect a transient suppressive effect of the benzodiazepines on the hypothalamic-pituitary-adrenal axis.

Regarding the autonomic nervous system, short-term benzodiazepine use was repeatedly found to suppress sympathetic nervous system activity and heart rate variability. However, findings between studies were inconsistent. Furthermore, it was unclear if benzodiazepines maintain their effects on the autonomic nervous system in chronic use. Therefore, we investigated the prospective association between transitions in benzodiazepine use and autonomic nervous system alterations. After adjustment for covariates, subjects who had initiated benzodiazepine use during the follow-up period displayed a decrease in sympathetic activity while chronic users showed an increase in sympathetic activity (chapter seven). No effects of benzodiazepines on parasympathetic activity were detected. This finding suggests that benzodiazepines suppress sympathetic activity in short-term use, and that these effects remain, but become smaller, in longer term users, potentially due to tolerance development.

Our third aim was to investigate whether the relationship between benzodiazepine use and increased reaction time would persist in long-term benzodiazepine use or whether tolerance to this effect of the BZDs would develop (chapter eight). Short-term administration of benzodiazepines was found to prolong reaction time in many experimental studies. However, studies on long-term benzodiazepine use did not always adjust for important confounders and showed inconsistent results. We investigated the relationship between benzodiazepine use and reaction time in benzodiazepine users of the NESDA study. We found that chronic high dosage benzodiazepine users had longer reaction times than non-users, which was not the case with low dosage users. This indicates

that tolerance to this side effect of the benzodiazepines did not develop (completely).

Conclusions

In this large research cohort, benzodiazepine use was mainly initiated by patients with a diagnosis of insomnia or anxiety. The most vulnerable patients, i.e. the old and psychologically or physically ill, were at highest risk of inappropriate (and especially chronic) benzodiazepine use. Patients with a diagnosis of insomnia and alcohol dependence or those who used antidepressants were at highest risk of benzodiazepine dependence. Benzodiazepine users only differed from non-users on few stresssystem measures, indicating small effects and the development of tolerance. However, a higher dose of benzodiazepine use was associated with prolonged reaction times, suggesting that tolerance to this psychomotor effect of benzodiazepines does not seem to develop completely.

Many chronic benzodiazepine users seem to believe in the maintained effectiveness of the benzodiazepines, although supportive research evidence is largely missing. Additionally, chronic benzodiazepine users are usually those who suffer from the most severe anxiety and insomnia. This raises the question whether benzodiazepines are actually still effective in reducing symptoms of anxiety and insomnia. Future research should focus on long-term therapeutic effects and side effects of benzodiazepine use, so that a clear risk-analysis can be established for long-term benzodiazepine users.

DEUTSCHE ZUSAMMENFASSUNG

Benzodiazepine sind psychotrope Medikamente mit angstlösender, zentral muskelrelaxierender, sedierender und hypnotischer Wirkung. In der klinischen Praxis werden sie vor allem verschrieben zur Reduktion von Angst-, Unruhe-, und Schlafstörungssymptomen. Für die *kurzfristige* Effektivität der Benzodiazepine besteht eine breite empirische Fundierung. Da die Einnahme jedoch mit einem hohen Risiko für Nebenwirkungen, Toleranzentwicklung und Abhängigkeit einhergeht, empfehlen internationale Verschreibungsrichtlinien, nur streng zeitlich befristete Benzodiazepine Rezepte für die Dauer von zwei bis drei Monaten auszustellen. Dennoch halten sich die Patienten und die verschreibenden Ärzte nicht immer an diese Richtlinien. Die Prävalenz des chronischen Benzodiazepine Gebrauchs – teilweise über den Zeitraum vieler Jahre - ist hoch. Darüber hinaus erhalten viele Patienten zu hohe Dosierungen oder Rezepte für mehr als einen Benzodiazepine Wirkstoff. Da viele Benzodiazepine Nutzer Langzeitkonsumenten sind, sollten Verschreibungsentscheidungen für diese Patienten auf den Ergebnissen klinischer Studien basieren. Dennoch beschäftigen sich nur wenige wissenschaftliche Studien mit Langzeitkonsumenten. Aus diesen Gründen untersuchte die vorliegende Dissertation die Determinanten und Konsequenzen von *langfristigem* Benzodiazepine Konsum. Als Grundlage dienten die Daten der Niederländischen Studie zu Depression und Angst (NESDA). Dabei handelt es sich um eine longitudinale Kohorten Studie mit einer Stichprobe von 2 981 Teilnehmern im Alter von 18 bis 65 Jahren.

Das erste Ziel dieser Dissertation war die Identifikation der unabhängigen Korrelate und Determinanten von Benzodiazepine Konsum im Allgemeinen, sowie von neuem, inadäquatem und chronischen Konsum und Benzodiazepine Abhängigkeit. In der NESDA Studie befanden sich 429 Benzodiazepine Konsumenten (15.0%). Nur 15.2% der Nutzer nahmen Benzodiazepine konform der internationalen

Verschreibungsrichtlinien ein. Die meisten Verstöße lagen in der Überschreitung der empfohlenen Länge des Gebrauchs (82.5%). Es wurde jedoch auch die vorgeschriebene tägliche Dosierung überschritten und/oder mehr als ein Benzodiazepine Wirkstoff zugleich eingenommen. Folgende Faktoren waren mit dem Gebrauch von Benzodiazepinen assoziiert: fortgeschrittenes Alter, alleinstehend sein, Arbeitslosigkeit, psychiatrische Behandlung, viele Hausarztkontakte im letzten halben Jahr, das Vorliegen einer ernsthaften Angststörung, Schlafstörungen, einer depressiven Störung oder einer komorbiden Störung (Angst und Depression) sowie der Gebrauch von Antidepressiva (Kapitel zwei). Je fortgeschrittener das Alter und und je höher die Anzahl der vorliegenden chronischen, körperlichen Erkrankungen waren, desto höher lag der inadäquate Konsum von Benzodiazepinen. Daraus lässt sich schließen, dass mentale und physische Anfälligkeit häufig mit der Einnahme von Benzodiazepinen einhergeht. Die empfindlichsten Menschen dieser Gruppe, nämlich Menschen fortgeschrittenen Alters, die an physischen Krankheiten litten, zeigten das höchste Risiko für die unangemessene Einnahme von Benzodiazepinen.

Während der zweijährigen follow-up Periode wurden 4.9% der Studienteilnehmer, die zuvor keine Benzodiazepine gebraucht hatten, zu Benzodiazepine Nutzern (Kapitel drei). Der Beginn der Einnahme von Benzodiazepinen wurde durch das Auftreten von Schlafstörungen, andauernden Angstsymptomen, dem Start einer Behandlung in einer psychiatrischen Einrichtung und Konsum von Benzodiazepinen in der Vergangenheit vorhergesagt. Positive Lebensereignisse, die während dieser zweijährigen Periode auftraten, reduzierten das Risiko der Einnahme von Benzodiazepinen. Mehr als die Hälfte der Teilnehmer, die zu Beginn der Studie Benzodiazepine nahmen (54.2%), setzten den Gebrauch über die komplette Messperiode hinweg fort. Dieser chronische Konsum wurde durch ein fortgeschrittenes Alter, ernsthafte Angst und eine lange vorangegangene Dauer des Konsums von Benzodiazepinen vorhergesagt. Wir schlussfolgerten daraus, dass Schlafstörungen und Angst die größten

Risikofaktoren für den Beginn der Einnahme von Benzodiazepinen sind. Fortgeschrittenes Alter und das Vorliegen ernsthafter Angstsymptome bilden jedoch die größten Risikofaktoren für den chronischen Gebrauch.

Abhängigkeit von Benzodiazepinen wurde durch die Dimensionen *Bewusstsein des problematischen Konsums von Benzodiazepinen*, (zwanghafte) *gedankliche Beschäftigung* (mit der Einnahme von) Benzodiazepinen und *mangelnde Befolgung der Rezeptvorgaben* gemessen (Kapitel vier). Die Anzahl der Kontakte mit dem Hausarzt in den letzten sechs Monaten sowie die Schwere der Schlafstörung gingen mit einem höheren Bewusstsein des problematischen Benzodiazepine Konsums einher. Der Schweregrad der Angstsymptome, der Gebrauch von Antidepressiva, Alkoholabhängigkeit und eine höhere Tagesdosierung der Benzodiazepine hingen mit einer stärkeren (zwanghaften,) gedanklichen Beschäftigung mit Benzodiazepinen zusammen. Fortgeschrittenes Alter, Arbeitslosigkeit, Schlafstörungen, Antidepressiva Gebrauch und Alkoholabhängigkeit waren assoziiert mit mangelnder Befolgung der Rezeptvorgaben (zum Beispiel durch Überschreitungen der Tagesdosis). Da Benzodiazepine Konsumenten mit Schlafstörungen, Alkoholabhängigkeit und gleichzeitigem Gebrauch von Antidepressiva hohe Werte auf zwei der drei Abhängigkeitsdimensionen hatten, ist dies die Gruppe mit dem höchsten Abhängigkeitsrisiko. Komorbide Psychopathologie und Substanzabhängigkeit kann die Lebensqualität der Betroffenen erheblich beeinträchtigen. Darum sollten die Symptome der betroffenen Patienten in regelmäßigen Kontrollbesuchen abgefragt und adäquat behandelt werden.

Da die verschreibenden Ärzte den Benzodiazepine Konsum ihrer Patienten möglicherweise beeinflussen, untersuchten wir zudem die Einstellungen und Eigenschaften von *Hausärzten* als mögliche Korrelate des Benzodiazepine Konsums ihrer Patienten (Kapitel fünf). Bislang existieren zu dieser Fragestellung nur sehr wenige empirische Studien. Der Fokus lag in der Vergangenheit meist auf den Eigenschaften der Patienten selbst. Die Prävalenz des Benzodiazepine Konsums der Patienten im

Allgemeinen sowie des inadäquaten Gebrauchs unterschieden sich nicht signifikant zwischen den untersuchten Hausärzten. Darüber hinaus war der Konsum von Benzodiazepinen unter den Patienten nur mit sehr wenigen Eigenschaften der Hausärzte assoziiert. Lediglich die vom Hausarzt wahrgenommene, eigene Unfähigkeit, Traurigkeit von Depression zu unterscheiden ging mit leicht weniger Benzodiazepine Konsum der Patienten einher. Bei Hausärzten, die sich im Umgang mit psychisch kranken Patienten kompetent fühlten, wichen weniger Patienten in ihrem Benzodiazepine Konsum von den Richtlinien ab. Dies weist darauf hin, dass die Einstellungen und Eigenschaften von Hausärzten kaum mit dem Konsum von Benzodiazepinen unter den Patienten einhergehen. Stattdessen scheinen die Patienteneigenschaften entscheidender für den (inadäquaten) Konsum von Benzodiazepinen zu sein.

Das zweite Ziel dieser Dissertation war es zu untersuchen, ob es empirische Belege dafür gibt, dass der chronische Konsum von Benzodiazepinen die Funktion der zwei menschlichen Stresssysteme (Hypothalamus-Hypophysen-Nebennierenrinden-Achse und Autonomes Nervensystem) beeinflusst. Der Großteil der bisherigen empirischen Studien war experimentell und untersuchte die kurzfristigen Effekte der Benzodiazepine auf das Stresshormon Kortisol als Endprodukt der Hypothalamus-Hypophysen-Nebennierenrinden- Achse. In diesen Studien wurde gezeigt, dass der Konsum von Benzodiazepinen die Kortisol Produktion unterdrückt, ob dieser Effekt bei langfristigem Gebrauch bestehen bleibt, wurde allerdings nicht betrachtet. In der NESDA Studie fanden wir, dass Konsumenten von Benzodiazepinen niedrigere Abendkortisolwerte hatten als Nicht-Konsumenten (Kapitel sechs). Es wurden allerdings auf keinem anderen Kortisolindikator Unterschiede gefunden. Da Benzodiazepine meist abends vor dem Schlafengehen eingenommen werden, könnten die reduzierten Kortisolwerte am Abend darauf hindeuten, dass Benzodiazepine auch bei Langzeitnutzern einen transienten, suppressiven Effekt auf die Hypothalamus-Hypophysen-Nebennierenrinden-Achse haben.

Bezüglich des Autonomen Nervensystems wurde bisher hauptsächlich der Effekt von kurzzeitigem Konsum von Benzodiazepinen in experimentellen Studien untersucht. Ein Teil der Studien berichtete, dass kurzzeitiger Benzodiazepine Konsum die Aktivität des sympathischen Nervensystems sowie die Herzratenvariabilität verringert. Jedoch existierten ebenso gegenteilige Resultate, die Ergebnisse waren also inkonsistent. Darüber hinaus war unklar, ob die Effekte der Benzodiazepine auf das Autonome Nervensystem bei Langzeitnutzern bestehen bleiben oder sich eine Toleranz entwickelt. Aus diesem Grund haben wir die prospektiven Zusammenhänge zwischen Veränderungen im Gebrauch von Benzodiazepinen und Veränderungen der Aktivität des Autonomen Nervensystems untersucht. Probanden, die während der zweijährigen follow-up Periode mit dem Gebrauch von Benzodiazepinen begonnen hatten, zeigten eine Verringerung der sympathischen Aktivität. Demgegenüber bestand bei chronischen Konsumenten von Benzodiazepinen ein Anstieg der sympathischen Aktivität (Kapitel sieben). Es konnten keine Effekte auf das parasympathische Nervensystem gefunden werden. Diese Ergebnisse legen nahe, dass Benzodiazepine die Aktivität des sympathischen Nervensystems im Kurzzeitgebrauch verringern. Dieser Effekt bleibt im Langzeitgebrauch bestehen, wird jedoch – möglicherweise durch Toleranzentwicklung - kleiner.

Das dritte Ziel dieser Dissertation war es zu untersuchen, ob der häufig gefundene Zusammenhang zwischen der Einnahme von Benzodiazepinen und längeren Reaktionszeiten langfristig bestehen bleibt oder eine Toleranzentwicklung stattfindet (Kapitel acht). Der Großteil der bestehenden Studien fand, dass sich die Reaktionszeiten im Labor nach Einnahme von Benzodiazepinen in der Interventionsgruppe gegenüber der Kontrollgruppe verlängerten. Vereinzelte Studien untersuchten auch die Effekte von Langzeitkonsum auf Reaktionszeiten. Diese zeigten allerdings, möglicherweise aufgrund von Designunterschieden, inkonsistente Ergebnisse. Wir betrachteten den Zusammenhang zwischen Langzeitbenzodiazepinegebrauch und Reaktionszeiten von Konsumenten

aus der NESDA Studie: Chronische Nutzer, die hohe Tagesdosierungen einnahmen, hatten in dieser Stichprobe erhöhte Reaktionszeiten. Dies war nicht der Fall für Konsumenten mit niedrigeren Dosierungen. Dieses Ergebnis deutet an, dass keine vollständige Toleranzentwicklung für die Effekte der Benzodiazepine auf Reaktionszeit in Langzeitkonsumenten vorliegt.

Schlussfolgerungen

Im Rahmen der vorliegenden Kohorten Studie begannen hauptsächlich Personen mit einer Angststörung oder Schlafproblemen mit der Einnahme von Benzodiazepinen. Die emotional anfälligsten Patienten, nämlich die fortgeschrittenen Alters und mit psychischen und körperlichen Erkrankungen, waren am meisten von inadäquater Benzodiazepine Nutzung betroffen. Probanden mit Schlafproblemen, Alkoholabhängigkeit und Antidepressiva Gebrauch waren häufig abhängig von Benzodiazepinen. Benzodiazepine Nutzung ging nur mit kleinen Aktivitätsveränderungen der beiden Stresssysteme einher, was auf eine Toleranzentwicklung hindeutet. Hohe Benzodiazepine-Tagesdosierungen waren mit einer verlängerten Reaktionszeit assoziiert. Dieses Ergebnis zeigt, dass sich keine komplette Toleranz bezüglich dieser Effekte der Benzodiazepine zu entwickeln scheint.

Viele chronische Benzodiazepine Nutzer scheinen an die anhaltende Effektivität dieses Medikaments zu glauben, obwohl kaum stützende, empirische Belege für die bleibende therapeutische Wirkung vorhanden sind. Darüber hinaus sind die chronischen Konsumenten von Benzodiazepinen meist diejenigen, die an den schwerwiegendsten Angst- und Schlafstörungen leiden. Dies wirft die Frage auf, ob Benzodiazepine im Langzeitgebrauch noch ausreichend effektiv sind, um Angst- und Schlafstörungssymptome zu verringern. Zukünftige Untersuchungen sollten sich auf die langfristigen therapeutischen Effekte und Nebenwirkungen richten, mit dem Ziel, eine deutliche Kosten-Nutzen-Analyse für Langzeitgebraucher zu erarbeiten.

NEDERLANDSE SAMENVATTING

Benzodiazepines zijn psychotrope middelen met anxiolytische, sederende, spierverslappende en hypnotische effecten. In de praktijk worden zij voornamelijk ingezet voor de symptoombehandeling van angst en slaapstoornissen. Korte termijn effectiviteit van benzodiazepines werd in verschillende experimentele studies aangetoond. Dit effect gaat gepaard met verschillende bijwerkingen (zoals slaperigheid overdag en verminderd reactie- en concentratievermogen), het ontstaan van tolerantie en het ontwikkelen van verslaving. Daarom bevelen internationale richtlijnen aan het gebruik te beperken tot korte termijn (2-3 maanden). Desondanks houden gebruikers en voorschrijvers van benzodiazepinen zich niet altijd aan deze richtlijnen, en langdurig gebruik – vaak gedurende vele jaren - is een veel voorkomend fenomeen. Bovendien krijgen veel benzodiazepinegebruikers meerdere soorten benzodiazepines tegelijk voorgeschreven, of gebruiken zij een te hoge dosering. Het is belangrijk om het voorschrijfgedrag te baseren op de resultaten van wetenschappelijke studies. Er zijn echter nog weinig studies uitgevoerd onder langetermijngebruikers. Om die reden werd het hoofddoel van dit proefschrift de determinanten en consequenties van lange termijn benzodiazepinegebruik in kaart te brengen. Daarvoor maakte dit proefschrift gebruik van de data van de Nederlandse Studie naar Depressie en Angst (NESDA). NESDA is een longitudinale, prospectieve cohort studie, in welke 2981 deelnemers in de leeftijd tussen 18 en 65 worden gevolgd.

Het eerste doel van dit proefschrift was het in kaart brengen van de onafhankelijke correlaten van benzodiazepinegebruik in het algemeen en van nieuw, inadequaat en chronisch gebruik, evenals van benzodiazepineverslaving. In het NESDA sample gebruikten 429 mensen (15.0%) benzodiazepines. Van deze groep gebruikten maar 15.2% volgens internationale behandelrichtlijnen. Deze overtreding werd meestal veroorzaakt door het overschreiden van de aanbevolen duur

van gebruik (82.5%). Sommige gebruikers overschreden de aanbevolen dagelijkse dosis of gebruikten meerdere soorten benzodiazepines tegelijk. Benzodiazepinegebruik was geassocieerd met oudere leeftijd, alleenstaand zijn, werkeloosheid, behandeld worden in de tweede lijn, meer contacten met de huisarts in de laatste zes maanden, ernst van de angststoornis, depressie, comorbiditeit van angst en depressie en het gebruik van antidepressiva (hoofdstuk twee). Onafhankelijke correlaten van inadequaat benzodiazepinegebruik waren oudere leeftijd en het aantal chronische ziekten. We concludeerden dat psychisch en fysiek kwetsbare mensen een verhoogd risico op het gebruik van benzodiazepines hebben. De meest kwetsbare uit deze groep, namelijk de ouderen en de somatisch zieken, lopen het hoogste risico op inadequaat gebruik.

Tijdens de twee-jaar follow-up periode begonnen 4.9% van de niet-gebruikers vanaf nul met het gebruik van benzodiazepines (hoofdstuk drie). Dit nieuwe benzodiazepinegebruik werd voorspeld door slaapproblemen, aanhoudende angstsymptomen, behandeling in de tweede lijn en benzodiazepinegebruik in het verleden. Positieve levensgebeurtenissen tijdens de follow-up periode reduceerden de kans op het beginnen met benzodiazepines. Van de nieuwe benzodiazepinegebruikers gingen 54.2% tijdens de gehele follow-up periode door met het gebruik van benzodiazepines. Dit chronisch gebruik werd voorspeld door oudere leeftijd, ernstige angstsymptomen, en een lange duur van benzodiazepinegebruik in het verleden. Mensen die uit de tweede lijn ontslagen werden hadden een grotere kans op stoppen van het benzodiazepinegebruik. Concluderend waren slapeloosheid en angst de belangrijkste voorspellers van nieuw benzodiazepinegebruik. Hogere leeftijd en de ernst van angst waren de belangrijkste risicofactoren van chronisch gebruik.

Benzodiazepineverslaving werd door drie dimensies gemeten: (bewustzijn van het) problematisch benzodiazepinegebruik, preoccupatie met de beschikbaarheid van benzodiazepines en gebrek aan therapietrouw (hoofdstuk vier). Het problematisch gebruik werd voorspeld door

meer huisartscontacten in de afgelopen zes maanden en ernst van de slapeloosheid. Preoccupatie met de beschikbaarheid van benzodiazepines was geassocieerd met de ernst van angst, het gebruik van antidepressiva, alcoholverslaving en een hogere dagelijkse dosis benzodiazepines. Gebrek aan therapietrouw was gerelateerd aan hogere leeftijd, werkeloosheid, slapeloosheid, het gebruik van antidepressiva, en een alcoholverslaving. Omdat benzodiazepinegebruikers met slaapproblemen, antidepressivagebruik en alcoholverslaving hoge scores op twee van drie verslavingsdimensies hadden, lopen deze mensen het hoogste risico op het ontwikkelen van een benzodiazepineverslaving. Comorbide psychopathologie en verslaving aan middelen kan de levenskwaliteit van de betrokken mensen ernstig compromitteren. Daarom is het belangrijk de symptomen regelmatig te monitoren en adequaat te behandelen.

Omdat de voorschrijvende huisartsen ook invloed op (inadequaat) gebruik door hun patiënten zouden kunnen hebben, hebben we de eigenschappen en attitudes van huisartsen als mogelijke correlaten van het benzodiazepinegebruik van hun patiënten in kaart gebracht (hoofdstuk vijf). Er is maar weinig onderzoek naar dit onderwerp gedaan en in de meeste studies stonden de karakteristieken van de patiënten centraal. Het benzodiazepinegebruik en het inadequate benzodiazepinegebruik van de NESDA deelnemers verschilden niet significant tussen de verschillende huisartsen. Het benzodiazepinegebruik van de patiënten was daarnaast slechts met enkele karakteristieken van huisartsen geassocieerd. Alleen de door de huisarts waargenomen eigen onbekwaamheid om bedroefdheid van een depressie te onderscheiden was geassocieerd met minder benzodiazepinegebruik onder de patiënten. Bij huisartsen, die zich comfortabel en competent in de omgang met patiënten met psychische stoornissen voelden, kwam minder inadequaat gebruik onder de onderzochte patiënten voor. Onze resultaten duiden erop dat de karakteristieken en attitudes van de huisartsen weinig invloed op het benzodiazepinegebruik van hun patiënten hadden. In plaats daarvan

blijken de karakteristieken van de patiënten veel belangrijker te zijn voor (inadequaat) gebruik van benzodiazepines.

Het tweede doel van dit proefschrift was te onderzoeken of er bewijs is voor de hypothese dat chronisch benzodiazepinegebruik de twee menselijke stresssystemen, de hypothalamus-hypofyse-bijnier-as en het autonome zenuwstelsel beïnvloed. Het grootste deel van onderzoek tot nu toe over de hypothalamus-hypofyse-bijnier as was experimenteel en bekeek de korte termijn effecten van benzodiazepines op het stress hormoon cortisol (als eindproduct van de hypothalamus-hypofyse-bijnier as). Deze korte termijn studies vonden, dat de inname van benzodiazepines cortisolspiegels verlaagden. Er was echter nog weinig onderzoek naar de effecten van lange termijn benzodiazepinegebruik op de hypothalamus-hypofyse-bijnier as gedaan. In de NESDA studie hadden benzodiazepinegebruikers lagere avondcortisolspiegels vergeleken met niet-gebruikers (hoofdstuk zes). Op de andere cortisolindicatoren werden echter geen verschillen tussen benzodiazepinegebruikers en niet-gebruikers ontdekt. Omdat benzodiazepines meestal in de avond voor het naar bed gaan worden ingenomen, zouden de verlaagden avondcortisolwaardes een indicator kunnen zijn voor een tijdelijk onderdrukkend effect van de benzodiazepines op de hypothalamus-hypofyse-bijnier as.

Met betrekking tot het autonome zenuwstelsel werd voornamelijk het effect van korte termijn benzodiazepinegebruik in experimentelen studies onderzocht. In deze studies werd herhaaldelijk gevonden dat benzodiazepines de werking van het sympathische zenuwstelsel onderdrukken en de hartslagvariabiliteit verlagen. Er waren echter ook studies die tegenovergestelde effecten rapporteerden. Bovendien was het onduidelijk of benzodiazepines hun effecten op het autonome zenuwstelsel tijdens langetermijngebruik zouden blijven houden of dat er tolerantie optreed. Vanwege deze tegenstrijdigheden, hebben wij de associatie onderzocht tussen veranderingen in benzodiazepinegebruik en autonome zenuwstelselactiviteit in een twee jaar durende prospectieve

studie. In NESDA lieten de deelnemers die tijdens de follow-up periode met benzodiazepinegebruik waren begonnen een verlaagde sympathische zenuwstelselactiviteit zien (hoofdstuk zeven). Daartegenover hadden chronische gebruikers een verhoogde sympathische zenuwstelselactiviteit. Er werden geen effecten gevonden van het benzodiazepinegebruik op de activiteit van het parasympathische zenuwstelsel. Deze bevindingen duiden erop dat kortetermijn benzodiazepinegebruik sympathische zenuwstelselactiviteit verlaagt en dat dit effect in langetermijngebruik blijft bestaan, maar kleiner wordt vanwege het ontstaan van tolerantie.

Het derde doel van dit proefschrift was de relatie tussen benzodiazepinegebruik en reactietijd te onderzoeken. De reactietijd-verhogende werking van benzodiazepines tijdens kortetermijngebruik is door diverse wetenschappelijke studies aangetoond. Of deze effecten in langetermijngebruik nog steeds aanwezig zijn is echter nauwelijks onderzocht. De weinige bestaande lange termijn studies corrigeerden niet altijd voor belangrijke verstorende variabelen en kwamen tot inconsistente resultaten. Daarom hebben wij de associatie tussen lange termijn benzodiazepinegebruik en reactietijd in deelnemers van de NESDA studie bekeken. We vonden langere reactietijden in chronische benzodiazepinegebruikers, die hoge doseringen gebruikten in vergelijking tot niet gebruikers. Dit verschil werd niet tussen gebruikers van lagere doseringen en niet gebruikers geconstateerd. Deze resultaten suggereren dat in hoge dosis gebruikers geen volledige tolerantie tot het effect van benzodiazepine op reactietijd ontstaat.

Conclusies

In deze grote cohortstudie begonnen voornamelijk deelnemers met angst en slaapproblemen het gebruik van benzodiazepines. De meest kwetsbare deelnemers, de ouderen met chronische lichamelijke ziektes, liepen het hoogste risico op inadequaat benzodiazepinegebruik. Deelnemers met slaapproblemen en alcoholverslaving en deelnemers die antidepressiva gebruikten waren ernstiger verslaafd aan benzodiazepines.

Benzodiazepinegebruikers verschilden maar weinig van niet gebruikers op de meeste indicatoren van de stress systemen. Deze kleine effecten van benzodiazepines op de stress systemen suggereren het ontstaan van tolerantie voor het suppressieve effect van benzodiazepines op het autonome zenuwstelsel en de hypothalamus-hypofyse-bijnier as. Desondanks waren de reactietijden in langetermijngebruikers nog steeds verhoogd.

Veel chronische benzodiazepinegebruikers lijken in de aanhoudende effectiviteit van de benzodiazepines te geloven, hoewel er maar weinig empirisch bewijs voor deze bewering is. Bovendien zijn chronische gebruikers over het algemeen die mensen met de meest ernstige angst en slaapproblematiek. Daarom is het maar de vraag of benzodiazepines die over een langere termijn gebruikt worden nog steeds effectief angstsymptomen en slaapproblemen kunnen reduceren. Toekomstig onderzoek moet zich op de therapeutische effecten en bijwerkingen in langetermijngebruikers richten, zodat een duidelijke kosten/batenanalyse kan worden uitgevoerd.

LIST OF ABBREVIATIONS

ACTH	adrenocorticotropic hormone
AD	antidepressant
ANOVA	analysis of variance
ANS	autonomic nervous system
ATC	anatomical therapeutic code
AUCg	area under the curve with respect to the ground
AUCi	area under the curve with respect to the increase
BAI	Beck Anxiety Inventory
Bendep-SRQ	Benzodiazepine-Dependence-Self-Report-Questionnaire
BZD	benzodiazepine
CAR	cortisol awakening response
CI	confidence interval
CIDI	Composite International Diagnostic Interview
CRH	corticotrophin-releasing-hormone
CRTT	choice reaction time task
CVD	cardiovascular disease
d	Cohen's d
DAQ	Depression Attitude Questionnaire
DDD	Defined Daily Dosage
DSM-IV	Diagnostic and Statistical Manual of Mental Disorder IV
DST	dexamethasone suppression test
ECG	electrocardiogram
fte	full-time equivalents
GABA	gamma-aminobutric acid
GP	general practitioner
GR	glucocorticoid receptor
HPA	hypothalamic - pituitary - adrenal axis
HR	heart rate
HRV	heart rate variability
IAT	Implicit Association Test
ICG	impedance cardiogram
IQR	interquartile range
IRS	Insomnia Rating Scale
IDS-SR	Inventory of Depressive Symptomatology Self Report
LCI	Life Chart Interview
LMM	Linear Mixed Models
LTE-Q	List of Threatening Events Questionnaire
MD	medical doctor
MDD	Major Depressive Disorder
MR	mineralocorticoid receptor
NESDA	Netherlands Study of Depression and Anxiety
NEO-FFI	Neuroticism Extraversion Openness-Five Factor Inventory
OR	odds ratio

PEP	pre-ejection period
PVN	paraventricular nucleus
PNS	parasympathetic nervous system
PNCQ	Perceived Need for Care Questionnaire
RSA	respiratory sinus arrhythmia
RT	reaction time
SD	standard deviation
SNS	sympathetic nervous system
SPSS	Statistical Package for Social Science
SSRI	selective serotonin reuptake inhibitor
t	time point
TCA	Tricyclic Antidepressant
TIC-P	Trimbos/iMTA questionnaire for costs associated with psychiatric illness
UBOS-C	Utrecht Burn-Out Scale
VU-AMS	Vrije Universiteit Ambulatory Monitoring System
WHO	World Health Organization

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Leonie Manthey was born on March 15th 1983 in Herdecke, Germany. After finishing secondary school at Gymnasium Ennepetal in 2002, Germany, she spent several months in France and England. In 2003 she started her studies of psychology at the Business and Information Technology School in Iserlohn, Germany. Three years later Mrs. Manthey received her Bachelor of Science with honours. After her graduation, she moved to the Netherlands to study Clinical Psychology at Leiden University and received her Master of Science with honours in 2007. During most of her study period and after her graduation, she worked at the human resources consultancy Kienbaum Executive Consultants in Gummersbach, Germany and Amsterdam. In June 2008, she started the work described in this dissertation at the Department of Psychiatry of the Leiden University Medical Center under supervision of E.J. Giltay (MD, PhD), T. van Veen (PhD), Prof. F.G. Zitman (MD, PhD) and Prof. B.W.J.H Pennix PhD). During her period as a PhD student, Mrs. Manthey was enrolled at the post-doc Master programme in Epidemiology at the Vrije Universiteit of Amsterdam and obtained the Master of Science degree in 2011. Furthermore, she was enrolled in an educational program for trainers in personality development. Mrs. Manthey attended national and international congresses in Amsterdam, Istanbul, Copenhagen and Bielefeld. In 2012 she moved back to Germany (Düsseldorf). Since April 2012 Mrs. Manthey is working at the Institute of Psychology of the Fernuniversität Hagen in the Department of Psychological Methods, Diagnostics and Evaluation of Prof. K.-H. Renner.