Determinants and consequences of long-term benzodiazepine use

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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.

Reference List

1. Lader M. Benzodiazepines - Opium of Masses. *Neuroscience*. 1978;3:159-165.
2. Neutel CI. The epidemiology of long-term benzodiazepine use. *International Review of Psychiatry*. 2005;17:189-197.
3. Van Hulten R, Heerdink ER, Bakker A, et al. Benzodiazepine pathways in the chronically ill. *Pharmacoepidemiol Drug Saf*. 1999;8:325-330.
4. Weil A, Rosen W. From Chocolate to Morphine: Everything You Need to Know About Mind-Altering Drugs (Paperback). Mariner Books (1998).
5. Kapadia N, Fox D, Rowlands G, et al. Developing primary care services for high-dose benzodiazepine-dependent patients: A consultation survey. *Drugs-Education Prevention and Policy*. 2007;14:429-442.
6. Lekka NP, Paschalis C, Beratis S. Suicide attempts in high-dose benzodiazepine users. *Comprehensive Psychiatry*. 2002;43:438-442.
7. College voor zorgverzekeringen. GIPeilingen 2009 Ontwikkelingen genees- en hulpmiddelengebruik. *Genees- en hulpmiddelen Informatie Project | september 2010*. 2010.
8. Manthey L, Giltay EJ, van Veen T, et al. Determinants of Initiated and Continued Benzodiazepine Use in the Netherlands Study of Depression and Anxiety. *Journal of Clinical Psychopharmacology*. 2011;31:774-779.
9. Bartlett G, Abrahamowicz M, Grad R, et al. Association between risk factors for injurious falls and new benzodiazepine prescribing in elderly persons. *Bmc Family Practice*. 2009;10:1.
10. Luijendijk HJ, Tiemeier H, Hofman A, et al. Determinants of chronic benzodiazepine use in the elderly: a longitudinal study. *Br J Clin Pharmacol*. 2008;65:593-599.
11. Kerngroep Multidisciplinaire Richtlijn Angststoornissen. Richtlijnherziening van de Multidisciplinaire richtlijn Angststoornissen (tweede revisie). Richtlijn voor de diagnostiek, behandeling en begeleiding van volwassen patiënten met een angststoornis. 2011.
12. Knuistingh Neven A, Lucassen P, Bonsema K, et al. Practice guideline for insomnia and hypnotics (Dutch College of Genera; Practitioners). [In Dutch: NHG-Standaard Slapeloosheid en slaapmiddelen]. *Huisarts & Wetenschap*. 2005;48:402-415.

13. Marks IM, Swinson RP, Basoglu M, et al. Alprazolam and Exposure Alone and Combined in Panic Disorder with Agoraphobia - A Controlled-Study in London and Toronto. *British Journal of Psychiatry*. 1993;162:776-787.
14. Westra HA, Stewart SH, Teehan M, et al. Benzodiazepine use associated with decreased memory for psychoeducation material in cognitive behavioral therapy for panic disorder. *Cognitive Therapy and Research*. 2004;28:193-208.
15. Landelijke Stuurgroep Multidisciplinaire Richtlijnontwikkeling in de GGZ. Multidisciplinaire Richtlijn Angststoornissen. Utrecht: CBO / Trimbosinstituut. 2003.
16. Jindal RD. Insomnia in Patients with Depression Some Pathophysiological and Treatment Considerations. *Cns Drugs*. 2009;23:309-329.
17. Boeuf-Cazou O, Niezborala M, Marquie JC, et al. Factors associated with psychoactive drug initiation in a sample of workers in France: results of the VISAT cohort study. *Pharmacoepidemiology and Drug Safety*. 2010;19:296-305.
18. Manthey L, van Veen T, Giltay EJ, et al. Correlates of (inappropriate) benzodiazepine use: the Netherlands Study of Depression and Anxiety (NESDA). *British Journal of Clinical Pharmacology*. 2011;71:263-272.
19. Dealberto MJ, Seeman T, Mcavay GJ, et al. Factors related to current and subsequent psychotropic drug use in an elderly cohort. *Journal of Clinical Epidemiology*. 1997;50:357-364.
20. Lader M. Benzodiazepines revisited-will we ever learn? *Addiction*. 2011;106:2086-2109.
21. Suzuki Y, Edge J, Mimaki T, et al. Intermittent Clonazepam Treatment Prevents Anticonvulsant Tolerance in Mice. *Epilepsy Research*. 1993;15:15-20.
22. Voshaar RO, Gorgels W, Mol A, et al. Predictors of relapse after discontinuation of long-term benzodiazepine use by minimal intervention: a 2-year follow-up study. *Family Practice*. 2003;20:370-372.
23. Jorm AF, Grayson D, Creasey H, et al. Long-term benzodiazepine use by elderly people living in the community. *Australian and New Zealand Journal of Public Health*. 2000;24:7-10.
24. Barnas C, Whitworth AB, Fleischhacker WW. Are Patterns of Benzodiazepine Use Predictable - A Follow-Up-Study of Benzodiazepine Users. *Psychopharmacology*. 1993;111:301-305.

25. Anthierens S, Habraken H, Petrovic M, et al. The lesser evil? Initiating a benzodiazepine prescription in general practice: a qualitative study on GPs' perspectives. *Scand J Prim Health Care*. 2007;25:214-219.
26. Bendtsen P, Hensing G, McKenzie L, et al. Prescribing benzodiazepines - a critical incident study of a physician dilemma. *Social Science & Medicine*. 1999;49:459-467.
27. Cook JM, Marshall R, Masci C, et al. Physicians' perspectives on prescribing benzodiazepines for older adults: A qualitative study. *Journal of General Internal Medicine*. 2007;22:303-307.
28. Parr JM, Kavanagh DJ, Young RM, et al. Views of general practitioners and benzodiazepine users on benzodiazepines: A qualitative analysis. *Social Science & Medicine*. 2006;62:1237-1249.
29. Herings RMC, Stricker BHC, Deboer A, et al. Benzodiazepines and the Risk of Falling Leading to Femur Fractures - Dosage More Important Than Elimination Half-Life. *Archives of Internal Medicine*. 1995;155:1801-1807.
30. Barbone F, McMahon AD, Davey PG, et al. Association of road-traffic accidents with benzodiazepine use. *Lancet*. 1998;352:1331-1336.
31. Pfeiffer PN, Ganoczy D, Zivin K, et al. Benzodiazepines and Adequacy of Initial Antidepressant Treatment for Depression. *Journal of Clinical Psychopharmacology*. 2011;31:360-364.
32. Zugelj U, Zupancic M, Komidar L, et al. Self-reported Adherence Behavior in Adolescent Hypertensive Patients: The Role of Illness Representations and Personality. *Journal of Pediatric Psychology*. 2010;35:1049-1060.
33. Chapman BP, Roberts B, Duberstein P. Personality and longevity: knowns, unknowns, and implications for public health and personalized medicine. *J Aging Res*. 2011;2011:759170(Epub).
34. Levine DA. 'Pharming': the abuse of prescription and over-the-counter drugs in teens. *Current Opinion in Pediatrics*. 2007;19:270-274.
35. Fresan A, Minaya O, Cortes-Lopez JL, et al. Demographic and clinical features related to benzodiazepine dependence in psychiatric patients. *Salud Mental*. 2011;34:103-109.
36. Myrick H, Anton RF. Treatment of alcohol withdrawal. *Alcohol Health Res World*. 1998;22:38-43.

37. Voyer P, Preville M, Martin LS, et al. Factors Associated with Self-Rated Benzodiazepine Addiction among Community-Dwelling Seniors. *Journal of Addictions Nursing*. 2011;22:46-56.
38. Kan CC, Hilberink SR, Breteler MHM. Determination of the main risk factors for benzodiazepine dependence using a multivariate and multidimensional approach. *Comprehensive Psychiatry*. 2004;45:88-94.
39. Kurtz SP, Surratt HL, Levi-Minzi MA, et al. Benzodiazepine dependence among multidrug users in the club scene. *Drug and Alcohol Dependence*. 2011;119:99-105.
40. Lavie E, Fatseas M, Denis C, et al. Benzodiazepine use among opiate-dependent subjects in buprenorphine maintenance treatment: correlates of use, abuse and dependence. *Drug Alcohol Depend*. 2009;99:338-344.
41. Jarbrink K, Carlsten A, Frederiksen SO. Swedish physicians' inclination to prescribe benzodiazepines: differences between regions and characteristics of the prescriber. *Scandinavian Journal of Public Health*. 1999;27:22-29.
42. Bjorner T, Laerum E. Factors associated with high prescribing of benzodiazepines and minor opiates - A survey among general practitioners in Norway. *Scandinavian Journal of Primary Health Care*. 2003;21:115-120.
43. Linden M, Gothe H. Specialty training and the personal use of benzodiazepines by physicians affect their proneness to prescribe tranquilizers. *Pharmacopsychiatry*. 1998;31:42-47.
44. Hadsall RS, Freeman RA, Norwood GJ. Factors Related to the Prescribing of Selected Psychotropic-Drugs by Primary Care Physicians. *Social Science & Medicine*. 1982;16:1747-1756.
45. Zandstra SM, Furer JW, van de Lisdonk EH, et al. What caused the ten-fold difference in the number of long-term prescriptions for benzodiazepines between the general practices? 2008;67-84.
46. Cormack MA, Howells E. Factors Linked to the Prescribing of Benzodiazepines by General-Practice Principals and Trainees. *Family Practice*. 1992;9:466-471.
47. Dutch Institute of Responsible Drug Use (2012).
48. Desouza EB. Neuroendocrine Effects of Benzodiazepines. *Journal of Psychiatric Research*. 1990;24:111-119.

49. Zahner MR, Li DP, Pan HL. Benzodiazepine inhibits hypothalamic presympathetic neurons by potentiation of GABAergic synaptic input. *Neuropharmacology*. 2007;52:467-475.
50. Rohrer T, VanRichthofen C, Schulz C, et al. The stress-, but not corticotropin-releasing hormone-induced activation of the pituitary-adrenal axis in man is blocked by alprazolam. *Hormone Metabolic Research*. 1994;26:200-206.
51. Marty J, Gauzit R, Lefevre P, et al. Effects of Diazepam and Midazolam on Baroreflex Control of Heart-Rate and on Sympathetic Activity in Humans. *Anesthesia and Analgesia*. 1986;65:113-119.
52. Pomara N, Willoughby LM, Ritchie JC, et al. Interdose elevation in plasma cortisol during chronic treatment with alprazolam but not lorazepam in the elderly. *Neuropsychopharmacology*. 2004;29:605-611.
53. Abelson JL, Curtis GC, Cameron OG. Hypothalamic-pituitary-adrenal axis activity in panic disorder: Effects of alprazolam on 24 h secretion of adrenocorticotropin and cortisol. *Journal of Psychiatric Research*. 1996;30:79-93.
54. Backberg M, Ultenius C, Fritschy JM, et al. Cellular localization of GABA(A) receptor alpha subunit immunoreactivity in the rat hypothalamus: Relationship with neurones containing orexigenic or anorexigenic peptides. *Journal of Neuroendocrinology*. 2004;16:589-604.
55. Loup F, Weinmann O, Yonekawa Y, et al. A highly sensitive immunofluorescence procedure for analyzing the subcellular distribution of GABA(A) receptor subunits in the human brain. *Journal of Histochemistry & Cytochemistry*. 1998;46:1129-1139.
56. Bateson AN. Basic pharmacologic mechanisms involved in benzodiazepine tolerance and withdrawal. *Current Pharmaceutical Design*. 2002;8:5-21.
57. Cowley DS, RoyByrne PP, Radant A, et al. Benzodiazepine Sensitivity in Panic Disorder - Effects of Chronic Alprazolam Treatment. *Neuropsychopharmacology*. 1995;12:147-157.
58. Tsigos C, Chrousos GP. Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. *Journal of Psychosomatic Research*. 2002;53:865-871.
59. Vreeburg SA, Hoogendijk WJG, van Pelt J, et al. Major Depressive Disorder and Hypothalamic-Pituitary-Adrenal Axis Activity Results From a Large Cohort Study. *Archives of General Psychiatry*. 2009;66:617-626.

60. Vreeburg SA, Zitman FG, van Pelt J, et al. Salivary Cortisol Levels in Persons With and Without Different Anxiety Disorders. *Psychosomatic Medicine*. 2010;72:340-347.
61. Tsuji H, Larson MG, Venditti FJ, et al. Impact of reduced heart rate variability on risk for cardiac events - The Framingham Heart Study. *Circulation*. 1996;94:2850-2855.
62. Carney RM, Blumenthal JA, Stein PK, et al. Depression, heart rate variability, and acute myocardial infarction. *Circulation*. 2001;104:2024-2028.
63. Curtis GC, Abelson JL, Gold PW. Adrenocorticotropic hormone and cortisol responses to corticotropin-releasing hormone: changes in panic disorder and effects of alprazolam treatment. *Biol Psychiatry*. 1997;41:76-85.
64. Fries E, Hellhammer DH, Hellhammer J. Attenuation of the hypothalamic-pituitary-adrenal axis responsivity to the Trier Social Stress Test by the benzodiazepine alprazolam. *Psychoneuroendocrinology*. 2006;31:1278-1288.
65. Lopez AL, Kathol RG, Noyes R, Jr. Reduction in urinary free cortisol during benzodiazepine treatment of panic disorder. *Psychoneuroendocrinology*. 1990;15:23-28.
66. McIntyre IM, Norman TR, Burrows GD, et al. Alterations to plasma melatonin and cortisol after evening alprazolam administration in humans. *Chronobiol Int*. 1993;10:205-213.
67. Osman OT, Hsiao JK, Potter WZ. Dose-dependent effects of intravenous alprazolam on neuroendocrine, biochemical, cardiovascular, and behavioral parameters in humans. *Psychopharmacology (Berl)*. 1993;111:295-300.
68. Coiro V, Volpi R, Casti A, et al. Naloxone decreases the inhibitory effect of alprazolam on the release of adrenocorticotropin/cortisol induced by physical exercise in man. *British Journal of Clinical Pharmacology*. 2011;71:951-955.
69. Manthey L, Giltay EJ, van Veen T, et al. Long-Term Benzodiazepine Use and Salivary Cortisol The Netherlands Study of Depression and Anxiety (NESDA). *Journal of Clinical Psychopharmacology*. 2010;30:160-168.
70. Christensen P, Lolk A, Gram LF, et al. Benzodiazepine-induced sedation and cortisol suppression. A placebo-controlled comparison of oxazepam

and nitrazepam in healthy male volunteers. *Psychopharmacology (Berl)*. 1992;106:511-516.

71. Gram LF, Christensen P. Benzodiazepine suppression of cortisol secretion: a measure of anxiolytic activity? *Pharmacopsychiatry*. 1986;19:19-22.
72. Giordano R, Grottoli S, Brossa P, et al. Alprazolam (a benzodiazepine activating GABA receptor) reduces the neuroendocrine responses to insulin-induced hypoglycaemia in humans. *Clinical Endocrinology*. 2003;59:314-320.
73. Ikeda T, Doi M, Morita K, et al. Effects of Midazolam and Diazepam As Premedication on Heart-Rate-Variability in Surgical Patients. *British Journal of Anaesthesia*. 1994;73:479-483.
74. Kitajima T, Kanbayashi T, Saito Y, et al. Diazepam reduces both arterial blood pressure and muscle sympathetic nerve activity in human. *Neuroscience Letters*. 2004;355:77-80.
75. Stratton JR, Halter JB. Effect of A Benzodiazepine (Alprazolam) on Plasma Epinephrine and Norepinephrine Levels During Exercise Stress. *American Journal of Cardiology*. 1985;56:136-139.
76. Tsugayasu R, Handa T, Kaneko Y, et al. Midazolam More Effectively Suppresses Sympathetic Activations and Reduces Stress Feelings During Mental Arithmetic Task Than Propofol. *Journal of Oral and Maxillofacial Surgery*. 2010;68:590-596.
77. Tulen JHM, Man in't Veld AJ. Noninvasive indices of autonomic regulation after alprazolam and lorazepam: Effects on sympathovagal balance. *Journal of Cardiovascular Pharmacology*. 1998;32:183-190.
78. Agelink MW, Majewski TB, Andrich J, et al. Short-term effects of intravenous benzodiazepines on autonomic neurocardiac regulation in humans: A comparison between midazolam, diazepam, and lorazepam. *Critical Care Medicine*. 2002;30:997-1006.
79. Linnoila M, Stapleton JM, Lister R, et al. Effects of Single Doses of Alprazolam and Diazepam, Alone and in Combination with Ethanol, on Psychomotor and Cognitive Performance and on Autonomic Nervous-System Reactivity in Healthy-Volunteers. *European Journal of Clinical Pharmacology*. 1990;39:21-28.
80. Vogel LR, Muskin PR, Collins ED, et al. Lorazepam reduces cardiac vagal modulation in normal subjects. *Journal of Clinical Psychopharmacology*. 1996;16:449-453.

81. Yazawa K, Adachi V, Owa N, et al. Can sedation reduce the cardiac stress during gastrointestinal endoscopy? A study with non-invasive automated cardiac flow measurement by color Doppler echocardiography. *Scandinavian Journal of Gastroenterology*. 2002;37:602-607.
82. Tulen JHM, Moleman P, Boomsma F, et al. Dose-Dependent Effects of Intravenous Lorazepam on Cardiovascular Activity, Plasma-Catecholamines and Psychological Function During Rest and Mental Stress. *Psychopharmacology*. 1991;105:77-83.
83. Adinoff B, Mefford I, Waxman R, et al. Vagal Tone Decreases Following Intravenous Diazepam. *Psychiatry Research*. 1992;41:89-97.
84. Farmer MR, Vaile JC, Osman F, et al. A central gamma-aminobutyric acid mechanism in cardiac vagal control in man revealed by studies with intravenous midazolam. *Clinical Science*. 1998;95:241-248.
85. Galletly DC, Williams TB, Robinson BJ. Periodic cardiovascular and ventilatory activity during midazolam sedation. *British Journal of Anaesthesia*. 1996;76:503-507.
86. Michaloudis D, Kochiadakis G, Georgopoulou G, et al. The influence of premedication on heart rate variability. *Anaesthesia*. 1998;53:446-453.
87. Wilhelm FH, Roth WT. Acute and delayed effects of alprazolam on flight phobics during exposure. *Verhaltenstherapie*. 1998;8:38-47.
88. Unrug A, Bener J, Barry RJ, et al. Influence of diazepam and buspirone on human heart rate and the evoked cardiac response under varying cognitive load. *International Journal of Psychophysiology*. 1997;25:177-184.
89. Tulen JHM, Mulder G, Pepplinkhuizen L, et al. Effects of Lorazepam on Cardiac Vagal Tone During Rest and Mental Stress - Assessment by Means of Spectral-Analysis. *Psychopharmacology*. 1994;114:81-89.
90. Licht CMM, De Geus EJC, Zitman FG, et al. Association Between Major Depressive Disorder and Heart Rate Variability in the Netherlands Study of Depression and Anxiety (NESDA). *Archives of General Psychiatry*. 2008;65:1358-1367.
91. Licht CM, de Geus EJ, Van DR, et al. Longitudinal evidence for unfavorable effects of antidepressants on heart rate variability. *Biol Psychiatry*. 2010;68:861-868.

92. Licht CMM, Penninx BWJH, De Geus EJC. Cardiac Sympathetic Activity Is Not Influenced by Depression But by Antidepressants. *Psychophysiology*. 2009;46:S116-S116.
93. Buffett-Jerrott SE, Stewart SH. Cognitive and sedative effects of benzodiazepine use. *Current Pharmaceutical Design*. 2002;8:45-58.
94. Gorenstein C, Bernik MA, Pompeia S. Differential Acute Psychomotor and Cognitive Effects of Diazepam on Long-Term Benzodiazepine Users. *International Clinical Psychopharmacology*. 1994;9:145-153.
95. Golombok S, Moodley P, Lader M. Cognitive Impairment in Long-Term Benzodiazepine Users. *Psychological Medicine*. 1988;18:365-374.
96. Kleykamp BA, Griffiths RR, Mintzer MZ. Dose Effects of Triazolam and Alcohol on Cognitive Performance in Healthy Volunteers. *Experimental and Clinical Psychopharmacology*. 2010;18:1-16.
97. O'Neill WM, Hanks GW, Simson P, et al. The cognitive and psychomotor effects of morphine in healthy subjects: a randomized controlled trial of repeated (four) oral doses of dextropropoxyphene, morphine, lorazepam and placebo. *Pain*. 2000;85:209-215.
98. Mcleod DR, Hoehn-Saric R, Labib AS, et al. Six weeks of diazepam treatment in normal women: effects on psychomotor performance and psychophysiology. *J Clin Psychopharmacol*. 1988;8:83-99.
99. Hindmarch I, Parrott AC, Arenillas L. Repeated Dose Comparison of Dichloralphenazone, Flunitrazepam and Amylobarbitone Sodium on Some Aspects of Sleep and Early Morning Behavior in Normal Subjects. *British Journal of Clinical Pharmacology*. 1977;4:229-233.
100. Smirne S, Ferini-Strambi L, Pirola R, et al. Effects of flunitrazepam on cognitive functions. *Psychopharmacology (Berl)*. 1989;98:251-256.
101. Voshaar RCO, Verkes RJ, van Luijtelaar GLJM, et al. Effects of additional oxazepam in long-term users of oxazepam. *Journal of Clinical Psychopharmacology*. 2005;25:42-50.
102. Sakol MS, Power KG. The effects of long-term benzodiazepine treatment and graded withdrawal on psychometric performance. *Psychopharmacology (Berl)*. 1988;95:135-138.
103. Schrijvers D, de Bruijn ERA, Maas Y, et al. Action monitoring in major depressive disorder with psychomotor retardation. *Cortex*. 2008;44:569-579.

104. Kruse WHH. Problems and Pitfalls in the Use of Benzodiazepines in the Elderly. *Drug Safety*. 1990;5:328-344.
105. Bowie MW, Slattum PW. Pharmacodynamics in older adults: a review. *Am J Geriatr Pharmacother*. 2007;5:263-303.
106. Albrecht S, Hering W, Ihmsen H, et al. Pharmacokinetic-pharmacodynamic modelling in early phase II drug development: A comparative study on young and old volunteers with a benzodiazepine as example. *Anasthesiologie Intensivmedizin Notfallmedizin Schmerztherapie*. 1999;34:634-637.
107. Ramadan M, Werder S, Preskorn S. Protect against drug-drug interactions with anxiolytics. Safe use of benzodiazepines, buspirone, and propranolol. *Family Practice*. 2006;5:
108. Desta Z, Soukhova NV, Flockhart DA. Inhibition of cytochrome P450 (CYP450) isoforms by isoniazid: Potent inhibition of CYP2C19 and CYP3A. *Antimicrobial Agents and Chemotherapy*. 2001;45:382-392.
109. Smith TA. Type A gamma-aminobutyric acid (GABAA) receptor subunits and benzodiazepine binding: significance to clinical syndromes and their treatment. *Br J Biomed Sci*. 2001;58:111-121.
110. Rudolph U, Knoflach F. Beyond classical benzodiazepines: novel therapeutic potential of GABA(A) receptor subtypes. *Nature Reviews Drug Discovery*. 2011;10:685-697.
111. Low K, Crestani F, Keist R, et al. Molecular and neuronal substrate for the selective attenuation of anxiety. *Science*. 2000;290:131-134.
112. Crestani F, Martin JR, Mohler H, et al. Mechanism of action of the hypnotic zolpidem in vivo. *British Journal of Pharmacology*. 2000;131:1251-1254.
113. Kales A, Kales JD. Sleep Laboratory Studies of Hypnotic Drugs - Efficacy and Withdrawal Effects. *Journal of Clinical Psychopharmacology*. 1983;3:140-150.
114. Tyrer P, Murphy S, Kingdon D, et al. The Nottingham Study of Neurotic Disorder - Comparison of Drug and Psychological Treatments. *Lancet*. 1988;2:235-240.
115. Russell E, Koren G, Rieder M, et al. Hair cortisol as a biological marker of chronic stress: Current status, future directions and unanswered questions. *Psychoneuroendocrinology*. 2012;37:589-601.

116. Parr JM, Kavanagh DJ, Cahill L, et al. Effectiveness of current treatment approaches for benzodiazepine discontinuation: a meta-analysis. *Addiction*. 2009;104:13-24.
117. Lader M, Russell J. Guidelines for the Prevention and Treatment of Benzodiazepine Dependence - Summary of A Report from the Mental-Health-Foundation. *Addiction*. 1993;88:1707-1708.
118. Hood S, O'Neil G, Hulse G. The role of flumazenil in the treatment of benzodiazepine dependence: physiological and psychological profiles. *Journal of Psychopharmacology*. 2009;23:401-409.
119. Lagro-Janssen AL. Benzodiazepines and the peace of mind of the general practitioner [Benzodiazepinen en de gemoedsrust van de huisarts]. *Huisarts & Wetenschap*. 1993;36:
120. Bridges PK. ". . . and a small dose of an antidepressant might help". *Br J Psychiatry*. 1983;142:626-628.
121. Little JD. Effect of Recommended Dosage Range on the Prescribing of Antidepressants. *Australian and New Zealand Journal of Psychiatry*. 1995;29:304-308.
122. Emerson R.W. Quotation (2012). Available via http://www.brainyquote.com/quotes/keywords/wonder.html. Accessed at May 2012.