Consecutive Treatment Strategies to discontinue Long-term Benzodiazepine Use

A Systematic Evaluation in General Practice

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A Systematic Evaluation in General Practice

Een wetenschappelijke proeve op het gebied van de Medische Wetenschappen

Proefschrift

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door

Richard Christiaan Oude Voshaar

geboren op 13 maart 1973
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The discovery of benzodiazepines

Once upon a time, Leo H Sternbach synthesized a series of compounds based on the quinazoline 3-oxides, which had been the basis of his PhD thesis in Cracow, Poland, in the early 1930s A ring system unknown at that time, a benzodiazepine, had been obtained No biological tests had been carried out with these compounds, but it was hoped that some useful activity might be discovered

In 1955, a team at Hoffmann-La Roche Inc led by Leo Sternbach, decided to study some of these compounds and their derivatives All, but one of these were pharmacologically inert The last one was not tested, instead, it was labeled Ro 5-0690 and shelved because of other research priorities In 1957 Lowell O Randall, one of Sternbach's chemists, turned up the compound and suggested it to be tested He discovered the pharmacologic profile of this compound, later named chlordiazepoxide, that included pronounced sedative, anticonvulsant, and muscle relaxant effects with excellent safety Following clinical confirmation of the useful pharmacologic profile of chlordiazepoxide, this benzodiazepine compound was launched in 1960 under the trade name Librium for the treatment of psychosomatic disorders, anxiety and related symptoms It was followed in 1963 by a second benzodiazepine named diazepam (Valium) When Librium and Valium became known to physicians, their popularity was almost instantaneous and their commercial success was assured In rapid succession many other benzodiazepine derivatives appeared leading to the so-called "benzodiazepine boom" in the 1960s and 1970s Benzodiazepines were generally accepted as a clear improvement upon older psychotropics such as barbiturates, were regarded to be of equally therapeutic efficacy, seemed to show only few side-effects and seemed to exhibit limited risk in overdosing This has led to a dramatically increase in use during 1970s, which would be a happy end if the fairy-tale ended here

Unfortunately, almost simultaneously some concern was growing about the increasing quantity of benzodiazepines consumed This concern is still fed in the 21st century by high prevalence rates of long-term benzodiazepine use, while associated complications become increasingly clear This way, the long-term use of once a promising therapeutic agent of which the synthesis had been described in a thesis in the early 1930s, could become an illness the treatment of which will be evaluated in this thesis

Contents

Chapter 1

Background of (long-term) benzodiazepine usage

[1] Based on Oude Voshaar RC, Gorgels WJMJ, Mol AJJ, Couvée JE, Van Balkom AJLM, and Zitman FG Behandelmethoden om langdung benzodiazepinegebruik te staken [Treatment modalities to discontinue long-term benzodiazepine use] Nederlands Tijdschrift voor Geneeskunde 2001, 137(45) 1347-1350

Introduction

In this chapter, the study is put in a wider perspective by discussing the background of (long-term) benzodiazepine usage First, the actual prevalence rate of benzodiazepine use is presented, followed by the indications and guidelines for benzodiazepine treatment Subsequently, the pharmacological effects of benzodiazepines and the long-term therapeutic efficacy are considered Thereafter, the different side-effects of long-term benzodiazepine use are discussed, classified as dependence, psychomotor functioning and cognitive decline, falls and accidents, and finally suicide/mortality, followed by some economic aspects of benzodiazepine use (costs) Factors are summarised that might explain or contribute to the observed discrepancy between guidelines and clinical practice Finally, some aspects of treatment modalities for the discontinuation of long-term benzodiazepine use are mentioned briefly with respect to the gaps in the literature addressed by this thesis

Prevalence of benzodiazepine use

Benzodiazepines belong to the most prescribed drugs in Western countries In 1998, when this study started, approximately 11 6 million prescriptions for benzodiazepines were issued in The Netherlands, most of them (89%) by general practitioners, and in the case of repeat prescriptions 89% were issued without even any patient-doctor contact [1 2] The demographic characteristics of benzodiazepine users show that two-thirds are female and half are aged 65 or over [1-4] Over the past 5 years, the absolute number of benzodiazepine prescriptions has increased by one million, although a slight decrease was found when corrected for population growth and senescence [1] In the same period, benzodiazepine use in other Western countries also slightly decreased or stabilised [6 7]

The number of benzodiazepine users in the Netherlands was estimated at 1 9 million in 1998, which corresponds to a prevalence rate of 12 2% At least one-third can be considered long-term users (prevalence 4 2 - 5 3% a year) This group received on average 13 prescriptions a year, with an amount of 311 defined daily dosages according to therapeutic dosages of the World Health Organisation (WHO) [1] However, reported prevalence rates of long-term benzodiazepine use differ considerably, which is partially explained by different definitions of long term use [7] In this thesis, long-term benzodiazepine use is defined as use for at least three months for the following reasons firstly, the likelihood of spontaneous discontinuation of benzodiazepine use dramatically decreases after this period [8 11] Secondly, this time window corresponds well with guidelines on the maximum duration of benzodiazepine treatment [12 20] Based on our definition, we estimated the actual prevalence rate of long-term benzodiazepine use in the population to be about 3%, i e , 72 patients in an average Dutch general practice

Indications and guidelines

In the Netherlands, benzodiazepines are registered for 'the symptomatic treatment of pathological anxiety, tension and insomnia' In addition, 'benzodiazepines should be used for short-term treatment of insomnia only if patients are severely disabled or suffering extreme distress' [12] The Dutch Health Care Insurance Council (College voor Zorgverzekeringen) has indicated the use of benzodiazepines for 'short-term treatment (two weeks) of severe insomnia' and 'pathological anxiety and tension', which is 'severe, disabling or subjecting the patient to unacceptable distress' [13] These indications are subject to certain limitations, for example (a) pharmacological treatment of insomnia is justified only in cases of poor daytime functioning, (b) benzodiazepines can be prescribed to make patients with generalised anxiety disorder (GAD) accessible for cognitive-behavioural therapy, and (c) benzodiazepines are only indicated as a temporary adjuvant for anxiety disorders other than GAD [13] The guidelines of the Dutch Society of General Practitioners (Nederlands Huisartsen Genootschap) advise prescribing benzodiazepines for short-term treatment of insomnia only if basic sleep advice does not give any relief [14] In addition, general practitioners should be cautious in using benzodiazepines for anxiety disorders, and should agree *a priori* with patients on the date of cessation [15] According to the Guidelines of the Dutch Society of Psychiatrists (Nederlandse Vereniging voor Psychiatrie), benzodiazepines have a limited place in the treatment of generalised anxiety disorder, uncomplicated panic disorder, and uncomplicated social phobia [16] Finally, none of the Dutch guidelines consider benzodiazepines as a first treatment option for any disorder

The Dutch guidelines correspond well with guidelines in other Western countries According to the recommendations of the US Food and Drug Administration and the US National Health and Medical Research Council, benzodiazepine use should not exceed four months [17 18] The American Psychiatric Association raises 'serious questions' about the long-term use of benzodiazepines [19] In the United Kingdom, the Committee on the Safety of Medicines stated that (a) benzodiazepines are indicated for the short-term relief (two to four weeks only) of anxiety that is severe, disabling or subjecting the individual to unacceptable distress, (b) the use of benzodiazepines to treat short-term mild 'anxiety' is inappropriate and unsuitable, and (c) benzodiazepines should be used to treat insomnia only when it is severe, disabling or subjecting the individual to extreme distress In addition, the lowest dose should be used and treatment should not be continued beyond four weeks [20]

Pharmacological effects of benzodiazepines

Benzodiazepines exert their effects by binding on the gamma-aminobutyric acid receptor type A ($GABA_A$ receptor) The $GABA_A$ receptor complex is a glycoprotein that consists of five subunits, which together form a Cl channel This receptor can be activated by the interaction of two gamma-aminobutyric acid (GABA) molecules, leading to an allosteric modulation, which results in a Cl

influx in the neuron and causes inhibition of that neuron Benzodiazepines bind to a specific site at the $GABA_A$ receptor, and exert their effect by enlarging the inhibitory effects of GABA GABA is the most frequently used inhibitory neurotransmitter in the central nervous system it is used by approximately 40% of the neurones This might explain the broad effects of benzodiazepines [21 23]

Benzodiazepines exert anxiolytic, sedative/hypnotic, muscle relaxant, anticonvulsant, and amnesic effects Different benzodiazepines have different pharmacokinetics, i e , rate of absorption (T_{max}), elimination half-life ($t_{½}$), forming of (in)active metabolites and the apparent volume of distribution, and different pharmacodynamics, i e , the affinity to the receptor (potency) Benzodiazepines are classified as being either hypnotic or anxiolytic depending on the rate of absorption and elimination half-life This classification, however, is rather arbitrary as in certain circumstances the duration of action depends more on dosage than on the elimination half-life [13 24 26]

An important issue in the long-term use of benzodiazepines is the development of tolerance to the differential effects of benzodiazepines Tolerance is defined as a reduced response to a certain dosage or the need for higher dosages to obtain a certain effect Tolerance can be scientifically established by comparing the dose-response curves of long-term benzodiazepine users with those of benzodiazepine-naive controls Most studies on the development of tolerance for the effects of benzodiazepines in humans, however, have been confined to healthy subjects receiving treatment for several weeks [27 30] Studies including long-term benzodiazepine users are scarce, while dose-response studies for most benzodiazepine effects, including the anxiolytic properties, are lacking altogether Nonetheless, many reports present data, which are suggestive for the development of tolerance This issue will therefore be dealt with in the following sections on therapeutic efficacy and adverse effects, looking at each effect separately

Long-term therapeutic efficacy

Benzodiazepines have been proven to be effective for the short-term treatment of both insomnia and anxiety However, long-term use of benzodiazepines is controversial because of the associated side-effects (see below) and the apparent development of tolerance to the therapeutic action Furthermore, it remains unclear to what extent the suppression of withdrawal symptoms are mixed up with long-term efficacy [31] Also significant is the fact that most long-term benzodiazepine users report high levels of psychopathology[32] and high levels of residual anxiety[33 34], which suggests only partial efficacy Moreover, the observation that the severity of these symptoms decreases in patients who lowered their daily dose by taking part in a discontinuation programme[35 36], suggests that long-term benzodiazepine use might even increase their psychopathology level For these patients, continued benzodiazepine treatment might obstruct a more appropriate therapy In addition, recent treatment studies show that

previous or co-morbid long-term benzodiazepine use independently predicted a poorer pharmacological and psychological treatment outcome in patients with anxiety disorders [37 39]

Tolerance to the sedative and hypnotic effects of benzodiazepines is reported to develop after treatment lasting only a few days or weeks [13 14 31] Sleep laboratory studies show a return to baseline values within one to four weeks of treatment with benzodiazepines [40] Nonetheless, most patients claim that some benefit remains and may insist on continuing with the medication Schneider-Helmert *et al* (1988) found that patients reported sleeping longer while taking the drug than after discontinuation It has been suggested that this misperception might be due to the amnesic effect of benzodiazepines [41] A recent meta-analysis on the treatment efficacy of benzodiazepines and zolpidem drew attention to the lack of well-controlled evidence regarding the efficacy of long-term exposure to benzodiazepines in patients with primary insomnia [42] Oswald *et al* (1982) evaluated the self-reported effects of lormetazepam 2 mg, nitrazepam 5 mg, and placebo during treatment week one and treatment week 24 in 100 patients complaining of poor sleep not diagnosed as having primary or secondary insomnia Compared to placebo both benzodiazepines significantly improved the quality of sleep in the first week, but not in the last week of treatment Sleep latency significantly decreased in patients treated with benzodiazepines compared to those treated with placebo in the first as well as the last week of treatment However, the graphs show that for patients receiving nitrazepam this effect was not found consistently throughout the whole treatment period [43]

Recent studies have questioned the anxiolytic efficacy of prolonged benzodiazepine treatment [31 44] Moreover, hardly any randomised controlled treatment trials have been carried out on the continuous therapeutic value of benzodiazepines for chronic anxiety Only two controlled studies addressing this aspect have been published [45 46] Rickels *et al* (1983) concluded that a significant number of patients with generalised anxiety disorder benefited from prolonged diazepam treatment, and that tolerance to the anxiolytic effect did not develop over a 22 week period A closer inspection of this data raises numerous questions It shows that 50% of patients were already using benzodiazepines before entering the study, which meant the baseline anxiety severity was unknown, 30% dropped out, because of fear of addiction, and 50% maintained improvement after switching to placebo [45] The study of Schweizer *et al* (1993) randomised 106 patients diagnosed with panic disorder during an eight-week treatment period with either alprazolam (n=37), imipramine (n=30), or placebo (n=35), after which they were offered a six-month maintenance phase [46] Both alprazolam and imipramine were superior to placebo after eight weeks of treatment All the patients who completed the maintenance phase were panic free after eight months This phase was completed by 27 (73%) patients on alprazolam, 11 (37%) on imipramine, and 10 (29%) on placebo During the maintenance phase, neither tolerance nor increase of daily dosage was observed [46] This study suggests long-term efficacy of alprazolam in panic disorder, although no significant differences between the three groups were detected during the maintenance phase due to low patient numbers at follow-up A subsequent

report of this study on the discontinuation of alprazolam showed that one third of the users could not discontinue alprazolam [47]

Side-effects

The side-effects of benzodiazepine use are discussed below For the purpose of discussion, these effects are categorised as dependence, psychomotor functioning and cognitive decline, falls and accidents, and suicide / mortality

Dependence

Directly after their introduction in the 1960s, the potential of benzodiazepines to induce a state of physical dependence was described in chronic psychiatric patients who abruptly discontinued high-dose benzodiazepine treatment (300 - 600 mg chlordiazepoxide a day) [48 49] In the early 1970s, the first case reports appeared in the scientific literature of patients who had escalated their benzodiazepine dosage beyond the upper limit of the recommended therapeutic range [50-53] At that time, however, little notice was taken of these reports, partly because of the many reports on, and the widespread perception of, the safety of benzodiazepines In 1978, for example, Marks estimated the dependence risk with benzodiazepines as approximately one case per five million patient months 'at risk' for all recorded cases, and probably less than one case per 50 million months in therapeutic use [54] This conclusion was almost entirely based on patients who had escalated their dose beyond therapeutic levels

The first study of physical dependence in normal-dose benzodiazepine usage was by Covi *et al* (1969, 1973), who described a withdrawal syndrome after discontinuation of 20-week chlordiazepoxide treatment [55 56] Maletzky & Klotter (1976), who reported a survey of 50 patients on therapeutic doses of diazepam, found that some patients had difficulty in discontinuing their diazepam use, experiencing anxiety, tremor, and insomnia [57] Concern about the dependence liability of benzodiazepines grew subsequently This was reflected, for example, in a paper by Lader (1978) entitled "Benzodiazepines - The opium of the masses?" and a paper by Tyrer (1974) entitled "Benzodiazepine Bonanza" [58 59] In the years thereafter, both authors came forward with accumulating evidence for the existence of normal-dose dependence

Tyrer conducted his studies within a clinical context substituting placebo (or propranolol) for diazepam or lorazepam [60] The studies of Lader were laboratory based [61] These studies unequivocally proved that normal-dose dependence, as manifested by a physical withdrawal syndrome, was a real entity and supervened even if the dosage was tapered off Moreover, the withdrawal symptoms of patients withdrawing form high- and low-dose usage were identical [62] Table 1 shows the symptoms of the benzodiazepine withdrawal syndrome

Table 1

Benzodiazepine withdrawal symptoms

Frequently	Less frequently	Rarely
Palpitations	Diarrhoea	Epileptic seizures
Insomnia	Hypersensitivity to sensory stimuli	Confusion / incoherence
Anxiety	Depersonalisation / derealisation	Delusions
Irritability	Abnormal perception of movement	Hallucinations
Restlessness	Appetite loss	
Muscular spasms	Depressed mood	
Tremor	Impaired concentration	
Muscular stiffness	Loss of interest	
Headache	Feeling of sickness	
	Blurred vision	
	Fatigue	

Although normal-dose benzodiazepine dependence was generally accepted, the prevalence rate of withdrawal symptoms remained controversial. Reported prevalence rates of withdrawal symptoms after discontinuation varied widely (range 0 - 100%) mainly because of different study populations or type of assessment.[45 56 60 63 66] A well-controlled study of Busto *et al* (1986) established that about 15-25% of long-term (over 12 months) users develop a definite withdrawal syndrome.[67 68] Generally, the withdrawal syndrome is relatively mild, although a small percentage of patients experience major distress. Most symptoms diminish two weeks after benzodiazepine discontinuation, but prolonged withdrawal syndromes for over a year have been described.[69 70] Large-scale prospective studies evaluating the epidemiology of benzodiazepine withdrawal, however, have not been carried out.

The literature on benzodiazepine dependence mainly concentrates on physical dependence. However, the term dependence also involves certain *psychological* phenomena induced by the repeated taking of a substance.[71 72] The WHO proposed a psycho-physiological-biological model in 1981 for dependence on psycho-active substances, which led to the general substance dependence criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R/IV) and the International Classification of Diseases (ICD-10) (see table 2).

A recent literature review on the definition of benzodiazepine dependence showed that the DSM and ICD substance dependence criteria had only been used in a small number of the 250 papers reviewed.[73] Definitions of benzodiazepine dependence that emphasised the physical aspects were still predominant. Two research groups found, independently of each other, that benzodiazepine dependence can be regarded as a multidimensional concept, including both physical and psychological aspects.[74 75] In 1997, the first study was published that assessed the prevalence of benzodiazepine dependence according to the DSM-III-R and ICD-10 substance dependence criteria.[76] Past-year prevalence rates were found in primary care and psychiatric outpatients of 40% and 63% respectively based on DSM-III-R criteria, and 52% and 69% respectively based on ICD-10 criteria.

Table 2

Criteria for benzodiazepine dependence according to DSM-IV and ICD-10.

DSM-IV: *Three (or more) of the following have been experienced or exhibited at any time in the same 12-month period*	**ICD-10:** *Three or more of the following have been experienced or exhibited at some time during the last year*
- Tolerance	- Tolerance
- Withdrawal	- Physiological withdrawal by reducing or ceasing intake
- Persistent desire or repeated unsuccessful efforts to cut down or control use	- Loss of control
- Substance taken in a larger amount or over a longer period of time than was intended	- -
Great deal of time involved in obtaining or using the substance or recovering from its effects	- Progressive neglect of alternative pleasures or interests, increased amount of time necessary to obtain or take the substance or to recover from its effects
- Important social, occupational or recreational activities given up	- -
- Continued use despite knowledge of persistent or recurrent physical or psychological problems caused or exacerbated by the substance	Persistent use despite evidence of harmful physical or mental consequences
- -	- Craving

Psychomotor functioning and cognitive decline

Experimental studies clearly showed that initial administration of benzodiazepines negatively affected psychomotor performance.[77] Many of the performance-impairing effects of benzodiazepines diminished after repeated administration of benzodiazepines for just a few weeks.[78,79] However, acute challenge tests on long-term benzodiazepine users showed that tolerance does not fully develop for most measures of psychomotor performance. Especially high-dose users and elderly users experienced psychomotor-impairing effects after prolonged use.[80 82]

Benzodiazepines also cause anterograde amnesia, which means benzodiazepines impair recall of what happened or what is learned under drug influence.[84-86] Studies where no effect of benzodiazepines on amnesia was found mostly assessed patients at a specific time of day without taking into account when the previous dose of medication was taken, since the amnesia only lasted a certain number of hours after drug intake. Challenge tests on long-term benzodiazepine users indicated that tolerance did not develop for anterograde amnesia.[83,87 88] Verwey *et al* (2000) evaluated a clinical aspect of anterograde amnesia by prospectively evaluating the presence of anterograde amnesia in people who tried to commit suicide with benzodiazepines.[89] They found considerable memory impairments, also in patients who did not seem to be sedated, and suggested the efficacy of psychiatric consultation could be impaired because patients did not remember the content of the consultation.

Several authors reported a global cognitive deterioration in benzodiazepine users.[90 91] Some researchers are even concerned for prolonged cognitive and generalized intellectual impairment long after benzodiazepine use has been discontinued.[92-94] Rickels *et al* (1999) found that cognitive functions improved for many long-term benzodiazepine users after discontinuation of benzodiazepine intake. It

is not clear whether the cognitive functions fully recovered after discontinuation since no control group was included [44] Rummans *et al* (1993) found that detoxified benzodiazepine dependent patients had significantly more difficulty with tests on learning, and short-term and delayed recall, than the alcohol-dependent and the control group [95] In addition, Tata *et al* (1994) found significant impairment six months after discontinuation of long-term benzodiazepine use in patients' verbal learning and memory, psychomotor, visuo-motor, and visuo-conceptual abilities compared with controls [96] The latter two studies, however, did not match the detoxified benzodiazepine users with controls for the level of anxiety, which might have acted as a confounder Kilic *et al* (1999) found no impairment in explicit memory 3 5 years after treatment with alprazolam compared with patients treated with placebo The difference they found in the weeks immediately after withdrawal was explained by interference of the drug with practice effects on the tests and habituation of anxiety after repeated exposure to the test situation [97]

Recently, a significant association was found between dementia and former use of benzodiazepines in a nested case-control study [98] Furthermore, in a large population-based longitudinal study, chronic benzodiazepine use was associated with an accelerated decline in a global cognitive test (Mini Mental State Examination) and two attention tests (Trail Making Test, part B, Digit Symbol Substitution Test) compared to non-users over a four-year period This study controlled for potential confounders, including the level of depressive symptoms and anxiety, but not for psychiatric diagnosis [99]

Falls and accidents

Benzodiazepines have been associated with a higher incidence of falls, which are presumed to be caused by their sedative and myorelaxant effects A recent meta-analysis on the association between psychotropic drug use and falls in the elderly found an increased risk of 20 - 48% for users of benzodiazepines [100] Five studies directly evaluated the relationship between the use of benzodiazepines and falls leading to hip fractures Four of these studies used a case-control design[101] [104], while the fifth was a prospective cohort study [105] Three of the four case-control studies found a significant increased risk of falls leading to hip fractures in benzodiazepine users [101 103] The four-year prospective cohort study comprised 9516 patients, and found a relative risk ratio of 1 6 for the use of long-acting benzodiazepines [105] A study especially designed to examine differences between short (temazepam) and ultra-short (triazalom) acting benzodiazepines did not find any differences between these agents with respect to the relative risk of falls [106] Moreover, benzodiazepine dosage and simultaneous use of two different benzodiazepines seems to contribute more to an increased risk of falls leading to hip fractures than elimination half-life [103]

The deleterious effects of benzodiazepines on a wide variety of driving-related performance tasks as well as actual driving performance have been demonstrated [107 108] Although an association between the use of benzodiazepines and traffic accidents could not always be confirmed in

epidemiologic studies - three studies did not find a significant association[110-112] - most epidemiologic studies confirmed that the use of benzodiazepines was associated with an increased risk of traffic accidents [112 119] A recent review of case-control studies in this field suggests the use of benzodiazepines approximately doubles the risk of motor vehicle accidents, placing elderly and high-dose users at the highest risk [118] Although the highest risk ratio was found in the first week of benzodiazepine use, the risk ratio for long-term benzodiazepine use remained also significant [118] A recent study also found a greater risk of traffic accidents associated with benzodiazepine use in people younger than 65 A dose-response relationship was evident, while the increased risk was significant for long-acting benzodiazepines used as anxiolytics, as well as for short-acting hypnotics [119]

It is not clear whether the relationship between benzodiazepine use and falls and accidents is a causal one, since depression, anxiety, and insomnia also have an impact on driving behaviour and falls [120] However, a study of psychotropic drugs and accidents in general practice found that benzodiazepine users had a significantly higher risk of having an accident compared with controls, while no elevated risk was found compared to the controls in the periods benzodiazepine users were (temporarily) not taking the drugs [121]

Suicide / mortality

Benzodiazepines are generally thought to be safe in overdose [122] Death after benzodiazepine intoxication is rare, and caused by respiratory depression with aspiration of gastric contents [123] However, benzodiazepines are involved in almost half of suicide attempts [124] Over a ten-year period, 1576 fatal poisonings in the United Kingdom were attributed to benzodiazepines Within this period, the number of suicides based on an overdose of paracetamol was 2002, and for amitryptiline 1083 The fatal toxicity index of benzodiazepines was calculated at 5 9 deaths per million prescriptions, when analyses were restricted to adult deaths classified as suicides, undetermined deaths, and accidents caused by benzodiazepines alone or together with alcohol [125]

Costs

Benzodiazepines are low-priced drugs the median price for a 30-day treatment period of the recommended dosage in the Netherlands varies from € 2 24 for diazepam to € 7 26 for medazepam and clobazam An exception is ketazolam, which is priced at € 18 76 [13] Due to the high prevalence rate of benzodiazepine usage, however, the pharmaceutical costs for benzodiazepines were estimated at € 95 million per year in 1998 Moreover, benzodiazepines had the 7th highest annual increase in drug costs in the Netherlands [1] The costs of associated side-effects, such as falls and traffic accidents, are difficult to estimate Herings *et al* (1994) estimated the costs for treatment of hip fractures associated with the use of benzodiazepines in 1994 at € 15 9 million per year in the Netherlands [126]

Discrepancy between guidelines and clinical practice

The prevalence of long-term benzodiazepine use contrasts with current guidelines on treatment with benzodiazepines Many factors are thought to contribute to this situation These factors include the characteristics of the drugs themselves, the users, the prescribing physicians, as well as certain practical or regulatory aspects There is little scientific evidence, however, about the extent to which, if any, these factors contribute to prolonged use

A major drug-related factor is the dependence liability of benzodiazepines, which can result in craving, drug-seeking behaviour, dose escalation, and a withdrawal syndrome after discontinuation Moreover, the temporary increase of symptoms of anxiety and insomnia as part of the withdrawal syndrome may persuade both patient and doctor to continue treatment Scientific evidence to support this hypothesis is, however, not available

Long term benzodiazepine users are less concerned about the dependence liability and other side-effects of benzodiazepines than the prescribing physicians [127 128] Patients also report a high level of usage satisfaction [129] Satisfaction however, is primarily a subjective factor and could be a consequence of dependence Moreover, the view of patients might be affected by their benzodiazepine use For example, patients might not remember nocturnal awakenings due to anterograde amnesia induced by the use of benzodiazepines [41 130] In addition, the excellent initial efficacy of benzodiazepines might persuade patients to continue their usage despite decreasing effects in the long term It has also been suggested that benzodiazepine intake is a coping mechanism for stress and anxiety, which might decrease the likelihood of discontinuation [131 133] Neurotic or dependent personality traits, frequently found to be associated with long-term benzodiazepine use[134 135], have also been suggested to contribute to a prolonged use of these agents [136] Although many patient factors are thought to contribute to continued benzodiazepine use a survey in England reported that 50% of long-term users expressed a desire to stop taking the medication However, the majority were uncertain whether or not their general practitioner wanted them to continue taking the drugs [127 137]

Physicians also contribute to prolonged benzodiazepine use Despite the lack of evidence for such, some physicians are convinced of the long term therapeutic value of benzodiazepines Furthermore, a survey in the Netherlands showed that a minority of the long term benzodiazepine users were judged by their GPs to be able to discontinue benzodiazepine use [129] Moreover, Cormack and Howells (1992) found that 19 of 24 interviewed GPs expected to save consultation time by prescribing benzodiazepines [138] If alternative treatments have been tried repeatedly in the past, physicians might think they have nothing else to offer [1 132 133] The attitude and capability of individual physicians vary widely, and probably contribute to prolonged benzodiazepine use if they are not interested in psychiatry or do not consider long-term benzodiazepine use a major issue in daily practice [139] Cripwell (1988), for example, pointed out that some GPs cannot tolerate the emotional distress of their patients, as they may believe they have neither the time nor the skills to explore this

distress.[140] Intervention in prescription policy, by giving information to general practitioners, resulted in a decrease in benzodiazepine prescription.[141 142] Moreover, Catalan & Gath (1985) found that brief counselling is as effective as benzodiazepines, and no more time-consuming in the long term than writing a prescription.[143]

Some practical aspects also contribute to a prolonged use of benzodiazepines. Repeat prescriptions, for example, are mainly issued without patient-doctor contact. Moreover, in 10% of such cases, the GP does not know the patient uses benzodiazepines.[129] Such strategies limit the opportunity to evaluate and discuss the necessity of continued treatment with patients. Moreover, in the case of psychiatric co-morbidity, psychiatric screening may prevent long-term benzodiazepine use when alternatives are first choice. Finally, a substantial proportion of long-term users started benzodiazepine treatment during hospital admission and continues treatment thereafter thinking they need it on a long-term basis.[144]

Treatment modalities to discontinue long-term benzodiazepine use

The discrepancy between current guidelines and clinical practice stimulated the development of several treatment strategies to discontinue long-term benzodiazepine use. Because chapter 3 deals specifically with the available knowledge on benzodiazepine discontinuation strategies, this section is limited to some definitions and to the major gaps in literature addressed by this thesis.

Treatment strategies for discontinuation of long-term benzodiazepine usage can be divided into so-called 'minimal interventions' and systematic discontinuation programmes. Minimal interventions invite patients to quit their long-term benzodiazepine usage of their own accord by making them aware of the side-effects. This type of intervention is successful with about one-fifth of patients. Long-term follow-up data about 'minimal' interventions is, however, not available.

Systematic discontinuation programmes are more extensive interventions in which patients discontinue their doses gradually and are guided a by physician. Two-thirds of patients successfully discontinue their benzodiazepine use with the aid of these programmes. To increase the effect, these programmes have been combined with either psychological or pharmacological treatment. Certain methodological issues, however, prevent a clear interpretation of these results. Firstly, systematic discontinuation programmes have never been compared with standard treatment in a randomised controlled fashion. Secondly, these programmes have mainly been tested in second-line settings, while most benzodiazepine users receive their prescriptions from general practitioners. Thirdly, long-term effects are largely unknown as follow-up data are scarce, and available follow-up studies have considerable methodological limitations. Fourthly, although some small, uncontrolled trials suggested that the addition of psychological treatment enhances the success rate of discontinuation, it has never

been examined in a randomised controlled trial. Finally, the associated economic consequences of these programmes have not yet been evaluated.

To tackle the problem of long-term benzodiazepine use in general practice, advisory boards in both the Netherlands and the United Kingdom suggest a minimal intervention to start off with, and to only offer a more intensive, systematic discontinuation programme to those patients who fail to stop by themselves.[145 146] A systematic evaluation of this two-stage care strategy, has never been carried out.

References

1 College voor zorgverzekeringen Gebruik van benzodiazepinen 1993 - 1998 Edited by Piepenbrink JF Geneesmiddelen Informatie Project (GIP-signaal) 2000

2 Van der Waals FW, Mohrs J, Foets M Sex differences among recipients of benzodiazepines in Dutch general practice *British Medical Journal* 1993, 307 363 366

3 Salinsky JV and Doré CJ Characteristics of long-term benzodiazepine users in general practice *Journal of the Royal College of General Practitioners* 1987, 37 202-204

4 Ashton H and Golding JF Tranquillisers prevalence, predictors and possible consequences Data from a large United Kingdom survey *British Journal of Addiction* 1989, 84 541-546

5 Tu K, Mamdani MM, Hux JE, *et al* Progressive trends in the prevalence of benzodiazepine prescribing in older people in Ontario, Canada *Journal of the American Geriatric Society* 2001, 49 1341 1345

6 Taylor S McCracken CFM, Wilson, KCM Extent and appropriateness of benzodiazepine use *British Journal of Psychiatry* 1998, 173 433-438

7 Zandstra SM, Fuhrer JW, Van de Lisdonk EH, *et al* Different study criteria affect the prevalence of benzodiazepine use *Social Psychiatry and Psychiatric Epidemiology* 2002, 37(3) 139 144

8 Williams P, Murray J and Clare A A longitudinal study of psychotropic drug prescription *Psychological Medicine* 1982, 12(1) 201-206

9 Williams P Factors influencing the duration of treatment with psychotropic drugs in general practice a survival analysis approach *Psychological Medicine* 1983, 13(3) 623-633

10 Mant A, Duncan-Jones P, Saltman D, *et al* Development of long-term use of psychotropic drugs by general practice patients *British Medical Journal (Clinical Research Edition)* 1988, 296(6617) 251 254

11 Ishigooka J, Sugiyama T, Suzuki, *et al* Survival analytic approach to long-term prescription of benzodiazepine hypnotics *Psychiatry and Clinical Neurosciences* 1998, 52(5) 541 545

12 Repertorium 98/99 Utrecht Nefarma & Neprofarm, 1999

13 Commissie Farmaceutische Hulp van het College voor zorgverzekekeringen (CVZ) Farmacotherapeutische kompas Amstelveen CVZ, 2002 P 53 66, P 69-81

14 Knuistingh Neven A, Graaff WJ de, Lucassen PLBJ, *et al* NHG-standaard Slapeloosheid en slaapmiddelen *Huisarts en Wetenschap* 1992, 35 212-219

15 Neomagus GJH, Terluin B, Aulbers LPJ, *et al* NHG-standaard Angststoornissen *Huisarts en Wetenschap* 1997, 40 167-175

16 Van Balkom AJLM, Van Dyck R, Van Megen HJGM, *et al* Richtlijn farmacotherapie angststoornissen Nederlandse Vereniging voor Psychiatrie 1998

17 Food and Drug Administration Prescribing of minor tranquillizers *FDA Drug Bulletin* 1980, 10 2 3

18 National Health and Medical Research Council Guidelines for the prevention and management of benzodiazepine dependence Canberra NHMRC, 1991 Monograph series N3

19 Salzman C The APA Task Force report on benzodiazepine dependence, toxicity, and abuse [editorial] *American Journal of Psychiatry* 1991, 148 151-152

20 Committee on the Safety of Medicines Systematic review of the benzodiazepines *British Medical Journal* 1980, 1 910-912

21 Uwe R, Crstanl F, Benke D, *et al* Benzodiazepine actions mediated by specific γ-aminobutyric acid$_A$ receptor subtypes *Nature* 1999, 401 796 800

22 Martin JR and Haefely WE Drugs used for the treatment of anxiety and sleep disorders P 243-278 In Principles of Pharmacology Basic Concepts & Clinical Applications Chapman & Hall, New York 1995

23 Nutt DJ and Malizia AL New insights into the role of the GABA$_A$-benzodiazepine receptor in psychiatric disorder *British Journal of Psychiatry* 2001, 179 390 396

24 Roth T, Roerhs TA A review of the safety profiles of benzodiazepine hypnotics *Journal of Clinical Psychiatry* 1991, 52(suppl 9) 38 41

25 Roth T, Roehrs TA Issues in the use of benzodiazepine therapy *Journal of Clinical Psychiatry* 1992, 53(suppl 6) 14-18

26 Nicholson AN The use of short- and long-acting hypnotics in clinical medicine *British Journal of Clinical Pharmacology* 1981, 11 61S-69S

27 McLeod DR, Hoehn-Saric R, Labib AS, *et al*, Six weeks of diazepam treatment in normal women effects on psychomotor performance and psychophysiology *Journal of Clinical Psychopharmacology* 1988 83 99

28 Lader MH, Curry S, Baker WJ Physiological and psychological effects of clorazepate in man *British Journal of Clinical Pharmacology* 1980, 9 83-90

29 Van Steveninck AL, Wallnofer AE, Schoemaker RC, *et al*, A study of the effects of long term use on individual sensitivity to temazepam and lorazepam in a clinical population *British Journal of Clinical Pharmacology* 1997, 44 267-275

30 Potokar J, Coupland N, Wilson S, *et al* Assessment of $GABA_A$ benzodiazepine receptor (GBzR) sensitivity in patients on benzodiazepines *Psychopharmacology* 1999, 146 180 184

31 Lader MH Limitations on the use of benzodiazepines in anxiety and insomnia are they justified? *European Neuropsychopharmacology* 1999, 9 (Suppl 6) S399 S405

32 Rickels K, Case WG, Schweizer E, *et al* Benzodiazepine dependence management of discontinuation *Psychopharmacology Bulletin* 1990, 26(1) 63-68

33 Haskell D, Cole JO, Schniebolk S, *et al* A survey of diazepam patients *Psychopharmacology Bulletin* 1986, 22(2) 434-438

34 Zitman FG, Couvee JE Chronic benzodiazepine use in general practice patients with depression an evaluation of controlled treatment and taper off Report on behalf of the Dutch Chronic Benzodiazepine Working Group *British Journal of Psychiatry* 2001, 178(4) 317-324

35 Couvée JE, Timmermans EAY, Zitman FG The long-term outcome of a benzodiazepine discontinuation programme in depressed outpatients *Journal of Affective Disorders* 2002, 70(2) 133 141

36 Rickels K, Case WG, Schweizer E, *et al* Long term benzodiazepine users 3 years after participation in a discontinuation program *American Journal of Psychiatry* 1991, 148(6) 757-761

37 Fava GA, Rafanelli C, Grandi S, *et al* Long-term outcome of panic disorder with agoraphobia treated by exposure *Psychological Medicine* 2001, 31(5) 891-898

38 Fava GA, Grandi S, Rafanelli C, *et al* Long term outcome of social phobia treated by exposure *Psychological Medicine* 2001, 31(5) 899-905

39 Van Balkom AJ, de Beurs E, Koele P, *et al* Long term benzodiazepine use is associated with smaller treatment gain in panic disorder with agoraphobia *Journal of Nervous and Mental Disorders* 1996, 184(2) 133 135

40 Kales A, Kales J Sleep laboratory studies of hypnotic drugs Efficacy and withdrawal effects *Journal of Clinical Psychopharmacology* 1983, 3 40-150

41 Schneider-Helmert D Why low-dose benzodiazepine dependent insomniacs can't escape their sleeping pills *Acta Psychiatrica Scandinavica* 1988, 78 706 711

42 Nowell PD, Mazumbar S, Buysse DJ, *et al* Benzodiazepines and zolpidem for chronic insomnia A meta-analysis of treatment efficacy *Journal of the American Medical Association* 1997, 278(24) 2170 2177

43 Oswald I, French C, Adam K, *et al* Benzodiazepine hypnotics remain effective for 24 weeks *British Medical Journal* 1982, 284 860-863

44 Rickels K, Lucki I, Schweizer E, *et al* Psychomotor performance of long-term benzodiazepine users before, during and after benzodiazepine discontinuation *Journal of Clinical Psychopharmacology* 1999, 19(2) 107-113

45 Rickels K, Case G, Downing RW *et al* Long term diazepam therapy and clinical outcome *Journal of the American Medical Association* 1983, 250 767-771

46 Schweizer E, Rickels K, Weiss S, *et al* Maintenance drug treatment of panic disorder I Results of a prospective, placebo controlled comparison of alprazolam and imipramine *Archives of General Psychiatry* 1993 50 51 60

47 Rickels K, Schweizer E, Weiss S, *et al* Maintenance drug treatment of panic disorder II Short- and long-term outcome after drug taper *Archives of General Psychiatry* 1993, 50 61-68

48 Hollister LE, Motzenbecker FP, Degan RO Withdrawal reactions from chlordiazepoxide ("Librium") *Psychopharmacologia* 1961, 2 63-68

49 Hollister LE, Bennett JL, Kimbell I, *et al* Diazepam in newly admitted schizophrenics *Diseases of the Nervous System* 1963, 24 746-750

50 Peters UH, Boeters U Valium-sucht Eine analyse anhand von 8 fallen *Pharmacopsychiatrie-Neuropsychopharmacologie* 1970, 3 339-348

51 Venzlaff V Valiumsucht *Internist Praxis* 1972, 12 349

52 Woody GE, O'Brien CP, Greenstein R Misuse and abuse of diazepam An increasingly common medical problem *International Journal of Addiction* 1975, 10 843-848

53. Blinding A The abuse potential of benzodiazepines with special reference to oxazepam *Acta Psychiatrica Scandinavica* 1978; 60(suppl. 274): 111-116.

54 Marks J. The benzodiazepines: Use, overuse, misuse, abuse *Lancaster* 1978 U K.: MTP.

55 Covi L, Park LC, Lipman RS, *et al* factors affecting withdrawal response to certain minor tranquilizers In J Cole & Wittenborn (Eds.), Drug abuse: Social and psychopharmacological aspects (pp. 93-108). Springfield, IL: Charles C Thomas 1969.

56. Covi L, Lipman RS, Pattison JH, *et al.* Length of treatment with anxiolytic sedatives and response to their sudden withdrawal. *Acta Psychiatrica Scandinavica* 1973; 49: 51-64.

57. Maletzky BM, Klotter J. Addiction to diazepam. *International Journal of Addiction* 1976, 11. 95-115.

58. Lader MH. Benzodiazepines - the opium of the masses? *Neuroscience* 1978, 3 159-165

59. Tyrer, P The benzodiazepine bonanza *The Lancet* 1974; 2. 709-710

60. Tyrer P, Rutherford D, Huggett T Benzodiazepine withdrawal symptoms and propranolol *The Lancet* 1981; 1: 520-522.

61. Petursson H, Lader M Dependence on tranquillizers Oxford: Oxford University Press 1984

62 Hallstrom C, Lader MH Benzodiazepine withdrawal phenomena *International Pharmacopsychiatry* 1981, 16 235-244

63 Laughren TP, Battey Y, Greenblatt DJ, *et al.* A controlled trial of diazepam withdrawal in chronically anxious outpatients. *Acta Psychiatrica Scandinavica* 1982, 65 171-179

64 Hartelius H, Larsson A-K, Lepp M, *et al* A controlled long-term study of flunitrazepam, nitrazepam and placebo, with special regard to withdrawal effects *Acta Psychiatrica Scandinavica* 1978; 58 1-15

65. Tyrer P, Owen R, Dawling S Gradual withdrawal of diazepam after long-term therapy *The Lancet* 1983, 1 1402-1406

66. Petursson H, Lander MH Withdrawal from long-term benzodiazepine treatment *British Medical Journal* 1981; 283: 643-645.

67. Busto U, Sellers EM, Naranjo CA, *et al* Withdrawal reaction after long-term therapeutic use of benzodiazepines. *New England Journal of Medicine* 1986, 315 854-859

68. Busto U, Sellers EM, Naranjo CA *et al* Patterns of benzodiazepine abuse and dependence *British Journal of Addiction* 1986; 81: 87-94.

69 Ashton H. Benzodiazepine withdrawal: An unfinished story? *British Medical Journal* 1984; 288 1135-1140

70. Higgitt A, Fonagy P, Toone B, *et al* The prolonged benzodiazepine withdrawal syndrome. anxiety or hysteria? *Acta Psychiatrica Scandinavica* 1990, 82(2) 165-168

71 WHO Expert committee on addiction-producing drugs, thirteenth report World Health Organisation Technical Report Series 1964, no. 273

72 Edwards G, Arif A, Hodgson R Nomenclature and classification of drug- and alcohol-related problems a WHO Memorandum *Bulletin WHO* 1981, 59 225-242

73. Linssen SM, Breteler MHM, Zitman FG Defining benzodiazepine dependence: the confusion persists *European Psychiatry* 1995; 10 306-311

74. Baillie AJ, Mattick RP. The benzodiazepine dependence questionnaire development, reliability and validity *British Journal of Psychiatry* 1996; 169 276-281

75 Kan CC, Breteler MH, van der Ven AH, *et al* An evaluation of DSM-III-R and ICD-10 benzodiazepine dependence criteria using Rasch modelling *Addiction* 1998; 93 349-359.

76 Kan CC, Breteler MHM, Zitman FG High prevalence of benzodiazepine dependence in outpatient users, based on DSM-III-R and ICD-10 criteria *Acta Psychiatrica Scandinavica* 1997, 96: 85-93

77 Vogel JR Objective measurement of human performance changes produced by antianxiety drugs In Fielding, S , and Lal, H. (eds), Anxiolytics, New York. Futura Publishing Co , 1979, pp 343-374.

78. Aranko K, Mattila MJ, Seppala T Development of tolerance and cross-tolerance to the psychomotor actions of lorazepam and diazepam in man *British Journal of Clinical Psychopharmacology* 1983, 15 545-552

79 Liljequist R, Palva E, Linnoila M. Effects of learning and memory of 2-week treatments with chlordiazepoxide lactam, N-desmethyldiazepam, oxazepam and metholoxazepam, alone or in combination with alcohol. *International Journal of Pharmacopsychiatry* 1979, 14. 190-198

80. Pomara N, Stanley B, Block R, *et al* Increased sensitivity of the elderly to the central depressant effects of diazepam *Journal of Clinical Psychiatry* 1985: 46 185-187

81 Greenblatt DJ, Shader RI, Harmatz JS. Implications of altered drug disposition in the elderly Studies of benzodiazepines *Journal of Clinical Pharmacology* 1989, 29· 866-872.

82 Lord SR, Anstey KJ, Williams P, *et al* Psychoactive medication use, sensory-motor function and falls in older women *British Journal of Clinical Pharmacology* 1995; 39· 227-234

83. Pomara N, Tun H, DaSliva D, *et al* The acute and chronic performance effects of alprazolam and lorazepam in the elderly Relationship to duration of treatment and self-rated sedation *Psychopharmacology Bulletin* 1998, 34(2). 139-153

84 Ghoneim MM, Mewaldt SP Benzodiazepines and human memory a review. *Anesthesiology* 1990, 72. 231-236

85 Curran HV, Schifano F, Lader M. Models of memory dysfunction? A comparison of the effects of scopolamine and lorazepam on memory, psychomotor performance and mood *Psychopharmacology* 1991, 103 83-91

86 Curran H. Benzodiazepines and vigilance performance a review. *Psychopharmacology* 1989; 98: 145-156

87 Lucki I, Rickels K. The behavioural effects of benzodiazepines following long-term use *Psychopharmacology Bulletin* 1986; 22(2): 424-433

88 Lucki I, Rickels K, Geller AM Chronic use of benzodiazepines and psychomotor and cognitive test performance *Psychopharmacology* 1986; 88: 426-433.

89. Verwey B, Eling P, Wientjes H, *et al* Memory impairment in those who attempted suicide by benzodiazepine overdose. *Journal of Clinical Psychiatry* 2000, 61(6) 456-459

90 Bedry R, Dartigues J, Gagnon M, *et al.* The role of benzodiazepines consumption on cognitive functioning in elderly French community residents Group ATPS *Journal of Clinical Research Epidemiology* 1990, 4. 113-145.

91 Golombok S, Moodley P, Lader M. Cognitive impairment in long-term benzodiazepine use *Psychological Medicine* 1988, 18· 365-374

92. Hendler N, Cimini C, Terrence MA, *et al.* A comparison of cognitive impairment due to benzodiazepines and to narcotics *American Journal of Psychiatry* 1980, 137 215-217

93. Bergman H, Borg S, Holm L. Neuropsychological impairment and exclusive abuse of sedatives or hypnotics. *American Journal of Psychiatry* 1980; 137: 215-217.

94. Petursson H, Gudjonsson GH, Lader MH. Psychometric performance during withdrawal from long-term benzodiazepine treatment. *Psychopharmacology (Berl)* 1983, 81. 345-349

95 Rummans TA, Davis LJ, Jr., Morse RM, *et al.* Learning and memory impairment in older, detoxified, benzodiazepine-dependent patients. *Mayo Clinics Proceedings* 1993, 68. 731-7

96. Tata PR, Rollings J, Collins M, *et al* Lack of cognitive recovery following withdrawal from long-term benzodiazepine use *Psychological Medicine* 1994, 24. 203-13

97. Kilic C, Curran HV, Noshirvani H, *et al.* Long-term effects of alprazolam on human memory a 3 5 year follow-up of agoraphobia/panic patients. *Psychological Medicine* 1999, 29 225-231

98 Lagnaoui R, Bégaud B, Moore N, *et al.* Benzodiazepine use and risk of dementia. A nested case-control study. *Journal of Clinical Epidemiology* 2002, 55: 314-318

99. Paterniti S, Dufouil C, Alpérovitch A Long-term benzodiazepine use and cognitive decline in the elderly· the epidemiology of vascular aging study. *Journal of Clinical Psychopharmacology* 2002, 22(3)· 285-293

100 Leipzig RM, Cumming RG, Tinetti ME Drugs and falls in older people a systematic review and meta-analysis. I Psychotropic drugs *Journal of the American Geriatric Society* 1999, 47 30-9.

101. Ray WA, Taylor JA, Meador KG, *et al.* A randomised trial of a consultation service to reduce falls in nursing homes *Journal of the American Medical Association* 1997, 278(7) 557-562

102 Cummings RG, Klineberg RJ Psychotropics, thiazide diuretics and hip fractures in the elderly *The Medical Journal of Australia* 1993, 158(6) 414-417

103. Herings RM, Stricker BH, De Boer A, *et al* Benzodiazepines and the risk of falling leading to femur fractures Dosages more important than elimination half-life *Archives of Internal Medicine* 1995, 155: 1801-1807

104 Peirfitte C, Macouillard G, Thicoipe M, *et al* Benzodiazepines and hip fractures in elderly people case-control study *British Medical Journal* 2001, 322 704-708.

105 Cummings SR, Nivett MC, Browner WS, *et al.* Risk factors for hip fracture in white women *The New England Journal of Medicine* 1995; 332(12)· 767-773

106 Wysowski DK, Baum C, Ferguson WJ, *et al* Sedative-hypnotic drugs and the risk of hip fracture *Journal of Clinical Epidemiology* 1996, 49(1). 111-113

107 Brookhuis KA, Volkerts ER, O'Hanlon JF Repeated dose effects of lormetazepam and flurazepam upon driving performance *European Journal of Clinical Pharmacology* 1990, 39 83-87

108 Van Laar MW, Volkerts ER, Van Willigenburg APP Therapeutic effects and effects on actual driving performance of chronically administered buspirone and diazepam in anxious outpatients *Journal of Clinical Psychopharmacology* 1992, 12 86-95

109 Jick H, Hunter JR, Dinan BJ, *et al* Sedating drugs and automobile accidents leading to hospitalization *American Journal of Public Health* 1981, 71(12) 1399-1400

110 Anonymous Are benzodiazepines a risk factor for road accidents? 'Benzodiazepine/Driving' Collaboration Group *Drug and Alcohol Dependence* 1993, 33(1) 19-22

111 Leveille SG, Buchner DM, Koepsell TD, *et al* Psychoactive medications and injurious motor vehicle collisions involving older drivers *Epidemiology* 1994, 5(6) 591-598

112 Skegg DC, Richards SM, Doll R Minor tranquillisers and road accidents *British Medical Journal* 1979, 1(6168) 917 919

113 Honkanen R, Ertama L, Linnoila M, *et al* Role of drugs in traffic accidents *British Medical Journal* 1980, 281(6251) 1309 1312

114 Ray WA, Fought RL, Decker MD Psychoactive drugs and the risk of injurious motor vehicle crashes in elderly drivers *American Journal of Epidemiology* 1992, 136(7) 873-883

115 Neutel CI Risk of traffic accident injury after a prescription for a benzodiazepine *Annals of Epidemiology* 1995, 5(3) 239-244

116 Longo MC, Hunter CE, Lokan RJ, *et al* The prevalence of alcohol, cannabinoids, benzodiazepines and stimulants amongst injured drivers and their role in driver culpability Part I the prevalence of drugs use in drivers, and characteristics of the drug positive group *Accident Analysis & Prevention* 2000, 32 613 622

117 Longo MC, Hunter CE, Lokan RJ, *et al* The prevalence of alcohol, cannabinoids, benzodiazepines and stimulants amongst injured drivers and their role in driver culpability Part II The relationship between drug prevalence and drug concentration, and driver culpability *Accident Analysis & Prevention* 2000, 32 623-632

118 Hemmelgarn B, Suissa S, Huang A, *et al* Benzodiazepine use and the risk of motor vehicle crash in the elderly *Journal of the American Medical Association* 1997, 278 27-31

119 Barbone F, McMahon AD, Davey PG, *et al* Association of road traffic accidents with benzodiazepine use *The Lancet* 1998, 352 1331 1336

120 Ray WA Psychotropic drugs and injuries among the elderly a review *Journal of Clinical Psychopharmacology* 1992, 12(6) 386-396

121 Binnie GA Psychotropic drugs and accidents in a general practice *British Medical Journal (Clinical Research Edition)* 1983, 287(6402) 1349-1350

122 Gaudreault P, Guay J, Thivierge RL, *et al* Benzodiazepine poisoning Clinical and pharmacological considerations and treatment *Drug safety* 1991, 6 247-265

123 Hojer J, Baehrendtz S, Gustafsson L Benzodiazepine poisoning experience of 702 admissions to an intensive care unit during a 14 year period *Journal of Internal Medicine* 1989, 226 117-122

124 Michel K, Waeber V, Valach L, *et al* A comparison of the drugs taken in fatal and non-fatal self-poisoning *Acta Psychiatrica Scandinavica* 1994, 90 184 189

125 Serfaty M, Masterton G Fatal poisonings attributed to benzodiazepines in Britain during the 1980s *British Journal of Psychiatry* 1993, 163 386-393

126 Herings RMC Geneesmiddelen als determinant van ongevallen Utrecht Universiteit van Utrecht, Faculteit Farmacie, 1994

127 Kendall C Use of benzodiazepines *British Journal of General Practice* 1993, page 34

128 Mah L, Upshur REG Long-term benzodiazepine use for insomnia in patients over the age of 60 discordance of patient and physician perceptions *BMC Family Practice* 2002, 3(9)

129 Vissers FHJA Gebruik van slaap en kalmeringsmiddelen in het dagelijks leven Determinanten, gevolgen en de rol van de huisarts Dissertatie Universiteit van Maastricht, 1998

130 Schneider Helmert D, Kumar A Sleep, its subjective perception, and daytime performance in insomniacs with a pattern of alpha sleep *Biological Psychiatry* 1998, 37 99-105

131 Bish A, Golombok S, Hallstrom C *et al* The role of coping strategies in protecting individuals against long term tranquillizer use *British Journal of Medical Psychology* 1996, 69 101 115

132 Lagro-Janssen ALM, Liberton IJW Profielen van regelmatige gebruikers van benzodiazepinen in een huisartspraktijk *Nederlands Tijdschrift voor Geneeskunde* 1993, 137(39) 1969-1973

133 Lagro-Janssen ALM Benzodiazepinen en de gemoedsrust van de huisarts *Huisarts en Wetenschap* 1993, 36 402-404

134 Nicholas D, Hammond SM Personality characteristics of long-term benzodiazepine users *Personality and Interindividual Differences* 1992, 13(2) 221-223

135 Tonne U, Hiltunen AJ, Engelbrektsson K, *et al* Personality characteristics in primary benzodiazepine-dependent patients comparison with controls and polydrug users *Personality and Interindividual Differences* 1998, 24(6) 797-804

136 Tyrer P Risks of dependence on benzodiazepine drugs the importance of patient selection *British Medical Journal* 1989, 298 102-105

137 King MB, Gabe J, Williams P, *et al* Long term use of benzodiazepines the views of patients *British Journal of General Practice* 1990, 40 194-196

138 Cormack MA, Howells E Factors linked to the prescribing of benzodiazepines by general practice principals and trainees *Family Practice* 1992, 9(4) 466-471

139 Hemminki E Review of the literature on factors affecting drug prescribing *Social Science and Medicine* 1975, 9 111-115

140 Cripwell M Tranquillisers Why do we prescribe them? What are the alternatives? Paper given to the annual of the Society for the Study of Addiction to Alcohol and Other Drugs London, 1988

141 De Burgh S, Mant A, Mattick RP, *et al* A controlled trial of educational visiting to improve benzodiazepine prescribing in general practice *Australian Journal of Public Health* 1995, 19 142-148

142 Holm M Intervention against long-term use of hypnotics/sedatives in general practice *Scandinavian Journal of Primary Health Care* 1990, 8 113-117

143 Catalan J, Gath D Benzodiazepines in general practice time for a decision *British Medical Journal* 1985, 290 1374 1376

144 Surendrakumar D, Dunn M, Roberts CJC Hospital admission and the start of benzodiazepine use *British Medical Journal* 1992, 304 881

145 Anonymous Stoppen met benzodiazepinen *Geneesmiddelen Bulletin* 1994, 28(12)

146 Russel J, Lader MH Guidelines for the prevention and treatment of benzodiazepine dependence on behalf of the Substance Abuse Committee of the Mental Health Foundation Edited by Russel J, Lader MH The Mental Health Foundation 1993

Chapter 2

Objectives and structure of the thesis

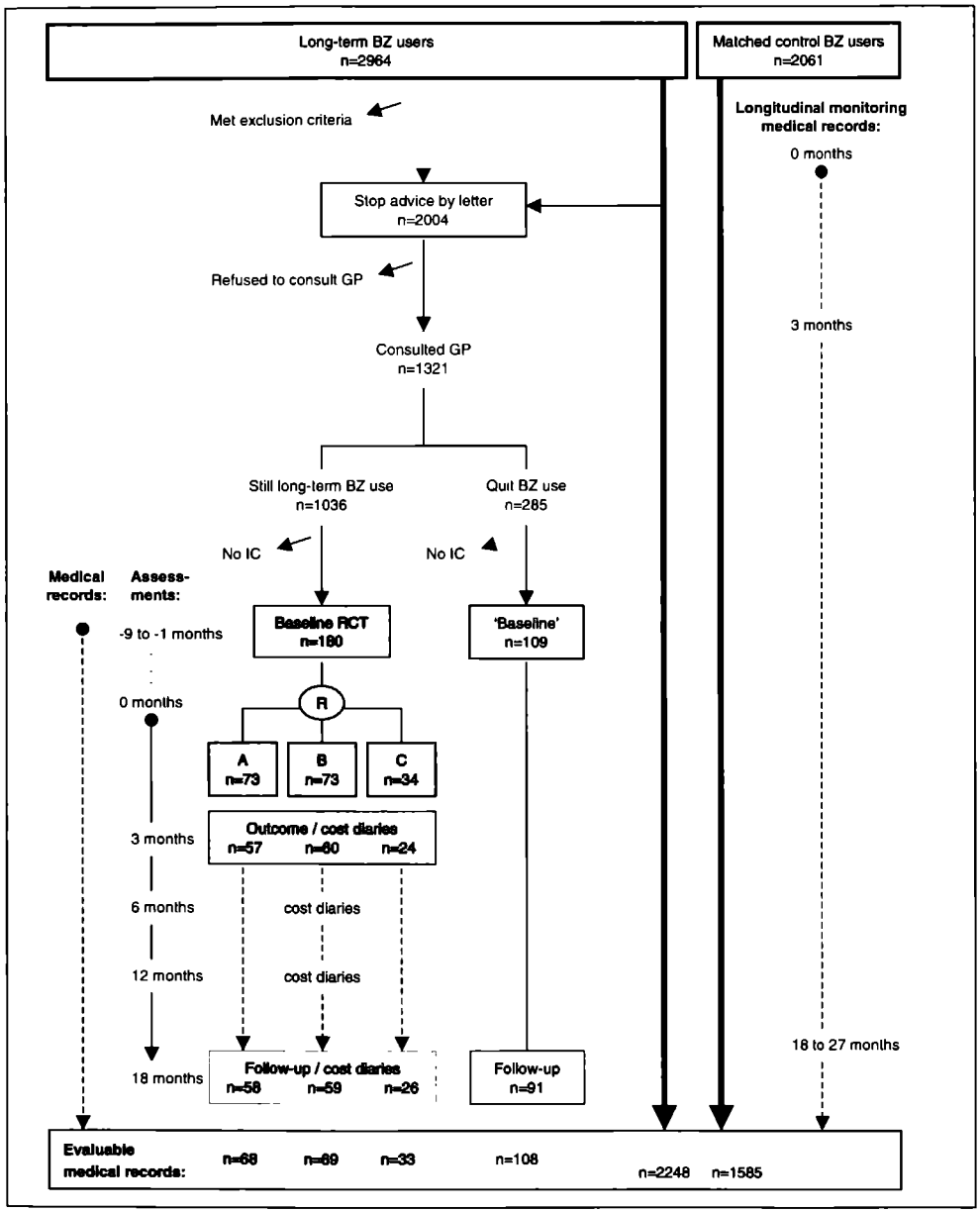
Study objectives

Design of the Benzoredux Project

Outline of the thesis

Figure 1

Design of the Benzoredux project



Abbreviations: BZ, benzodiazepine(s); GP, general practitioner; RCT, randomised controlled trial; A, systematic dosage reduction combined with group cognitive-behavioural group therapy; B, systematic dosage reduction only; C, control group;

Study objectives

The focus of this thesis is the outcome of different strategies aimed at the reduction of long-term benzodiazepine use in general practice. The main objectives are:

- To summarise the available knowledge on strategies to discontinue long-term benzodiazepine use in the literature.
- To evaluate the long-term outcome on benzodiazepine prescription of a 'minimal' intervention strategy to cut down long-term benzodiazepine use in general practice.*
- To evaluate the short- as well as the long-term outcome on benzodiazepine consumption and psychological functioning of a systematic discontinuation programme, with or without simultaneous group cognitive-behavioural therapy, as strategies to discontinue long-term benzodiazepine use.
- To provide insight into factors that affect the outcome of the different benzodiazepine discontinuation strategies examined, especially with respect to the severity of benzodiazepine dependence.
- To evaluate the two systematic discontinuation programmes economically with no treatment at all.

All data, except the literature review presented in chapter 3, were collected within the Benzoredux project. The general structure of this project is therefore briefly presented here.

Design of the Benzoredux Project

The Benzoredux Project was carried out to evaluate a stepped care approach to reduce long-term benzodiazepine use (longer than three months) in general practice. The first step was the so-called 'minimal' intervention strategy, i.e., a letter from the general practitioner (GP) containing advice to discontinue benzodiazepine use of their own accord. Patients who continued benzodiazepine consumption after this intervention were motivated to participate in the consecutive, more intensive step, i.e., a benzodiazepine tapering-off programme with or without simultaneous group cognitive-behavioural therapy.

The Benzoredux Project was carried out in 30 general practices in the Netherlands, with a total of 58 GP's. All long-term benzodiazepine users were identified in these practices through a computerised search in the GP prescription administration system (practice pharmacy records). All long-term benzodiazepine users meeting the in- and exclusion criteria received the minimal intervention. Three months later, patients were sent a second letter inviting them to make an appointment to evaluate the effect of this intervention. All patients included in the minimal

* The 'minimal' intervention strategy of the Benzoredux project will be elaborated in a second thesis by WJMJ Gorgels

intervention, whether or not they visited their GP after three months, were followed up for 21 months based on anonymous pharmacy records since no informed consent was required At the end of the follow-up period, the results were compared with a control group matched among others for benzodiazepine use at the beginning of the study period This control group was composed retrospectively in additional general practices in order to avoid bias by a more restricted policy regarding benzodiazepine use of GP's taking part in a benzodiazepine discontinuation project

At the evaluation consultation three months after the minimal intervention, patients were asked to give their consent If they had stopped their benzodiazepine use, informed consent was requested for two additional follow-up assessments, one directly after giving informed consent and one at the end of follow-up, i e , 18 months after the baseline assessment, and 21 months after receiving the initial letter For patients still using benzodiazepines, informed consent was requested for participation in a consecutive benzodiazepine discontinuation study

This second study consisted of a randomised controlled trial on the differential efficacy of tapering off long-term benzodiazepine use combined with group cognitive-behavioural therapy, tapering off alone, and a no-intervention control group given usual care The patients were assessed in three different ways Firstly, a computerised extraction of all drug prescription data from the GP information system (= computerised medical records) was carried out This extraction was comparable to the follow-up of all patients selected and included for the minimal intervention Secondly, a self-report assessment was carried out at baseline, at end of treatment (i e , 3 months after the start of the randomised controlled trial), and at 18 months follow-up Thirdly, patients were asked to fill out five three-week cost-diaries to evaluate the medical consumption at baseline and 3, 6, 12 and 18 months after the start of the trial

Figure 1 shows a flow chart of the study, including the number of patients in each stage The setting of the study, the selection and recruitment of patients, and the assessments and analyses will be described in more detail in Parts II, III and IV of this thesis Each chapter has been written as a separate article Consequently, although they discuss different topics, the chapters overlap each other is some areas The study received ethical approval of the University Medical Centre Nijmegen and was carried out between 1998 and 2001 The Benzoredux Project was funded by the Dutch Health Care Insurance Council (College voor Zorgverzekeringen, project OG97-015)

Outline of the thesis

This thesis consists of four parts The first part presents a systematic review of the literature on benzodiazepine discontinuation strategies In chapter 3, we focus on the discontinuation success rates of the different methods identified to discontinue long-term benzodiazepine use, and the factors related to discontinuation outcome Moreover, we address the most important areas where knowledge is lacking

Part II deals with the long-term term outcome of the first stage of the Benzoredux project, i.e., the 'minimal' intervention strategy. Chapter 4 evaluates the clinical outcome with respect to benzodiazepine consumption among all patients that received the minimal intervention (n=2004). A more detailed evaluation of relapse into benzodiazepine usage after this intervention is presented in chapter 5 concerning those patients who gave informed consent (n=109) for the additional follow-up assessments.

Part III addresses the short-term efficacy of the two taper-off strategies using a randomised controlled design for patients who were not able to discontinue benzodiazepine use by themselves. Chapter 6 deals with the short-term outcome of this randomised controlled trial (n=180). Special attention is paid to the feasibility of these programmes in general practice and the added value of group cognitive-behavioural therapy. In chapter 7 we carry out a cross-validation of the Benzodiazepine Dependence Self-Report Questionnaire (Bendep-SRQ) on the baseline data of the randomised controlled trial to establish the clinical utility of this questionnaire in benzodiazepine taper-off programmes. In addition to previous studies on the Bendep-SRQ, we also investigated the predictive validity and time course during benzodiazepine withdrawal.

Part IV evaluates the long-term efficacy of the two taper-off strategies. Long-term outcome of the two taper-off strategies with respect to benzodiazepine prescription, prescription for other psychotropic drugs, and psychological functioning is presented in chapter 8. In chapter 9, the results of a prediction analysis on long-term outcome is presented. Finally, the cost-effectiveness of both taper-off strategies is compared with the no-intervention control group in chapter 10.

In conclusion, chapter 11, summarises the main research findings of this thesis, and the implications are discussed for the management of long-term benzodiazepine use in general practice.

PART I

STATE OF THE ART

Chapter 3

Strategies to discontinue long-term benzodiazepine use: A systematic review and meta-analysis

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(submitted for publication)

Abstract

Background - Success rates of benzodiazepine discontinuation outcome vary substantially in literature.

Aims - To systematically review outcome and associated variables of various methods to discontinue chronic benzodiazepine use.

Method - Systematic literature review and meta-analysis of 60 papers identified using MEDLINE and PSYCHLIT from 1966-2003. Success rates were calculated at a patient level and the impact of the identified variables was tested.

Results - The abstinence rate was 22% for minimal interventions and 63% for systematic discontinuation programmes. The latter was influenced by transfer to a long-acting benzodiazepine before discontinuation, dose level, hospitalisation and diagnosis. Limited evidence suggested a positive effect of adding carbamazepine and imipramine, while tapering off benzodiazepines. The addition of psychotherapy was poorly investigated. Long-term results are limited due to methodological differences.

Conclusions - Although the heterogeneity in patient groups and study methodology, robust discontinuation rates were found. Long-term effects remain to be established.

Introduction

Since the early 1960s benzodiazepines have become widely available reaching prescription peaks in the 1970s [1] Then, more and more data were reported indicating the disadvantages of long-term benzodiazepine use, such as the risk of dependence, a higher risk of accidents and falls, and cognitive disturbances [2] Although long-term therapeutic use of benzodiazepines is controversial, limited evidence suggests long-term efficacy in specific diagnostic groups such as panic disorder and social phobia [3 4] The prevalence of these disorders, however, is relatively low in the light of the widespread use of benzodiazepines in the population [5]

Problems with stopping benzodiazepines in patients after long-term use initiated the development of treatment strategies to discontinue long-term benzodiazepine use Discontinuation studies suggest a successful discontinuation with low potency benzodiazepines, a longer half-life, use of low dosages, a shorter duration of use, less personality disturbances, and less psychopathological symptoms In this meta-analysis success rates of benzodiazepine discontinuation strategies and the influence of the above mentioned factors on successful discontinuation will be examined systematically

Methods

Study design

An initial search of the databases Medline and Psychinfo (2003) was performed for the period 1966 to April 2003, using the keywords "benzodiazepine(s)" in combination with "withdrawal", "detoxification", "dependence", "discontinuation" or "long-term" This search was extended by a manual search of the reference lists of the included papers Papers were included in the review if they met the following criteria (a) evaluation of benzodiazepine discontinuation strategies, (b) presentation of outcome of discontinuation for each treatment arm separately or presentation of follow-up results, and (c) long-term benzodiazepine use defined as daily use for over three months (or longer) Review papers, double publications, animal research, clinical trials evaluating the efficacy of benzodiazepine treatment for a fixed period, and case reports less than five cases were excluded from this meta-analysis

Assessments

ROV and JEC independently reviewed the selected studies by completing a coding form After the studies were coded twice, discrepancies in the two coding forms were resolved by consensus after discussion or by referring to the data in the original article This method yielded one coding form per article

In the coding form, the intervention type was added by distinguishing between minimal interventions and systematic discontinuation programmes Minimal interventions were defined as simple interventions applicable to large groups of patients, e g an advisory letter or a meeting in which long-term benzodiazepine users are advised to stop their use Systematic discontinuation programmes were defined as treatment programmes guided by a physician or psychologist The treatment programmes were subcategorised into systematic discontinuation alone or combined with either psychotherapy or pharmacotherapy Psychotherapy was divided into three groups (anxiety management, cognitive behavioural therapy or other) based on the terminology used in the original articles Outcome data were classified as end of treatment outcome versus outcome at follow-up divided in 3 follow-up categories 3-6 months, 6-12 months or longer than one year

Furthermore, the coding form consisted of the following items inclusion criteria (minimal duration of benzodiazepine use [3, 6 or 12 months] and diagnosing benzodiazepine dependence [yes/no]), results at post treatment outcome and at follow-up, year of publication, randomised controlled trial (RCT) [yes/no], domain of use (i e psychiatric diagnosis or symptoms of included patients), steps of taper [abrupt, fixed, symptom guided], taper-off after transfer to a long-acting benzodiazepine [yes/no], history of benzodiazepine use (dose, type, duration of use), hospitalisation [inpatient/outpatient treatment], and setting [primary care, psychiatric clinic, addiction clinics]

Mean equivalent benzodiazepine dosages were obtained from the articles or calculated in diazepam equivalents [6] If no information was available to calculate the dosage in diazepam equivalent, the dosages were categorised as low (within the therapeutic range, or < 15 mg), high (above the therapeutic range, or > 30 mg) or medium (patients using benzodiazepines within and above the therapeutic range, or 15-30 mg)

Statistical analysis

Success rates were calculated at a patient level for each intervention type per coded variable Studies were weighted for the number of patients evaluated at outcome and results were separately described over controlled and uncontrolled studies

The estimation of the success rate of systematic discontinuation programmes without additional treatment was conducted by putting all treatment arms evaluating such programmes together The success rates of systematic discontinuation combined with psychotherapy, respectively pharmacotherapy was compared to the success rates of all control groups lumped together as well as to the control groups of studies evaluating that particular therapy (f e control groups of all studies evaluating imipramine)

Since success rates could be biased by publication year, inclusion criteria or study design (uncontrolled versus controlled) these variables were analysed Subsequently, we analysed the effects of the coded variables by means of Pearson's chi-square tests Since these variables could also be

related, all results were controlled for possible two-way interaction effects using additional Pearson chi-square tests over the confounding variables. Only significant confounding effects are presented.

Results

The initial search yielded 4855 reference titles. Of these, 664 papers were identified with a possible relevance to discontinuation of long-term benzodiazepine use. After screening of the abstracts, and if necessary the full text, 606 papers were excluded (table 1) and 58 papers met the inclusion criteria. A manual search of the references of these papers yielded another 5 papers of possible relevance, of which two papers were included, resulting in a total of 60 papers: five papers on minimal interventions and 55 papers on systematic discontinuation (of which four papers exclusively reported follow-up data). These 55 papers were divided into systematic discontinuation without additional treatment (n=21) and systematic discontinuation combined with either psychotherapy (n=11) or pharmacotherapy (n=23). Although follow-up data were presented in 30 study reports, in only five the duration was longer than one year.[6-10] A full list of references included in this review can be obtained through the corresponding author.

Table 1

Reasons of not included papers

Excluded on abstract / full text (n=606):	**n**	**%**
Case report (n≤5)	61	10 0%
No success rate reported	12	2 0%
Overlap of patient sample with earlier reported studies	3	0 5%
Traditional review benzodiazepine dependence	66	10 9%
Review epidemiology / phenomenology BZ dependence	170	28 1%
Treatment study (with discontinuation phase)	63	10 4%
Animal research	61	10 1%
Experimental research benzodiazepine dependence	55	9 1%
Multiple drug use treatment studies	19	3 1%
Other (mainly letters / editorials)	96	15 8%

The characteristics of the included papers are summarised in table 2. Age and gender distribution of patients recruited in the minimal intervention studies is comparable to that of long-term benzodiazepine users in the population.[5] With the exception of two studies in an elderly population[11,12], the systematic discontinuation studies included patients with a somewhat lower age and a relatively high proportion of men. The number of dropouts was low in all study types, minimal intervention studies having the highest dropout rates.

Table 2

Overview of the design and characteristics of the selected studies

Subject of selected studies	N (studies)	N (patients) Total	Dropout	Completers	Sex ratio M F	Mean age (years)
Minimal Intervention:						
Uncontrolled	2	328	54	274	1 3 0	71
Controlled with usual care	3	601	75	526	1 2.8	67
Systematic Discontinuation alone:						
Uncontrolled	20**	1269	117	1152	1 1.5	47
Controlled with other discontinuation scheme	1	40	0	40	1 2 1	82
Controlled with usual care	-	-	-	-		
Systematic Discontinuation with Psychotherapy:						
Uncontrolled	5	87	20	67	1 3.0	44
Controlled with SD alone	3*	125	0	125	1 1 2	40
Controlled with other psychotherapy	2	34	8	26	1 . 0.6	46
Controlled with other discontinuation scheme	1	42	0	42	1 1 0	41
Systematic Discontinuation with Pharmacotherapy:						
Uncontrolled	4	51	0	51	1 1 8	42
Controlled with SD alone	2	67	0	67	1 3 1	70
Controlled with placebo**	17***	1127	94	1018	1 1 5	52

* One study did not randomise the patients over the two conditions
** Three studies exclusively reported data at follow-up
*** One study exclusively reported data at follow-up

Minimal interventions (appendix A)

A total of 800 patients were investigated in five studies; 572 patients actually received a minimal intervention and 228 patients were included in control groups receiving usual care. All minimal intervention studies were conducted in primary care with patients using various benzodiazepines in low dosages. The follow-up period varied from 6 to 12 months with one study not reporting the duration of the follow-up period.[13] The mean success rate was 16% (90/572) with a range of 5% to 38%: the lowest success rate was obtained in the only study having a 12-month follow-up period and the highest success rate in a study evaluating a selected group of patients, namely the visitors of an informative meeting in stead of all patients invited to visit this meeting.[13,14] The mean success rate over the three remaining randomised controlled trials was 22% (66/298), significantly superior to the mean discontinuation rate of 9% (20/228) in the usual care control groups (χ^2=16.9; df=1; p<0.001). No long-term data (>1 year) have been reported.

Systematic discontinuation without additional therapies (appendices B, C and D)

Of the 21 studies, 3 studies were excluded as they only reported follow-up success rates. The remaining 18 studies (998 patients) evaluated systematic discontinuation programmes without

additional therapies at the end of treatment None of these studies included a usual care control group, while only one study used a randomised controlled design evaluating 2 different discontinuation programmes (abrupt cessation versus one week of lorazepam replacement therapy) [12] A substantial number of studies evaluating systematic discontinuation combined with additional psychotherapy or pharmacotherapy also included a treatment arm consisting of systematic discontinuation alone (five studies, 92 patients) or systematic discontinuation combined with placebo (16 studies, 416 patients) Although such treatment arms also evaluate systematic discontinuation without additional therapies, they differ methodologically from each other and the 18 uncontrolled studies Therefore, we first tested the difference in success rates between these three conditions (success rates uncontrolled 68% (674/998), controlled 48% (44/92), controlled with placebo 57% (237/416), which appeared to be significant (χ^2=24 4, df=2, p<0 001) Factors that might be associated with discontinuation success are therefore analysed in these three groups separately

In table 3 an overview of success rates per study type and prognostic factors are shown Firstly, we checked for confounding factors influencing the success rates These factors were the year of publication or inclusion criteria (minimal duration of benzodiazepine use and diagnosing benzodiazepine dependence) Comparing the success rates of 4 consecutive 5-year periods showed a significant trend towards a less favourable outcome in time 1981-1985 68% (120/176), 1986-1990 67% (263/390), 1991-1995 63% (286/455), 1996-2003 59% (286/485) (χ^2=8 6, df=3, p=0 04), which could be explained by an increase in controlled studies over time The minimal duration of use for inclusion in the study showed no meaningful association with outcome since studies exclusively including patients using benzodiazepines for over one year had significantly higher success rates (66%, 449/682) than those including patients using benzodiazepines at least three (63%, 301/602) or six months (56%, 125/222) (χ^2=6 6, df=2, p=0 04) Moreover, success rates of studies in which participants had to fulfil the criteria of benzodiazepine dependence (67%, 126/187) did not differ from those including patients based on a specific duration of use only (63%, 829/1319) (χ^2=1 5, df=1, p=0 23)

Transfer to long-acting benzodiazepines gave a significant 9% improvement in the success rate (see table 3) Subsequent analyses showed confounding with hospitalisation and dose level Transfer to long-acting agents resulted in significantly higher success rates in outpatient treatment (p=0 003), but not in inpatient treatment (p=0 87) It also resulted in higher success rates in patients using medium (p=0 002) or high dosages (p=0 02), but not in patients using low dosages (p=0 56)

With respect to the mode of discontinuation three steps of taper were distinguished abrupt cessation, fixed taper-off schemes lasting from 1 to 8 weeks and symptom-guided taper-off methods which varied in time from 1 week to 15 months Improved success rates for symptom-guided taper-off methods were identified Abrupt cessation (58%, 84/116) and gradual taper (62%, 654/1063), however, did not differ significantly (χ^2=0 9, df=1, p=0 35) The comparison of abrupt cessation and

Table 3

Associations with success rate of systematic discontinuation without additional treatment

		Uncontrolled		Controlled		Controlled with placebo		Total group	
		18 studies / 998 patients		5 studies / 92 patients		19 studies / 416 patients		42 studies / 1506 patients	
Variables	**Outcome categories**	Success % (n/N)	Statistics	Success % (n/N)	Statistics	Success % (n/N)	Statistics	Success % (n/N)	Statistics
Transfer to long-acting BZ	Yes	74% (123/166)	p=0 05	100% (9/9)	p=0 001	65% (95/147)	p=0 01	71% (227/322)	p=0.003
	No	66% (551/832)		42% (35/83)		52% (129/248)		62% (715/1163)	
Steps of taper	Abrupt	61% (77/126)	p<0 001		p=0 91	35% (7/20)	p=0 08	58% (84/116)	p<0 001
	Gradual	67% (420/626)		48% (41/86)		55% (193/351)		62% (654/1063)	
	Symptom guided	98% (49/50)		50% (3/6)		-		93% (52/56)	
Dose (diazepam eqv.)	≤ 15 mg	67% (431/645)	p=0 08	57% (22/44)	p=0 45	58% (128/220)	p=0 60	64% (581/905)	p=0 73
	15 - 30 mg	37% (208/311)		50% (3/6)		56% (109/196)		62% (320/513)	
	≥ 30 mg	83% (35/42)		41% (19/46)		-		61% (54/88)	
Duration of use	≤ 5 years	69% (157/227)	p=0 13	-	p=0 69	50% (16/32)	p=0 20	67% (173/259)	p=0 70
	5 - 10 years	67% (384/577)		41% (19/46)		62% (127/204)		64% (530/827)	
	≥ 10 years	77% (70/91)		50% (3/6)		54% (59/110)		64% (132/207)	
Hospitalisation	Inpatient treatment	78% (88/113)	p=0 01	82% (27/33)	p<0.001	-	-	79% (115/146)	p<0.001
	Outpatient treatment	66% (571/869)		29% (17/59)		57% (237/416)		61% (825/1344)	
Setting	Primary care	60% (72/120)	p=0 08	-	p=0 001	71% (84/119)	p<0 001	65% (156/239)	p=0 005
	Psychiatric clinic	70% (539/775)		52% (16/31)		52% (153/297)		64% (708/1103)	
	Addiction clinic	59% (37/63)		27% (10/37)		-		47% (47/100)	
	Other	65% (26/40)		75% (18/24)		-		69% (44/64)	
Domain of use	Hypnotic use	59% (26/44)	p=0 47	-	p=0 04	25% (4/16)	p=0 02	50% (30/60)	p=0.004
	Anxiolytic use	70% (110/158)		25% (4/16)		62% (51/82)		65% (165/256)	
	Hypnotic/anxiolytic use	68% (481/713)		53% (40/76)		57% (182/318)		64% (703/1107)	
	Multidrug use	61% (23/38)		-		-		61% (23/38)	

gradual taper was confounded by hospitalisation gradual discontinuation was significantly better compared to abrupt cessation among inpatient treatment (50% versus 90%, χ^2=19 5, df=1, p<0 001), but not in an outpatient setting (59% versus 58%, χ^2<0 1, df=1, p=0 86) In contrast to our expectations, this finding was not confounded by dose level

Dose level was not associated with success rate However, after controlling for hospitalisation, high dose users in the outpatient sample had significantly lower success rates (23%, 10/34), compared to low (61%, 371/609) or medium dose users (58%, 241/419) Moreover, the higher success rate of high dose users in the sample of uncontrolled studies (see table 3) could be explained by confounding with hospitalisation as most high dose users in this condition were treated as inpatients The duration of benzodiazepine use before discontinuation was not related to outcome The average duration of use was 6 9 years (s d ± 3 3)

Hospitalisation (i e inpatient versus outpatient treatment) showed a significant difference in success rates in favour of inpatient treatment Setting had a significant effect on the success rate, achieving lower success rates in addiction clinics compared to primary care and psychiatric care However, subsequent analyses showed that these effects were due to interaction with the other variables studied

Due to a lack of adequate psychiatric diagnosing in most studies, we defined psychopathology as a "domain of use" variable Based on inclusion criteria and/or patient characteristics, we classified them as suffering from insomnia, from anxiety disorders, from neurotic disorders (defined as including patients with a combination of insomnia, anxiety disorders, and/or depression) and patients diagnosed as multiple drug users Although patient numbers are low and considerable overlap exists in diagnoses of each category, the selective use of benzodiazepines for insomnia tended to be associated with a less favourable outcome The fact that multiple drug users achieved comparable success rates as other patient groups could be explained by confounding as multiple drug users more often received inpatient treatment

Systematic discontinuation combined with psychotherapy (appendix C)

Eleven studies were identified using psychotherapy to facilitate systematic benzodiazepine discontinuation programmes Fifty-nine patients received no additional psychotherapy (control groups) and 201 patients received additional psychotherapy The median number of patients per treatment condition was 12 The success rates ranged from 0% to 100% (overall success rate 54%, 109/201) Discriminating between different types of psychotherapy or group versus individual therapy failed due to low patient numbers and due to predominance of one large study evaluating the effect of additional individual cognitive-behavioural therapy (CBT) in multiple drug users [15]

Two of the 11 studies compared systematic discontinuation without additional treatment to systematic discontinuation combined with psychotherapy in a *randomised* controlled design The first study was conducted in patients with panic disorder and found a significantly higher success rate

among patients receiving additional group CBT.[16] The second study was conducted among multiple drug users and found a significant lower success rate among patients receiving additional CBT.[15]

Systematic discontinuation combined with pharmacotherapy (appendix D)

Twenty-three studies evaluated the effect of systematic discontinuation combined with pharmacotherapy. We excluded five studies from analyses. Four small, uncontrolled studies (up to 17 patients per study) evaluated the use of drugs that have also been examined in larger controlled trials. The fifth study was excluded, because it reported outcome data at 6 months follow-up only. Table 4 presents the end of treatment results per agent of the remaining studies, as well as compared to the control groups within the aggregated studies (within studies control group) as compared to all 18 control groups of these studies lumped together (overall control group)

Table 4

Success rates of systematic discontinuation with pharmacotherapy

		Active drug	Control group			
	No of		Within studies		Overall	
	studies*	Success % (n/n)	Success % (n/n)	statistics	Success % (n/n)	statistics
Propranolol	2	43% (15/35)	50% (18/36)	p=0 55	59% (264/449)	p=0 07
Buspirone	5	59% (60/101)	54% (69/128)	p=0 41	"	p=0 91
Trazodone	2	71% (43/61)	60% (22/37)	p=0 26	"	p=0 08
Carbamazepine	4	92% (54/59)	67% (62/93)	**p<0.001**	"	**p<0.001**
Progesteron	1	48% (11/23)	42% (5/12)	p=0 73	"	p=0 30
Dothiepin	1	31% (11/36)	42% (17/41)	p=0.32	"	p=0 001
Hydroxyzine	1	84% (79/94)	82% (37/45)	p=0 79	"	**p<0.001**
Melatonin	1	78% (14/18)	25% (4/16)	**p=0.002**	"	p=0 11
Sodium valproate	1	79% (11/14)	31% (4/13)	**p=0.01**	"	p=0 14
Paroxetine	1	67% (32/48)	64% (47/74)	p=0 72	"	p=0 29
Alpidem	1	31% (4/13)	75% (9/12)	p=0 03	"	p=0 04
Imipramine	2	81% (30/37)	51% (35/69)	**p=0.002**	"	**p=0.008**

Number of studies is > 18, since some studies had more than 2 treatment arms

Four drugs (carbamazepine, melatonin, sodium valproate and imipramine) were significantly better compared with systematic discontinuation alone as shown by the aggregated results of the studies evaluating these drugs (within studies control group). Carbamazepine and imipramine were also significantly better when compared to the overall control group of all studies lumped together, whereas melatonin and sodium valproate were not. The significant effects of melatonin and sodium valproate, therefore, can be explained by a relatively low success rate in the control group in the studies evaluating these drugs. Although addition of hydroxyzine yielded a relatively high success rate, it was only tested in one study having also high success rates in the control group.

Long-term follow-up studies

To evaluate long-term results, all treatment arms of the systematic discontinuation studies of appendix B, C and D were grouped together Sixteen studies reported results at 3-6 months follow-up, nine studies at 6-12 months follow-up and five studies reported follow-up data for over one year The success rates of studies reporting a follow-up duration of less than one year did not differ significantly (3-6 months follow-up 57%, 338/598 versus 6-12 months follow-up 59%, 180/304) (χ^2=0 6, df=1, p=0 44), while both categories had significantly higher success rates compared to studies reporting follow-up data for over one year (44%, 145/329) (χ^2=17 9, df=2, p<0 001)

A closer inspection of these data showed that all outcome data of studies reporting results with a duration of follow-up of less than one year were measured cross-sectionally The success rates of studies reporting results for over one year varied widely depending on outcome criteria for benzodiazepine use Point prevalence of abstinence as measured during the month before follow up assessment revealed success rates of 54% and 58%[7 9], while longitudinal monitoring yielded much lower success rates of 15% and 25% [6 10] The long-term success rate of 94%, reported by Ashton (1987), seemed the most favourable [8] Investigating these data more thoroughly we found that 5 successfully treated patients relapsed and discontinued their benzodiazepine use after a second attempt, giving a continuous abstinent rate of 82% (41 of 50 patients)

Discussion

Main findings

The main finding of this meta-analysis was that 22% (66/298) of patients were able to discontinue benzodiazepine use after a minimal intervention, whereas 63% (955/1506) manages to discontinue benzodiazepine use with the aid of a systematic discontinuation programme Although outcome of the minimal interventions has only been tested in primary care, patient groups were comparable to the 'average' benzodiazepine user in the population suggesting a high generalisability Follow-up data for discontinuation over one year are lacking Systematic discontinuation studies have been tested in various settings However, the age and gender distribution of these studies show selective recruitment towards younger, male patients The impact of the predefined variables and additional therapies on outcome of systematic discontinuation will be discussed below Follow-up success rates of systematic discontinuation studies depended highly on the type of measurement cross-sectional measures resulted in high and longitudinal measures in low success rates This discrepancy suggests intermittent usage patterns in patients after taking part in a systematic discontinuation programme, which has also been reported by Couvée *et al* (2002) [17] The main limitation interpreting the success rates of systematic discontinuation studies, especially the low success rates at follow-up, is the lack of studies including a no-intervention control group

Limitations

The heterogeneity of the included studies implies that large generalisations may not be possible In an attempt to overcome this problem, success rates were separated by some pre-defined variables, known or suggested to be associated with discontinuation success (see below) The clinical impression that patients with specific disorders - for example panic disorder, substance use disorder or borderline personality disorder - have more difficulty than others could not be examined due to the lack of information in the selected studies Although specified diagnoses of psychiatric condition were not reported in the studies of this meta-analysis, a distinction was possible between patients with exclusively insomnia, with exclusively anxiety disorders, with neurotic disorders (insomnia, anxiety or depressive disorder or a combination) or substance use disorders, being aware that these four categories are also not mutually exclusive Moreover, one might argue if the diagnosis at study start reflects the underlying disorder adequately, since psychiatric symptomatology is known to be affected by benzodiazepine treatment [18]

Variables associated with successful outcome of systematic discontinuation

Transfer to a long-acting agent (most often diazepam) before systematic discontinuation yielded higher success rates for patients using benzodiazepine dosages of over 15 mg diazepam equivalent and for patients treated in an outpatient setting The theoretical advantage of the transfer to long-acting agents is the occurrence of less severe withdrawal symptoms caused by a more gradual blood level decrease and as a consequence a superior effect on outcome

Symptom-guided benzodiazepine withdrawal indicated to result in the highest success rates, but this method was dominated by the results of one centre [8] Fixed gradual discontinuation programmes were superior over abrupt cessation in an inpatient setting However, both strategies resulted in comparable success rates in an outpatient setting Although no head-to-head comparisons have been conducted comparing abrupt and gradual discontinuation, Petrovic *et al* (2002) showed significant superior effects of abrupt cessation with lorazepam 1 mg replacement for one week compared to abrupt cessation in a randomised controlled fashion [12] Moreover, it is well-known from controlled trials that abrupt discontinuation of short-acting benzodiazepines leads to lower success rates [19]

High dose users (over 30 mg diazepam equivalent daily) had significantly lower success rates compared to low or medium dose users in an outpatient setting Since no differences were found between low or medium doses we may conclude that for the majority of patients treated within the 1-30 mg range, dose level has no critical influence on success rates When treated as inpatients, dose level was not associated with success rate The duration of treatment with benzodiazepines did not critically influence outcome

Success rates were comparable in primary care and psychiatric care, while significantly lower success rates were achieved in addiction clinics Studies evaluating inpatient treatment showed an important difference in favour of outpatient treatment This might indicate that a controlled

environment, with no patients "lost-to-follow-up", leads to higher success rates. Two diagnosis groups could be identified having lower success rates: multiple drug users and patients suffering from insomnia, although the latter finding was based on only two studies.[20,21]

Addition of psychotherapy

The addition of psychotherapy did not result in higher success rates in the whole group of long-term benzodiazepine users, although definite conclusions are hampered as most studies had low patient numbers and a poor methodological quality. In addition, two well-designed randomised controlled trials suggest different efficacy in different diagnostic patient groups. The addition of CBT proved to be efficacious in patients diagnosed with panic disorder, but not in substance abusers.[15,16] This discrepancy may be explained by the fact that additional psychotherapy only affects the success rate when it is based on the treatment of the underlying disease.

Addition of pharmacotherapy

The addition of the psychoactive drugs carbamazepine and imipramine significantly increases the success rates compared to systematic discontinuation alone based on the aggregated results of 4, respectively 2 randomised controlled trials. Sodium valproate and melatonin showed also higher success rates than systematic discontinuation alone. However, both agents were tested in single controlled trials with low patient numbers per treatment arm (up to 18 patients) and with a relatively low success rates in the control groups. Therefore, replication of these results is suggested before using sodium valproate and melatonin in clinical practice.

Clinical implications

Whether long-term benzodiazepine use must be discontinued should be balanced on diagnosis, current symptoms, side-effects, treatment history and alternative treatment modalities. If one decides to discontinue long-term benzodiazepine treatment, the following guidelines based on the results of this meta-analysis can be given.

We advice a first treatment in primary care starting with a minimal intervention by providing general information to patients and encouraging them to stop the use of benzodiazepines by themselves. If patients are unable to stop their benzodiazepine use this way, a systematic discontinuation programme should be offered to them, since 63% of the patients can be successfully discontinued. The results suggest that patients must be transferred to a long-acting agent and tapered-off a by fixed discontinuation programme.

If this strategy fails, patients could be referred for second line treatment At this stage it remains unclear which treatment options should be used. We suggest the following options, depending on local circumstances and patient characteristics. Patients could be offered a symptom-guided taper-off scheme offering specialised care to prevent significant deterioration or relapse of the underlying

disease during or after discontinuation. Patients using high dosages (> 30 mg diazepam equivalent) might be offered inpatient treatment. Adding carbamazepine or imipramine could be offered or a psychotherapy programme during discontinuation aimed to treat the underlying disease. In case of substance abusers, we suggest to start with inpatient treatment in a specialised treatment setting.

Future research

Future research should acknowledge the gaps in literature identified in this review, for example head to head comparisons of systematic discontinuation programmes with different taper rate and direct comparisons over settings. Special attention should be paid to diagnostic evaluation before and after tapering-off, stepwise programmes for treatment resistant patients and long-term follow-up studies. As the high prevalence of long-term use of benzodiazepines concerns a public topic, a cost-effectiveness analyses should guide the long-term treatment with benzodiazepines as well as the discontinuation of this treatment to shed more light on the economic costs.

References

Article

1 Lader M History of benzodiazepine dependence *Journal of Substance Abuse and Treatment* 1991, 8 53 59

2 Taylor S, McCracken CFM, and Wilson KCM Extent and appropriateness of benzodiazepine use *British Journal of Psychiatry* 1998, 173 433 438

3 Schweizer E, Rickels K, Weiss S, *et al* Maintenance drug treatment of panic disorder I Results of a prospective, placebo-controlled comparison of alprazolam and imipramine *Archives of General Psychiatry* 1993, 50 51 60

4 Otto MW, Pollack MH, Gould RA *et al* A comparison of the efficacy of clonazepam and cognitive behavioral group therapy for the treatment of social phobia *Journal of Anxiety Disorders* 2000, 14 345 358

5 Zandstra SM, Fuhrer JW, Van de Lisdonk EH, *et al* Different study criteria affect the prevalence of benzodiazepine use *Social Psychiatry and Psychiatric Epidemiology* 2002, 37 139-144

6 Zitman FG and Couvée JE Chronic benzodiazepine use in general practice patients with depression an evaluation of controlled treatment and taper-off Report on behalf of the Dutch Chronic Benzodiazepine Working Group *British Journal of Psychiatry* 2001, 178 317 324

7 Golombok S, Higgitt A, Fonagy P, *et al* A follow up study of patients treated for benzodiazepine dependence *British Journal of Medical Psychology* 1987, 60 141 149

8 Ashton H Benzodiazepine withdrawal outcome in 50 patients *British Journal of Addiction* 1987, 82 665 671

9 Rickels K, Case WG, Schweizer E, *et al* Long-term benzodiazepine users 3 years after participation in a discontinuation program *American Journal of Psychiatry* 1991, 148 757-761

10 Holton A, Riley P, and Tyrer P Factors predicting long-term outcome after chronic benzodiazepine therapy *Journal of Affective Disorders* 1992, 24 245 252

11 Petrovic M, Pevernagie D, Van Den NN, *et al* A programme for short-term withdrawal from benzodiazepines in geriatric hospital inpatients success rate and effect on subjective sleep quality *International Journal of Geriatric Psychiatry* 1999, 14 754 760

12 Petrovic M, Pevernagie D, Mariman A, *et al* Fast withdrawal from benzodiazepines in geriatric inpatients a randomised double-blind, placebo-controlled trial *European Journal of Clinical Pharmacology* 2002, 57 759 764

13 O'Leary M A novel approach to tackling the benzodiazepine problem in general practice *Psychiatric Bulletin* 1989, 13 180 181

14 Morgan JD, Wright DJ and Chrystyn H Pharmacoeconomic evaluation of a patient education letter aimed at reducing long term prescribing of benzodiazepines *Pharmacy World and Science* 2002, 24 231 236

15 Vorma H, Naukkarinen H, Sarna S, *et al* Treatment of out-patient with complicated benzodiazepine dependence comparison of two approaches *Addiction* 2002, 97 851 859

16 Otto MW, Pollack MH, Sachs GS, *et al* Discontinuation of benzodiazepine treatment efficacy of cognitive behavioral therapy for patients with panic disorder *American Journal of Psychiatry* 1993, 150 1485-1490

17 Couvée JE, Timmermans EAY and Zitman FG The long term outcome of a benzodiazepine discontinuation programme in depressed outpatients *Journal of Affective Disorders* 2002, 70 133-141

18 Birkenhaeger TD, Moleman P, and Nolen WA Benzodiazepines for depression? A review of the literature *International Journal of Psychopharmacology* 1995, 10 181-195

19 Rickels K, Schweizer E, Case WG, *et al* Long-term therapeutic use of benzodiazepines I Effects of abrupt discontinuation *Archives of General Psychiatry* 1990, 47 899 907

20 Drake J Temazepam Planpak' a multicentre general practice trial in planned benzodiazepine hypnotic withdrawal *Current Medical Research Opinion* 1990, 12 390 393

21 Garfinkel D, Zisapel N, Wainstein J *et al* Laudon M Facilitation of benzodiazepine discontinuation by melatonin a new clinical approach *Archives of Internal Medicine* 1999, 159 2456-2460

Appendices

Appendix A

Minimal interventions

Authors (pub. Year)	Interventions (n)*	Results end of treatment Ratio* (% stopped)	Results follow-up Ratio* (% stopped)
O'Leary (1989)	Visitors of the meeting invitated by letter for informative meeting concerning long-term BZ use		12 / 32 (38%)
Jones (1990)	1 Advisory consultation followed by offering relaxation therapy & counselling 2 Usual care		*9 months* 1 21 / 112 (19%) 2 11 / 115 (10%)
Cormack et al (1994)	1 Advisory letter 2 Advisory letter + information sheet 3 Usual care		*6 months* 1 23 / 65 (35%) 2 13 / 75 (17%) 3 6 / 69 (9%)
Bashir et al (1994)	1 Personal advice + self-help booklet 2 Usual care		*6 months* 1 9 / 46 (20%) 2 3 / 44 (7%)
Morgan et al (2002)	Advisory letter		*12 months* 12/242 (5%)

Appendix B

Systematic discontinuation programmes without additional treatment

Authors	Tapering-off scheme(s) (n)	Results End of treatment Ratio* (% stopped)	Results Follow-up Ratio* (% stopped)
Petursson et al (1981)	Placebo-controlled, double-blind, fixed discontinuation in 2 or 4 weeks	15 / 16 (94%)	Not evaluated
Hopkins et al (1982)	Fixed discontinuation with weekly visits (median 3 weeks)	46 / 76 (61%)	*5 months* 49 / 70 (70%)
Tyrer et al (1983)	Fixed discontinuation with two weeks 100%, two weeks 50% and finally two weeks 25%	36 / 41 (81%)	*6 months* 26 / 41 (63%)
Harrison et al (1984)	Fixed discontinuation in 10 days (range 2 - 18)	16 / 23 (70%)	Not evaluated
Rickels et al (1986)	1 Abrupt discontinuation 2 Failed abrupt, followed by fixed discontinuation in 4 weeks 3 Not accepted in study protocol 4 Abrupt outside study protocol	1 38 / 59 (64%) 2 Not reported 3 Not reported 4 Not reported	*6 - 12 months* All patients together 32 / 62 (51%)
Ghodse et al (1987)	Abrupt discontinuation for 24-48 hours, followed by diazepam substitution and fixed discontinuation if necessary to restrain withdrawal symptoms	14 / 25 (56%) (10 abrupt, 14 gradual)	Not evaluated
Ashton et al (1987)	Symptom-guided discontinuation in 1 week to 125 months	49 / 50 (98%)	*10 - 42 months* 44 / 47 (94%)
Golombok et al (1987)	Symptom-guided discontinuation	Not reported	*1 - 5 years* 25 / 46 (54%)
Soyka et al (1988)	Fixed discontinuation every 5 days steps 50%, 25%, 12% of the original dose	20 / 20 (100%)	Not evaluated
Rickels et al (1990)	Abrupt discontinuation	29 / 47 (62%)	*5 weeks* 20 / 47 (43%)
Schweizer et al (1990)	Fixed discontinuation 25% a week in the first 2 weeks and 4x 12 5% in the last two weeks	39 / 63 (62%)	*5 weeks* 34 / 63 (54%)
Drake (1991)	Fixed discontinuation with dose reductions every 2 weeks from 10 mg to 5 mg to 2 mg	26 / 44 (59%)	*3-6 months* 23 / 44 (52%)
Murphy et al (1991)	*Randomised allocation to* Fixed discontinuation 25% reduction every 2 weeks after randomised allocation to lorazepam, diazepam or bromazepam	44 / 68 (65%)	-
Rickels et al (1991)*	Abrupt & fixed discontinuation in 4 weeks	-	*2 7 - 5 0 years* 50 / 86 (58%)
Brenner et al (1991)	Fixed discontinuation with 50% of the previous dose every 5 days	12 / 12 (100%)	Not evaluated
DuPont et al (1992)	Fixed discontinuation in 4 weeks by 1 mg / 3 days	95 / 142 (67%)	Not evaluated

Holton et al (1992)*	Fixed discontinuation two weeks 100%, two weeks 50% and finally two weeks 25%	*End of treatment* 36 / 41 (81%) *6 months follow-up* 26 / 41 (63%)	*5 years* 6 / 41 (15%)
McDuff et al (1993)	Fixed discontinuation (average 7 8 weeks, range 2 - 22) according to dose and patient, early reduction steps were typically greater than subsequent ones	7 / 15 (47%)	Not evaluated
Habraken et al (1997)	*Double-blind* 1 Fixed discontinuation in 5 weeks 3x 25% a week followed by 2x 12 5% a week 2 No-intervention	Not reported	*12 months* 1 17 / 27 (63%) 2 Control group
Schweizer et al (1998)	Abrupt & fixed discontinuation in 4 weeks	114 / 171 (67%)	Not evaluated
Petrovic et al (2002)	1 Abrupt discontinuation 2 Fixed discontinuation by 1 week of lorazepam replacement	1 10/10 (50%) 2 16/20 (80%)	Not evaluated

* Rickels et al 1991 is the long-term follow-up of patients included of different short-term studies of Rickels & Schweizer,
Holton et al 1992 is the long-term follow-up study of Tyrer et al 1983

Appendix C

Systematic discontinuation programmes with psychotherapy

Authors	Treatment arms (n)	Results End of treatment Ratio* (%)	Results follow-up Ratio* (%)
			Six months
Cormack et al (1983)	11-13 weeks AMT without structured tapering-off	5 / 11 (45%)	17 / 50 (34%) of consent and non-consent patients
			12 months
Nathan et al (1986)	1 Fixed discontinuation + relaxation and stress management training	1 1 / 4 (25%)	1 0 / 4 (0%)
	2 Fixed discontinuation + psychoanalytic psychotherapy	2 0 / 3 (0%)	2 -
			12 months after baseline
Higgitt et al (1987)	1 Fixed discontinuation alone	1 3 / 6 (50%)	Combined results
	2 Fixed discontinuation + AMT	2 8 / 10 (80%)	4 / 16 (25%)
			12-months
Sanchez-Craig et al (1987)	1 Fixed discontinuation + CBT	1 9 / 23 (39%)	1 5 / 23 (22%)
	2 Abrupt discontinuation + CBT	2 11 / 19 (42%)	2 8 / 19 (42%)
Schmaus et al (1987)	Abrupt discontinuation + individual psychotherapy, relaxation - , occupational - and physical training	1 7 / 7 (100%) 2 7 / 7 (100%)	-
			3 months
Crouch et al (1988)	Fixed discontinuation + AMT	4 / 12 (33%)	6 / 9 (67%)
			6 months
Joughin et al (1991)	Fixed discontinuation + inpatient AMT and outpatient group therapy	21 / 21 (100%)	14 / 21 (67%)
			Three months
Otto et al (1993)	1 Fixed discontinuation alone	1 4 / 16 (25%)	1 5 / 16 (31%)
	2 Fixed discontinuation + group CBT	2 13 / 17 (80%)	2 10 / 17 (59%)
Elsesser et al (1996)	1 Fixed discontinuation + AMT	1 5 / 10 (50%)	-
	2 Fixed discontinuation + CBT	2 7 / 9 (78%)	
		3 months	
Charney et al (2000)	Fixed discontinuation + group and individual therapy	6 / 12 (50%)	-
Vorma et al (2002)	1 Fixed discontinuation alone	1 10 / 37 (27%)	-
	2 Fixed discontinuation + CBT	2 5 / 39 (13%)	

Abreviations: CBT, cognitive behavioral therapy, AMT, anxiety management therapy

Appendix D

Systematic discontinuation programmes with pharmacotherapy

Authors	Treatment arms (n)	Results End of treatment Ratio* (%)	Results Follow-up Ratio* (%)
Tyrer et al (1981)	1 Abrupt discontinuation + propranolol 60-120 mg 2 Abrupt discontinuation + placebo	4 11 / 20 (55%) 5 7 / 20 (35%)	-
Schweizer et al (1986)	Abrupt and fixed discontinuation + buspirone 20 mg	9 / 15 (60%)	-
Lader et al (1987)	1 Fixed discontinuation + buspirone 20-30 mg 2 Fixed discontinuation + placebo	1 5 / 13 (38%) 2 6 / 11 (55%)	-
Ries et al (1989)	Abrupt discontinuation + carbamazepine > 200 mg	9 / 9 (100%)	-
Ashton et al (1990)	3 Fixed discontinuation + buspirone 10 mg 4 Fixed discontinuation + placebo	1 4 / 11 (36%) 2 11 / 12 (92%)	*12 months* 1 6 / 11 (55%) 2 11 / 12 (92%)
Udelman et al (1990)	5 Fixed discontinuation + buspirone 15 mg 6 Fixed discontinuation + placebo	3 21 / 36 (58%) 4 17 / 36 (47%)	-
Cantopher et al (1990)	1 Abrupt discontinuation + propranolol 80 mg 2 Fixed discontinuation alone	1 4 / 15 (27%) 2 11 / 16 (69%)	*6 months* 1 4 / 15 (27%) 2 11 / 16 (69%)
Rickels et al (1990)	1 Fixed discontinuation + placebo 2 Fixed discontinuation + imipramine 100-300 mg 3 Fixed discontinuation + buspirone 25-45 mg 4 Fixed discontinuation + carbamazepine 200-600 mg	1 26 / 45 (58%) 2 11 / 14 (79%) 3 11 / 13 (85%) 4 12 / 13 (92%)	-
García-Borreguero et al (1991)	1 Fixed discontinuation alone 2 Fixed discontinuation + carbamazepine 300-600 mg	1 9 / 9 (100%) 2 9 / 9 (100%)	-
Schweizer Et al (1991)	1 Fixed discontinuation + carbamazepine 400-800 mg 2 Fixed discontinuation + placebo	1 18 / 19 (95%) 2 13 / 21 (62%)	*12 weeks* 1 14 / 19 (74%) 2 11 / 21 (52%)
Di-Costanzo et al (1992)*	1 Fixed discontinuation + carbamazepine (6-8 µg/ml) 2 Fixed discontinuation + placebo	1 15 / 18 (88%) 2 14 / 18 (78%)	-
Lader et al (1993)	1 Fixed discontinuation + alpidem (100-150 mg) 2 Fixed discontinuation + placebo	1 4 / 13 (31%) 2 9 / 12 (75%)	-
Anseau et al (1993)	Fixed discontinuation + trazodone 300 mg	8 / 10 (80%)	*12 months* 8 / 10 (80%)
Schweizer et al (1995)	1 Fixed discontinuation + progesteron 900-3600 mg 2 Fixed discontinuation + placebo	1 12 / 23 (52%) 2 7 / 12 (58%)	*12 weeks* 1 9 / 18 (50%) 2 7 / 10 (70%) *12 months* 1 9 / 18 (50%) 2 7 / 10 (70%)
Tyrer et al (1996)	1 Fixed discontinuation + dothiepin 150 mg 2 Fixed discontinuation + placebo	1 11 / 36 (31%) 2 17 / 41 (41%)	-
Kandler et al (1996)*	Abrupt discontinuation + carbamazepine 800 mg	15 / 17 (88%)	-

Lemoine et al (1997)*	1	Fixed & abrupt discontinuation + hydroxyzine 50 mg	1	43 / 49 (88%)	-
	2	Fixed & abrupt discontinuation + hydroxyzine 25 mg	2	36 / 45 (80%)	
	3	Fixed & abrupt discontinuation + placebo	3	37 / 45 (82%)	
					12 months
Romach et al (1998)	1	Fixed discontinuation + ondansetron 2 mg	-		66 / 97 (68%)
	2	Fixed discontinuation + placebo			
					Six months
Garfinkel et al (1999)	1	Fixed discontinuation + Melatonin 2 mg	1	14 / 18 (78%)	24 / 30 (80%)
	2	Fixed discontinuation + Placebo	2	4 / 16 (25%)	
					Three months
Rickels et al (1999)	1	Fixed discontinuation + trazodone 100-500 mg	1	23 / 36 (64%)	1 16 / 30 (53%)
	2	Fixed discontinuation + sodium valproate 0 5-2 5 mg	2	11 / 14 (78%)	2 11 / 14 (78%)
	3	Fixed discontinuation + placebo	3	4 / 13 (31%)	3 5 / 10 (50%)
Petrovic et al (1999)	1	Fixed discontinuation in 1 week	18 / 24 (75%)		-
	2	Abrupt discontinuation + 1 week trazodone 50 mg	20 / 25 (80%)		
					12 months
Rickels et al (2000)	1	Fixed discontinuation + imipramine 150 mg	1	19 / 23 (83%)	Combined results
	2	Fixed discontinuation + buspirone 30 mg	2	19 / 28 (68%)	39 / 57 (68%)
	3	Fixed discontinuation + placebo	3	9 / 24 (38%)	
					2-3 years
Zitman & Couvée (2001)	1	Fixed discontinuation + paroxetine 20 mg	1	32 / 48 (67%)	Combined results
	2	Fixed discontinuation + placebo	2	47 / 74 (64%)	26 / 207 (13%)

* Foreign language (Italian / German / French)

Reference List appendix A

1 O Leary M A novel approach to tackling the 'benzodiazepine problem' in general practice *Psychiatric Bulletin* 1989, 13 180-181

2 Jones D Weaning elderly patients off psychotropic drugs in general practice a randomised controlled trial *Health Trends* 1990, 22 164-166

3 Cormack MA, Sweeney KG, Hughes-Jones H, *et al* Evaluation of an easy, cost-effective strategy for cutting benzodiazepine use in general practice *British Journal of General Practice* 1994, 44 5-8

4 Bashir K, King M, and Ashworth M Controlled evaluation of brief intervention by general practitioners to reduce chronic use of benzodiazepines *British Journal of General Practice* 1994, 44 408-412

5 Morgan JD, Wright DJ and Chrystyn H Pharmacoeconomic evaluation of a patient education letter aimed at reducing long term prescribing of benzodiazepines *Pharmacy World and Science* 2002, 24(6), 231-236

Reference List appendix B

1 Petursson H, and Lader MH Withdrawal from long-term benzodiazepine treatment *British Medical Journal (Clinical Research Edition)* 1981, 283 643-645

2 Hopkins DR, Sethi KB, and Mucklow JC Benzodiazepine withdrawal in general practice *Journal of the Royal College of General Practitioners* 1982, 32 758-762

3 Tyrer P, Owen R, and Dawling S Gradual withdrawal of diazepam after long term therapy *Lancet* 1983, 1 1402 1406

4 Harrison M, Busto U, Naranjo CA, *et al* Diazepam tapering in detoxification for high-dose benzodiazepine abuse *Clinical Pharmacological Therapies* 1984, 36 527-533

5 Rickels K, Case WG, Schweizer EE, *et al* Low-dose dependence in chronic benzodiazepine users a preliminary report on 119 patients *Psychopharmacology Bulletin* 1986, 22 407-415

6 Ghodse AH, London M, Bewley TH, *et al* In patient treatment for drug abuse *British Journal of Psychiatry* 1987, 151 72-75

7 Ashton H Benzodiazepine withdrawal outcome in 50 patients *British Journal of Addiction* 1987, 82 665-671

8 Golombok S, Higgitt A, Fonagy P, *et al* A follow-up study of patients treated for benzodiazepine dependence *British Journal of Medical Psychology* 1987, 60 (Pt 2) 141-149

9 Soyka M, Steinberg R, and Vollmer M [Withdrawal phenomena in stepwise withdrawal of benzodiazepines] *Nervenarzt* 1988, 59 744-748

10 Rickels K, Schweizer E, Case WG, *et al* Long-term therapeutic use of benzodiazepines I Effects of abrupt discontinuation *Archives of General Psychiatry* 1990, 47 899-907

11 Schweizer E, Rickels K, Case WG, *et al* Long-term therapeutic use of benzodiazepines II Effects of gradual taper *Archives of General Psychiatry* 1990, 47 908 915

12 Drake J Temazepam Planpak a multicentre general practice trial in planned benzodiazepine hypnotic withdrawal *Current Medical Research Opinion* 1991, 12 390 393

13 Murphy SM, and Tyrer P A double blind comparison of the effects of gradual withdrawal of lorazepam, diazepam and bromazepam in benzodiazepine dependence *British Journal of Psychiatry* 1991, 158 511 516

14 Rickels K, Case WG, Schweizer E, *et al* Long term benzodiazepine users 3 years after participation in a discontinuation program *American Journal of Psychiatry* 1991, 148 757-761

15 Brenner PM, Wolf B, Rechlin T, *et al* Benzodiazepine dependence detoxification under standardized conditions *Drug and Alcohol Dependence* 1991, 29 195-204

16 DuPont RL, Swinson RP, Ballenger JC, *et al* Discontinuation of alprazolam after long term treatment of panic related disorders *Journal of Clinical Psychopharmacology* 1992, 12 352-354

17 Holton A, Riley P, and Tyrer P Factors predicting long-term outcome after chronic benzodiazepine therapy *Journal of Affective Disorders* 1992, 24 245 252

18 McDuff DR, Schwartz RP, Tommasello A, *et al* Outpatient benzodiazepine detoxification procedure for methadone patients *Journal of Substance Abuse and Treatment* 1993, 10 297 302

19 Habraken H, Soenen K, Blondeel L, *et al* Gradual withdrawal from benzodiazepines in residents of homes for the elderly experience and suggestions for future research *European Journal of Clinical Pharmacology* 1997, 51 355-358

20. Schweizer E, Rickels K, De Martinis N, *et al* The effect of personality on withdrawal severity and taper outcome in benzodiazepine dependent patients. *Psychological Medicine* 1998, 28 713-720

21 Petrovic M, D Pevernagie D, Mariman A, *et al* Fast withdrawal from benzodiazepines in geriatric inpatients a randomised double-blind, placebo-controlled trial *European Journal of Clinical Pharmacology* 2002, 57· 759-764

Reference List Appendix C

1 Cormack MA, and Sinnott A. Psychological alternatives to long-term benzodiazepine use *Journal of the Royal College of General Practitioners* 1983; 33:279-281

2. Nathan RG, Robinson D, Cherek DR, *et al* Alternative treatments for withdrawing the long-term benzodiazepine user a pilot study *International Journal of Addiction* 1986, 21 195-211

3 Higgitt A, Golombok S, Fonagy P, *et al.* Group treatment of benzodiazepine dependence *British Journal of Addiction* 1987, 82 517-532

4. Sanchez-Craig M, Cappell H, Busto U, *et al.* Cognitive-behavioural treatment for benzodiazepine dependence· a comparison of gradual versus abrupt cessation of drug intake *British Journal of Addiction* 1987, 82 1317-1327

5. Schmauss C, Apelt S, and Emrich HM Characterization of benzodiazepine withdrawal in high- and low-dose dependent psychiatric inpatients *Brain Research Bulletin* 1987, 19 393-400.

6. Crouch G, Robson M, and Hallstrom C Benzodiazepine dependent patients and their psychological treatment *Progressive Neuropsychopharmacology in Biological Psychiatry* 1988; 12 503-510.

7. Joughin N, Tata P, Collins M, *et al.* In-patient withdrawal from long-term benzodiazepine use *British Journal of Addiction* 1991; 86:449-455.

8. Otto MW, Pollack MH, Sachs GS, *et al* Discontinuation of benzodiazepine treatment: efficacy of cognitive-behavioral therapy for patients with panic disorder *American Journal of Psychiatry* 1993, 150 1485-1490

9. Elsesser K, Sartory G, and Maurer J The efficacy of complaints management training in facilitating benzodiazepine withdrawal. *Behavioural Research and Therapy* 1996; 34·149-156

10 Charney DA, Paraherakis AM, and Gill KJ. The treatment of sedative-hypnotic dependence evaluating clinical predictors of outcome *Journal of Clinical Psychiatry* 2000; 61 190-195

11. VormaH, Naukkarinen H, Sarna S, *et al* Treatment of out-patient with complicated benzodiazepine dependence comparison of two approaches. *Addiction* 2002, 97 851-859

Reference List Appendix D

1 Tyrer P, Rutherford D, and Huggett T. Benzodiazepine withdrawal symptoms and propranolol *Lancet* 1981; 1 520-522.

2 Schweizer E, and Rickels K. Failure of buspirone to manage benzodiazepine withdrawal *American Journal of Psychiatry* 1986, 143:1590-1592.

3. Lader M, and Olajide D. A comparison of buspirone and placebo in relieving benzodiazepine withdrawal symptoms *Journal of Clinical Psychopharmacology* 1987; 7·11-15

4 Ries RK, Roy-Byrne PP, Ward NG, *et al* Carbamazepine treatment for benzodiazepine withdrawal *American Journal of Psychiatry* 1989; 146·536-537.

5. Ashton CH, Rawlins MD, and Tyrer SP. A double-blind placebo-controlled study of buspirone in diazepam withdrawal in chronic benzodiazepine users. *British Journal of Psychiatry* 1990; 157:232-238

6 Udelman HD, and Udelman DL. Concurrent use of buspirone in anxious patients during withdrawal from alprazolam therapy. *Journal of Clinical Psychiatry* 1990, 51 Suppl 46-50

7 Cantopher T, Olivieri S, Cleave N, *et al* Chronic benzodiazepine dependence A comparative study of abrupt withdrawal under propranolol cover versus gradual withdrawal. *British Journal of Psychiatry* 1990, 156 406-411

8 Rickels K, Case WG, Schweizer E, *et al* Benzodiazepine dependence: management of discontinuation *Psychopharmacology Bulletin* 1990, 26 63-68

9 Garcia-Borreguero D, Bronisch T, Apelt S, *et al.* Treatment of benzodiazepine withdrawal symptoms with carbamazepine. *European Archives of Psychiatry Clinical Neuroscience* 1991, 241 145-150

10. Schweizer E, Rickels K, Case WG, *et al.* Carbamazepine treatment in patients discontinuing long-term benzodiazepine therapy Effects on withdrawal severity and outcome *Archives of General Psychiatry* 1991; 48 448-452

11. Di Costanzo E, and Rovea A. [The prophylaxis of benzodiazepine withdrawal syndrome in the elderly. the effectiveness of carbamazepine. Double-blind study vs. placebo]. *Minerva Psichiatrica* 1992, 33 301-304

12. Lader M, Farr I, and Morton S. A comparison of alpidem and placebo in relieving benzodiazepine withdrawal symptoms. *International Clinical Psychopharmacology* 1993; 8:31-36.

13 Ansseau M, and De Roeck J Trazodone in benzodiazepine dependence. *Journal of Clinical Psychiatry* 1993, 54:189-191.

14 Schweizer E, Case WG, Garcia-Espana F, *et al* Progesterone co-administration in patients discontinuing long-term benzodiazepine therapy effects on withdrawal severity and taper outcome. *Psychopharmacology (Berl)* 1995, 117:424-429.

15. Tyrer P, Ferguson B, Hallstrom C, *et al* A controlled trial of dothiepin and placebo in treating benzodiazepine withdrawal symptoms *British Journal of Psychiatry* 1996; 168 457-461.

16. Kaendler SH, Volk S, and Pflug B [Benzodiazepine withdrawal with carbamazepine] *Nervenarzt* 1996, 67 381-386

17 Lemoine P, Touchon J, and Billardon M [Comparison of 6 different methods for lorazepam withdrawal. A controlled study, hydroxyzine versus placebo] *Encephale* 1997, 23 290-299

18. Romach MK, Kaplan HL, Busto UE, *et al.* A controlled trial of ondansetron, a 5-HT3 antagonist, in benzodiazepine discontinuation *Journal of Clinical Psychopharmacology* 1998; 18·121-131

19. Garfinkel D, Zisapel N, Wainstein J, *et al* Facilitation of benzodiazepine discontinuation by melatonin a new clinical approach *Archives of Internal Medicine* 1999, 159.2456-2460

20 Rickels K, Schweizer E, Garcia EF, *et al.* Trazodone and valproate in patients discontinuing long-term benzodiazepine therapy· effects on withdrawal symptoms and taper outcome. *Psychopharmacology (Berl)* 1999, 141:1-5

21 Petrovic M, Pevernagie D, Van Den NN, *et al* A programme for short-term withdrawal from benzodiazepines in geriatric hospital inpatients· success rate and effect on subjective sleep quality *International Journal of Geriatric Psychiatry* 1999; 14:754-760.

22 Rickels K, DeMartinis N, Garcia-Espana F, *et al.* Imipramine and buspirone in treatment of patients with generalized anxiety disorder who are discontinuing long-term benzodiazepine therapy. *American Journal of Psychiatry* 2000, 157·1973-1979.

23. Zitman FG, and Couvee JE. Chronic benzodiazepine use in general practice patients with depression· an evaluation of controlled treatment and taper-off· Report on behalf of the Dutch Chronic Benzodiazepine Working Group *British Journal of Psychiatry* 2001, 178.317-324

PART II

MINIMAL INTERVENTION

Chapter 4

Discontinuation of long-term benzodiazepine use by sending a letter to users in family practice

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Abstract

Background - Minimal intervention strategies to decrease long-term benzodiazepine use in family practice have not yet been evaluated in large studies with a blinded control condition and a long follow-up period

Methods - The intervention evaluated in this study consisted of a letter with a discontinuation advice sent to long-term benzodiazepine users, followed by an invitation to consult the family physician after three months Prescription data were extracted from the physicians electronic medical dossier Primary endpoints were the amount of benzodiazepine prescription and the percentage of subjects without prescription (quitters) The course of long-term benzodiazepine users in practices receiving no intervention served as a control condition Duration of follow-up was 21 months

Results - The experimental group consisted of 2425 long term benzodiazepine users, 1707 of whom were adressed by letter The control group consisted of 1821 long term users In the short term (6 months) a reduction in benzodiazepine prescription of 24% was observed in the experimental group, versus 5% in the control group ($p<0.01$) A comparably large reduction was still present at the end of the follow-up Of the users in the experimental group 536 (24% of study completers) quit completely at short term, versus 183 (12%) in the control group ($p<0.01$) Of the quitters 42% in the control group and 56% in the experimental group remained benzodiazepine prescription free in the follow-up period ($p<0.01$)

Conclusion - This minimal intervention is an effective strategy to decrease long term benzodiazepine use in family practice

Introduction

Benzodiazepines are very effective drugs in the short-term treatment of anxiety and insomnia. However, with few exceptions, the use of benzodiazepines is recommended to be restricted for a short period,[1-3] as longer use may lead to benzodiazepine dependence and is associated with an increased risk of traffic accidents,[3 8] non-accidental falls with associated hip fractures,[9-11] and cognitive impairments.[12-14] In contrast to these recommendations, a prevalence range of long-term benzodiazepine use of 0.6-2.9% was found in the family practice, depending on the design of the study and the time frame of the assessment of use.[15]

10-40% of the long-term benzodiazepine users in family practice care was able to quit their benzodiazepine use as a result of minimal intervention strategies such as sending a letter, offering a special consultation, or offering family physician support combined with a self-help booklet.[16-18] Although sending patients a letter with discontinuation advice proved to be as effective as a group run by a psychologist,[19] a consultation with the family physician or sending information sheets in addition to a discontinuation letter,[16,17] the former intervention has not been evaluated in large samples with a substantial number of family physicians, a blinded control condition and a long-term follow-up, necessary to estimate the result of lasting intervention effects.

In the *Benzoredux* study, a family practice based intervention study, we created the opportunity to assess the short- and long-term effects of a benzodiazepine discontinuation letter in a large family practice care population in The Netherlands. In the Dutch Health Care system the family physician functions as a gatekeeper for secondary medical specialist care and all patients (70% in National Health Plan, 30% private insurance) are linked to one family physician, often for many years, allowing excellent opportunities for longitudinal research.

Methods

Study design

This prospective controlled intervention study in family practice received approval of the Committee on Research involving Human Subjects (known as CMO Arnhem/Nijmegen) The follow-up duration was 21 months and the study was carried out between August 1998 and December 2001.

Experimental group

We considered patients in 30 family practices, covering the primary care of 118,082 people. In these practices the electronic medical dossier (EMD) was used for patient administration and prescriptions. In the Netherlands 91% of the family physicians use a commercially available EMD.[20] Benzodiazepine users were selected from the EMD if they were actually using agents with the ATC (Anatomical Therapeutical Code) codes: N05BA, N05CD and N03AE01.[21] Current users met the

criteria for long term use if 1) the prescriptions for benzodiazepines covered a period of more than three months and 2) the amount of prescribed pills during the last three months before study inclusion was sufficient for 60 days use according to the family physician's prescription Long term users were excluded if they met one of the following criteria current treatment for mental illness in secondary care, drug or alcohol dependence, psychotic episodes in medical history, suffering from epilepsy, having a terminal disease, or not having mastered the Dutch language Additionally, subjects were excluded for specific individual reasons brought up by the family physician (severe co-morbidity, psychosocial conditions, high age, severe disability or having moved away from the practice, figure 1)

Intervention

The intervention consisted of a letter, with the advice to gradually discontinue benzodiazepine use, sent by the family physician (DL=discontinuation letter), followed by a written invitation to arrange an appointment with the family physician after 12 weeks in order to evaluate actual benzodiazepine use (EC=evaluation consultation) The letter used by Cormack *et al* served as a model because of the proven short-term effectiveness [17] The median time between sending the discontinuation letter and the evaluation consultation was 14 weeks

Assessments

Prescription data were automatically extracted from the family physician's EMD We used the sum of the prescribed daily doses (PDD) of all benzodiazepine prescriptions prescribed within 3-month time periods (each 3-month period consisted of 91 days exactly) PDD's were calculated according to the recommendations of Zitman and Couvee [22] Baseline recorded prescription covered the three months before sending the DL, follow-up recorded prescription covered the subsequent 3-month periods after the DL was sent Other patient assessments were age, gender and type of health insurance (private or National Health Plan)

Control group

At the end of the follow-up 19 control practices were selected from the LINH network This network reflects a valid sample of all Dutch family practices in which 3-monthly automated EMD extractions provide a longitudinal database of prescriptions, consultations and referral data [23] Practices were selected on the basis of two criteria 1) the EMD system of the practice corresponded with one of the EMDs in the experimental practices, 2) EMD data about prescriptions and consultations had been extracted from 1/1/1998 The practices corresponded on average with the experimental practices regarding location and organisational type We extracted the benzodiazepine prescription data of the selected practices covering the study period from the LINH database During the study period, the family physicians of the control practices were not aware of their later inclusion in the control group in order to avoid Hawthorne effects [24,25] The same definitions as in the experimental condition were used

in the control condition for long-term use and time periods

Statistical analysis

Statistical comparisons were performed over three time periods baseline (last 3 months before DL), short term evaluation (the period of 4-6 months after DL) and the end of the follow-up (the period of 19-21 months after DL) This was done for the experimental group as a whole, for the subjects in the experimental group who received the DL (DL intervention group), for the subjects in the experimental group who did not receive the DL (DL excluded group) and for the control group

Quitters were defined as subjects for whom no benzodiazepine prescription was prescribed in the period of 4-6 months after DL was sent Relapse among quitters was defined as any new issue of a benzodiazepine prescription in the follow-up period following the short term evaluation Any analysis of benzodiazepine precription was performed among subjects who completed the study (subjects in practice till 21 months after the DL was sent) Differences in the amount of benzodiazepine prescription were analysed with student t-tests and the signed rank test (in case of non-normal distribution) In comparisons of prevalences of quitters Chi-square tests were performed Two sided p-values were used, with alpha is 0 05

Within the follow-up period 260 DL intervention group subjects received a more intensive follow-up consisting of a maximum of 5 measurements at different moments with questionnaires concerning the subject of benzodiazepine dependence, personality, mood, general health, quality of life, medical costs and a memory test Of these subjects 104 reported at the EC that they had quit benzodiazepine use The other 156 subjects gave informed consent to participate in a 6-week benzodiazepine tapering-off trial, starting at least six months after the DL was sent (N=128 on active treatment and N=28 in a regular care control condition) For our assessment of the effects of the DL, and in order to avoid selection bias, we included these 156 subjects in the follow-up analysis assuming that they would have continued their use in the same amount as in the short term evaluation period of 4-6 months after the DL was sent (last observation carried forward method) This has a conservative influence on the effect sizes of the comparison The 104 quitters at the EC, were accepted unconditionally as they had not received any intervention aimed at preserving abstinence, allowing for relapse, thus also a conservative measure

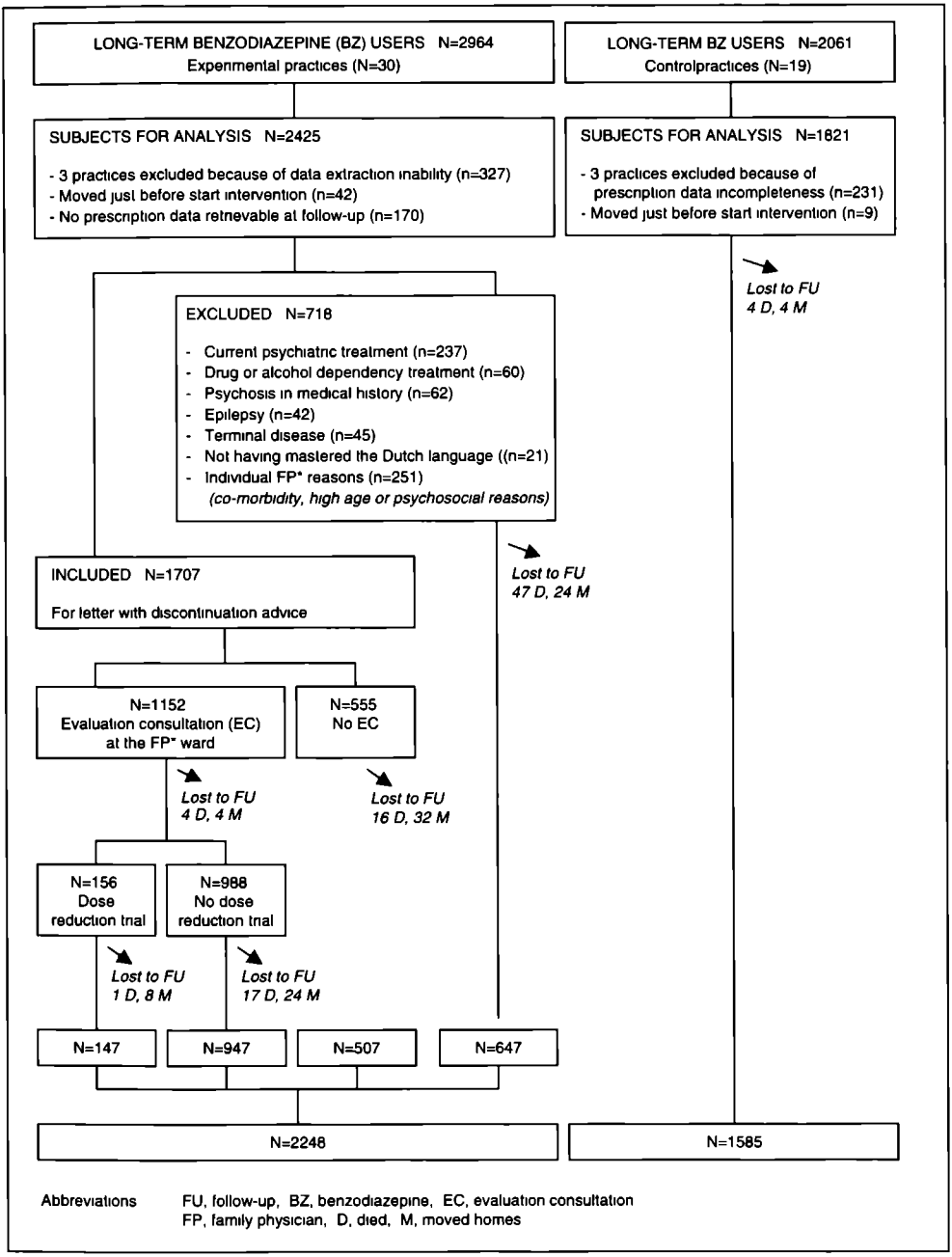
Results

Subjects, lost to follow-up and data completeness (figure 1)

Three experimental and three control practices were excluded from the analysis because no complete recovery of data could be attained Furthermore 170 experimental group subjects were excluded because the complete patient file (including baseline benzodiazepine prescription values) had been

Figure 1

Subjects, lost to follow-up and data completeness



deleted by the family physician, probably after deregistration due to having moved away from the practice or death. This left 2425 subjects in the experimental group versus 1821 subjects in the control group at baseline. At the end of the 21 month follow-up 93% (2248/2425) of the experimental group versus 87% (1585/1821) of the control group subjects were still in the practice ($p<0.01$). Lost to follow-up subjects in the experimental group were younger (66 years versus 72 years in the control group) and less of the female gender (65% versus 72% females in the control group).

Baseline characteristics (table 1)

No clinically significant baseline differences between the experimental group and the control group were observed in age, gender, insurance type or number of different benzodiazepines prescriptions at baseline. In the experimental practices oxazepam had been prescribed relatively more than in the control practices ($p<0.01$). Compared to the DL excluded group, the patients in the DL intervention group were younger, more were female and were less often on a National Health Plan. Also a lower percentage of subjects received prescriptions of more than one different benzodiazepine in the 3-month baseline period (all $p<0.05$).

Baseline benzodiazepine prescription was not significantly different between the control and the experimental group ($p=0.27$, $p=0.43$ when adjusted for age, gender and insurance type) (table 2). To subjects in the DL intervention group at baseline significantly less benzodiazepines were prescribed compared to the DL excluded group subjects ($p<0.01$). The prescription of benzodiazepines till date of intervention appeared stable: in the periods of 7-9 months and 4-6 months before the intervention the mean PDD number was 72 (SD:78){median:45} and 76 (78){52.5} in the control group and 76 (92){45} and 78 (88){45} in the experimental group respectively (not in table).

Table 1

Baseline characteristics

	Control group	Experimental group		
		Total	DL Intervention group	DL Excluded group
N long term benzodiazepine users	1821	2425	1707	718
Age (yr) (mean (SD))	64 9 (15.5)	62 2 (15.0)	63 1 (14 1)	59 9 (16 6)
Gender (% female)	72 9	70 6	73 1	64 6
Health insurance (% National Health)	80 2	79 6	78 0	83 3
Type of benzodiazepine (%):				
oxazepam	26 3 %	35 8 %	36.6 %	34 0 %
temazepam	23 6 %	20 7 %	21 4 %	19 1 %
diazepam	11 4 %	11 7 %	12.2 %	10 7 %
other	38 7 %	31 8 %	29.8 %	36.2 %
Prescriptions of more than one different benzodiazepine at baseline (% of subjects)	19.1 %	18 1 %	16 4 %	22.0 %

Table 3

Benzodiazepine prescription of quitters and non quitters in PDD[1]

		Control Group (N=1585)			Experimental Group (N=2248)					
				Total (N=2248)		DL Intervention Group (n=1601)		DL Excluded Group (n=647)	
		Non-quitters	Quitters	Non-quitters	Quitters	Non-quitters	Quitters	Non-quitters	Quitters
Number of patients[2]		(n=1402)	(n=183)	(n=1712)	(n=536)	(n=1155)	(n=446)	(n=557)	(n=90)
Baseline:	*mean ±sd*	80 ±75	52 ±55	91 ±99	44 ±49	82 ±85	44 ±51	108 ±120	42 ±36
(3 months before DL)[3]	*median*	60	34	60	30	60	30	66	30
Short term evaluation:	*mean ±sd*	81 ±86		80 ±97	-	68 ±74	-	106 ±127	-
(4-6 months after DL)	*median*	59		45	-	45	-	63	-
			relapse?[4] yes (n=107)	no (n=76)	relapse?[4] yes (n=237)	no (n=299)	relapse?[4] yes (n=195)	no (n=251)	relapse? yes (n=42)	no (n=48)
End of follow-up:	*mean ±sd*	75 ±89	32 ±52	-	74 ±94	23 ±40	-	66 ±75	22 ±38	-	91 ±124	28 ±46	-
(19-21 months after DL)	*median*	45	15	-	45	10	-	45	10	-	55	12	-

1. PDD = number of 3-month prescribed daily doses.
2. Subjects with complete 21-month follow-up only.
3. DL refers to the date of sending the discontinuation letter (DL Intervention group) or equivalent time point in case no letter was sent (DL excluded group and control group).
4. If yes, relapse refers to quitters who restart benzodiazepines during follow-up, if yes, relapse refers to remaining benzodiazepine prescription free till the end of follow-up.

Note: Mean (±sd) baseline PDD of the subjects that 'relapse / continue abstinence': in the control group 53 ±58 / 49 ±51; the total experimental group. 48 ±62 / 41 ±35; the DL intervention group: 49 ±62 / 40 ±34; the DL excluded group: 42 ±37 / 42 ±35.

Evaluation of the mean benzodiazepine prescription (table 2)

In all four groups (control, experimental total, experimental DL intervention, experimental DL excluded), a significant reduction in benzodiazepine prescription in the first 6 months after the DL was sent was observed (difference short-term evaluation with baseline: $p<0.01$ in all groups). The reduction of benzodiazepine prescription was significantly higher in the experimental group (24%) as compared to the control group (5%) ($p<0.01$). Among the subjects of the DL intervention group this reduction was in percentage the highest (32%) and in the DL excluded group it was 8%. In the 15 months following the short-term evaluation a further decrease in benzodiazepine prescription was observed in the control group (4%, $p<0.01$), and the DL excluded group (12%, $p<0.01$). No differences between end of follow-up values and short-term evaluation values were observed in the total experimental group (3%, $p=0.14$) and in the DL intervention group (2% increase, $p=0.4$).

Table 2

Mean benzodiazepine prescription per 3 months periods in PDD[1]

		Control Group (n=1585)	Experimental Group (n=2248)		
Number of patients[2]			Total (n=2248)	DL Intervention group (n=1601)	DL Excluded group (n=647)
Baseline					
PDD 3 months before DL[3]	mean ±sd	76 ±74	80 ±91	72 ±79	99 ±114
	median	54	45	45	60
Short term evaluation					
PDD 4-6 months after DL	mean ±sd	72 ±85	61 ±91	49 ±70	91 ±124
	median	45	30	30	46
End of follow-up					
PDD 19-21 months after DL	mean ±sd	69 ±86	59 ±88	50 ±70	80 ±118
	median	45	30	30	45

1 PDD = number of prescribed daily doses per 3-month period
2 Subjects with complete 21-month follow-up only
3 DL refers to the date of sending the discontinuation letter (DL Intervention group) or equivalent time point in case no letter was sent (DL excluded group and control group)

Evaluation of complete discontinuation (table 3)

Of the experimental group 536 subjects (24%) did not receive any benzodiazepine prescription in the period 4-6 months after the DL (quitters), versus 183 subjects (12%) in the control group ($p<0.01$). The crude Odds ratio for quitting, being a member of the experimental group was 2.4 (95%-c.i.: 2.0 – 2.9). Adjustment for age, gender, insurance, baseline benzodiazepine prescription and benzodiazepine type did not change the Odds ratio nor the 95% confidence interval boundaries. Of the 536 experimental group subjects the majority (N=446, 83%) had actually received the DL. The percentage of short term discontinuation in the DL intervention group was 28% (446/1601) and in the DL excluded group 14% (90/647).Non-quitters had a significantly higher baseline benzodiazepine

prescription than quitters (table 3, all 4 groups p<0 01) Among the non-quitters in the experimental group a reduction in benzodiazepine prescription in the first 6 months was observed of 11% (p<0 01), whereas no reduction was observed among non-quitters in the control group The reduction in benzodiazepine prescription in the 7-21 months follow-up was 7% in both the experimental and the control group of non-quitters (separate p<0 01)

Of the quitters 42% in the control group and 56% in the experimental group remained benzodiazepine prescription abstinent till the end of follow-up (difference control-experimental p<0 01) In both groups of quitters more than half of the subjects who relapsed, did so within the first 3 months The PDD level at 21 months of the subjects who relapsed was significantly lower compared with their baseline level, 60% of the baseline level in the control group and 48% in the experimental group respectively (separate p<0 01) Baseline PDD of continued abstinent subjects was not significantly different from the mean baseline level of quitters who relapsed

Discussion

The present study firmly demonstrated that a minimal intervention strategy with a discontinuation letter induces a substantial and lasting reduction of benzodiazepine use among long term benzodiazepine users in family practice

The effectiveness of the intervention was evident on both major endpoints a reduction of 24% (versus 5% in the control group) in the amount of benzodiazepine prescription and a doubled chance of quitting (24% versus 12%) in the first 6 months For the non-quitters in both the control and the experimental group, the course in follow-up after 6 months was characterised by a slow, further decline, indicating that the gain of the intervention established in the first 6 months was preserved Using our strict definition of relapse, about half of the quitters were able to remain benzodiazepine prescription free till the end of the study Relapse occurred significantly more often in the control group which suggests a long term intervention effect Furthermore, quitters who relapsed in use, fell back to dosage levels that might indicate a shift from continuous to intermittent use

The discontinuation letter used in the present study was based on a letter developed by Cormack e a and our short term results were comparable [17] The advantages of our study were that we included much larger numbers of family physicians and long term benzodiazepine users from different primary care settings, used a blinded control group and established the long term efficacy of the intervention

Benzodiazepine discontinuation is easier when using lower doses [18 26-28] Indeed, in our study, the baseline PDD of quitters was about half the baseline PDD of non-quitters

Fifty percent of all long term users received at baseline benzodiazepine precription for an average daily dose equal or less than 0 5-0 6 DDD Benzodiazepine prescription of up to 9 months before the intervention showed the consistency of use in this group and the results in the control group

indicated that only 5% of these users could obtain long term abstinence without an intervention. In which content this consistency reflects benzodiazepine dependence is not clear. Recently, using substance dependence criteria of the ICD-10 and DSM-IIIR, prevalence of benzodiazepine dependence was estimated at 40-52% of all benzodiazepine users in family practice in the Netherlands.[6]

Concerning the validity, first, there was a statistically significant difference between the experimental and control group in baseline benzodiazepine type, mainly for the use of oxazepam. Benzodiazepine type however was not critically related to the outcome as the crude Odds ratio of quitting was not affected after adjustment by benzodiazepine type. Second, in the absence of a valid control group for the DL intervention group only, the exact effect-size of the discontinuation letter intervention could not be determined. However it can be expected that family physicians in daily care will differ in the application of the exclusion criteria for this intervention. We consider it a major strength of this study that we surpassed the individual physician's level of choice by evaluating all experimental group long term users, regardless of having been included in receiving the letter, leading to a more pragmatic effect-size of the intervention. Third, a small percentage of the intervention group subjects received a second intervention (trial) aimed to reduce benzodiazepine use in the follow-up period. We believe that this may only have had a minor influence on our overall results. Actually, 128 subjects received an active treatment in this trial which is only 5% of the total experimental group. For these subjects in the analysis, the pre-trial level of benzodiazepine prescription was carried forward to serve as follow-up scores, which we believe is a conservative approach as this was a group motivated to undertake further action to quit. In addition, this trial couldn't have influenced the percentage of quitters and continued abstinent subjects.

We conclude that the present strategy is an effective and practical tool which can be used to decrease long term benzodiazepine use in family practice.

References

1 Ashton H Guidelines for the rational use of benzodiazepines When and what to use *Drugs* 1994,48 25-40

2 Committee on the Safety of Medicines (CSM) Benzodiazepines, dependence and withdrawal symptoms *Current Problems* 1988,21 1 2

3 Lader MH Limitations on the use of benzodiazepines in anxiety and insomnia are they justified? *European Neuropsychopharmacology* 1999,9 Suppl 6 S399 S405

4 American Psychiatric Association Benzodiazepine dependence, toxicity and abuse A task force report of the American Psychiatric Association Washington DC American Psychiatric Association, 1990

5 Tyrer P Benzodiazepine dependence a shadowy diagnosis *Biochem Soc Symp* 1993,59 107-119

6 Kan CC, Breteler MH, and Zitman FG High prevalence of benzodiazepine dependence in out-patient users, based on the DSM-III-R and ICD-10 criteria *Acta Psychiatrica Scandinavica* 1997,96 85-93

7 Barbone F, McMahon AD, Davey PG *et al* Association of road traffic accidents with benzodiazepine use *Lancet* 1998,352 1331 1336

8 Hemmelgarn B, Suissa S, Huang A, *et al* Benzodiazepine use and the risk of motor vehicle crash in the elderly *Journal of the American Medical Association* 1997,278 27 31

9 Ray WA, Griffin MR, Schaffner W, *et al* III Psychotropic drug use and the risk of hip fracture *New England Journal of Medicine* 1987,316 363-369

10 Wang PS, Bohn RL, Glynn RJ, *et al* Hazardous benzodiazepine regimens in the elderly effects of half life, dosage, and duration on risk of hip fracture *American Journal of Psychiatry* 2001,158 892 898

11 Herings RM, Stricker BH, De Boer 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

12 Curran HV Benzodiazepines, memory and mood a review *Psychopharmacology* 1991,105 1 8

13 Tata PR, Rollings J, Collins M, *et al* Lack of cognitive recovery following withdrawal from long term benzodiazepine use *Psychological Medicine* 1994,24 203-213

14 Verwey B, Eling P, Wientjes H, *et al* Memory impairment in those who attempted suicide by benzodiazepine overdose *Journal of Clinical Psychiatry* 2000,61 456-459

15 Zandstra SM, Furer JW, Van de Lisdonk EH, *et al* Different study criteria affect the prevalence of benzodiazepine use *Social Psychiatry and Psychiatric Epidemiology* 2002,37 139-144

16 Cormack MA, Owens RG, and Dewey ME The effect of minimal interventions by general practitioners on long- term benzodiazepine use *Journal of the Royal College of General Practitioners* 1989,39 408-411

17 Cormack MA, Sweeney KG, Hughes-Jones H, *et al* Evaluation of an easy, cost-effective strategy for cutting benzodiazepine use in general practice *British Journal of General Practice* 1994,44 5-8

18 Bashir K, King M, and Ashworth M Controlled evaluation of brief intervention by general practitioners to reduce chronic use of benzodiazepines *British Journal of General Practice* 1994,44 408-412

19 Cormack MA, and Sinnott A Psychological alternatives to long-term benzodiazepine use *Journal of the Royal College of General Practitioners* 1983,33 279-281

20 Wolters I, Van den Hoogen H, and De Bakker D Evaluatie invoering Elektronisch Voorschrijf Systeem Monitoringsfase de situatie in 2001 Utrecht NIVEL, 2002 45-46

21 WHO Collaborating Centre for Drugs Statistics Methodology Guidelines ATC classification and DDD assignment Oslo WHO/NCM, 1996

22 Zitman FG, and Couvee JE Chronic benzodiazepine use in general practice patients with depression an evaluation of controlled treatment and taper off report on behalf of the Dutch Chronic Benzodiazepine Working Group *British Journal of Psychiatry* 2001,178 317-324

23 De Bakker D, Jabaaij L, Abrahamse H, *et al* Jaarrapport LINH 2000 Contactfrequenties en verrichtingen in het Landelijk Informatie Netwerk Huisartsenzorg (LINH) Utrecht/Nijmegen NIVEL/WOK, 2001

24 De Burgh S, Mant A, Mattick RP, *et al* A controlled trial of educational visiting to improve benzodiazepine prescribing in general practice *Australian Journal of Public Health* 1995 19 142-148

25 Holm M Intervention against long-term use of hypnotics/sedatives in general practice *Scandinavian Journal of Primary Health Care* 1990,8 113-117

26 Linden M, Bar T, and Geiselmann B Patient treatment insistence and medication craving in long-term low-dosage benzodiazepine prescriptions *Psychological Medicine* 1998,28 721-729

27 Rickels K, Schweizer E, Case WG, *et al* Long-term therapeutic use of benzodiazepines. I. Effects of abrupt discontinuation. *Archives of General Psychiatry* 1990,47:899-907

28. Rickels K, Case WG, Schweizer E, *et al* Long-term benzodiazepine users 3 years after participation in a discontinuation program *American Journal of Psychiatry* 1991;148·757-761

Chapter 5

Predictors of relapse after discontinuation of long-term benzodiazepine use by minimal intervention: 2-year follow-up study

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Abstract

Background - Minimal intervention strategies to cut down benzodiazepine use in general practice are effective in 1 out of 5 long-term benzodiazepine users Long-term results, however, are not available

Objective - To evaluate the relapse rate over a two-year period and to search for predictors of relapse among patients who quit benzodiazepine use based on a minimal intervention, i e a letter containing advice to quit from their GP

Methods - Prospective monitoring of GP medical records and two additional assessments of 109 patients who quit their long-term benzodiazepine use of their own accord Cox-regression analyses were performed to search for independent predictors of relapse

Results - Of the 285 patients who quit benzodiazepines in the short-term, 109 patients (38%) gave informed consent for the follow-up study After 819 ±100 days of follow-up, 53 (49%) patients had remained completely abstinent, while 3 out of 5 patients who relapsed showed better usage patterns Two independent predictors of relapse were identified use of high dosage (more than 10 mg diazepam equivalent) before receiving the letter (RR = 2 4 [1 2 - 4 7]) and poor general health perception (RR = 0 98 [0 97 - 0 99]), the latter made only a marginal contribution to the prediction model

Conclusion - Short-term success rates after a minimal intervention were maintained well during long-term follow-up Patients using high dosages before the intervention had the highest risk of relapse and should be monitored more closely by the GP

Introduction

Several guidelines advise benzodiazepine prescription only in limited circumstances and for short periods of time [1,2,3] Nevertheless, a review study including some recent data on the Dutch population, points out that 2 to 3% of the population use benzodiazepines chronically [4] This proportion of long-term users has hardly changed over the past 10 years in the Netherlands The majority is treated, i e receive prescriptions for benzodiazepines, in primary care [5] About 20% of long-term users in primary care successfully quit their benzodiazepine use in the short term with the aid of a minimal intervention [6] Examples of minimal interventions are a letter containing advice to quit, an advisory consultation, or an informational meeting [6,7,8,9,10] These interventions are especially attractive in the context of general practice, where time is limited and consultations often last no more than 10 minutes The long-term effects of minimal interventions have not yet been evaluated [11] Such evaluations are essential to predict the outcome of implementation and to identify patients who are at most risk of relapse so that they can be monitored more closely

Therefore, we carried out a long-term prospective follow-up study on patients who successfully stopped their benzodiazepine use of their own accord after receiving a letter containing advice to quit from their general practitioner Our purpose was (a) to estimate the rate of relapse in the long-term and to describe the patterns of relapse, (b) to search for clinical predictors of relapse and (c) to monitor psychological functioning and switches to other medication

Methods

Design and recruitment

Long-term benzodiazepine users (n = 2964) were identified by means of a computerised search for benzodiazepine prescriptions at 30 general practices in rural and urban areas of the Netherlands, at which 58 GPs were covering primary care for about 118 000 patients Long-term use was defined as benzodiazepine use for at least three months with an amount sufficient for at least 60 days of consumption according to the prescription rules Exclusion criteria were current psychiatric treatment (n=281), current treatment for drug or alcohol dependence (n=82), medical history of psychosis (n=80), epilepsy (n=53), insufficient mastery of the Dutch language (n=59), and terminal illnesses (n=26) Furthermore, some people were excluded specifically at the GP's request because of severe co-morbidity or for current psychosocial reasons (n=379)

The remaining 2004 benzodiazepine users received a letter from their GP containing advice to quit gradually (=discontinuation letter, see appendix) They were invited to the surgery in a second letter sent three months later At this consultation, the study procedures were explained and informed consent to participate in the study was sought if they had been able to achieve complete abstinence

since receiving the discontinuation letter Patients who were still using benzodiazepines were asked to participate in a RCT, comparing tapering-off with or without group psychotherapy The results of this RCT are reported elsewhere The study received ethical approval from the University Medical Centre Nijmegen and was performed from 1998 to 2001

Measurements

The use of benzodiazepines and other prescribed drugs was monitored prospectively in the medical records for a mean (±sd) duration of 819 (±100) days Benzodiazepine use relapse was defined as receiving a prescription during follow-up In addition, patients were assessed by self-report questionnaires directly after giving informed consent (baseline) and in a follow-up assessment after a mean (±sd) follow-up of 659 (±43) days Both assessments took place at the participants' homes by trained research assistants We assessed the use of caffeine, nicotine, and alcohol (including the detection of problem drinkers based on the 18-item list of Cornel)[12], psychological well-being (GHQ 12-item version)[13], mood (the scales depression, anger, fatigue, vigour and tension of the 32-item shortened profile of mood states, POMS)[14], and quality of life on eight different health domains physical functioning, role functioning - physical problem, role functioning - emotional problem, vitality, mental health, social functioning, pain and general health (Medical Outcome Study Short-Form 36, SF-36)[15], and the personality characteristics negativism, somatisation, shyness, psychopathology and extraversion (Dutch shortened MMPI, NVM) [16]

Analyses

Patients' prescription patterns during follow-up were classified according to Couvée *et al* (2002) to provide detailed information for those patients who relapsed This classification system is based on general guidelines on the adequate maximum duration of treatment with benzodiazepines [17] It describes systematically 14 prescription patterns with pattern 1 benzodiazepine-free, to pattern 14 benzodiazepine use during more than 95% of the follow-up period at a higher dosage than at the beginning of the study Based on these prescription patterns, four outcome categories can be established category A, success, B, partial success, C, minor success, and D, failure

Predictors of relapse were analysed by means of Cox regression analysis, with time to relapse as the dependent variable, and the following independent variables daily dosage (dichotomised at 10 mg diazepam equivalent), half-life (dichotomised at 24 hours), potency (presence of a 4-aryl group), self-reported hypnotic or anxiolytic use, use of antidepressants (yes/no), use of pain medication (yes/no), and the variables measured at the baseline assessment Variables with univariate risk ratios of $p<0.10$ were entered into the multivariate Cox regression analysis using a backward elimination procedure

To compare the clinical status of patients who remained abstinent to those who relapsed, repeated measure ANOVAs were performed with one within subject factor with 2 levels (baseline versus follow-up assessment) and one between subject factor (relapse yes/no) with all continuous variables measured at both assessments. Categorical data were analysed by means of chi-square tests.

Results

Figure 1

Recruitment and participations of long-term benzodiazepine users in the trial

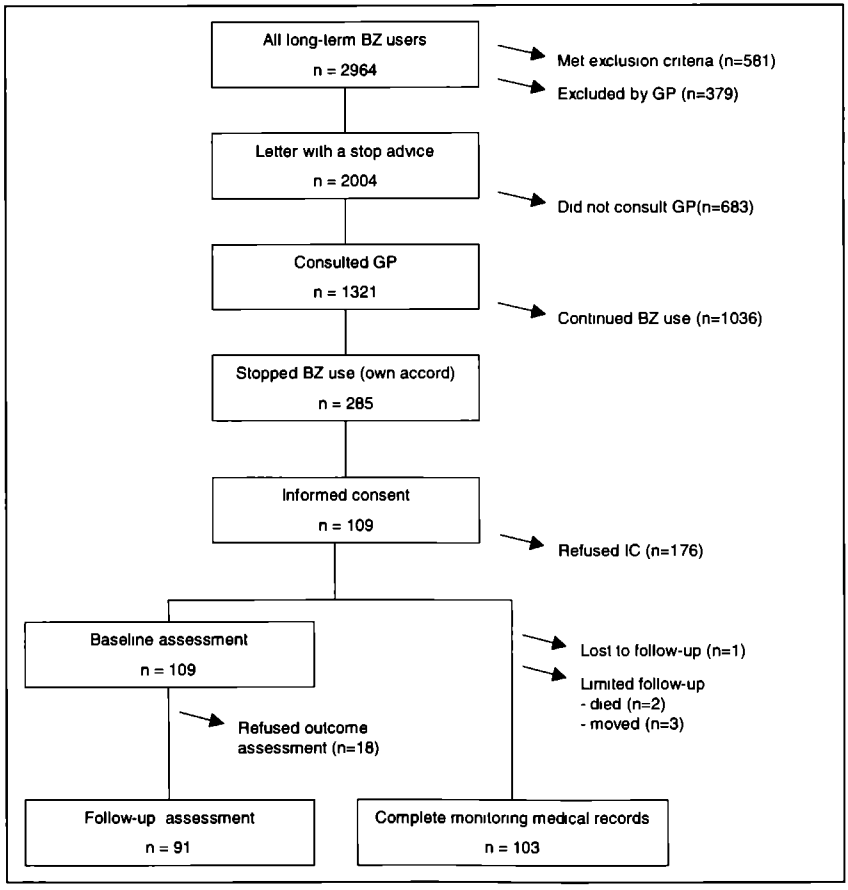


Table 1

Baseline characteristics of the study population

		Total group	Outcome at follow-up	
			Complete abstinence	Relapse
		n = 108	*n = 53*	*n = 55*
Demographic variables:				
Gender	Males (%)	**33 (31%)**	15 (28%)	**18** (33%)
Age (years)	Mean (S D)	**63 (13)**	61 (13)	65 (13)
Stable relationship	No relationship	**43 (40%)**	18 (34%)	25 (46%)
Only primary educational level	Yes (%)	**31 (29%)**	16 (30%)	15 (27%)
Income by profession	Yes (%)	**17 (16%)**	8 (15%)	9 (16%)
Benzodiazepine usage:				
Duration of benzodiazepine use (years)	Mean (S D)	**6.8 (6.5)**	6 9 (6 2)	6 7 (6 9)
Daily dose in mg diazepam equivalent	Mean (S D)	**6.2 (6.0)** *	5 0 (3.4)	7 4 (7 5)
Benzodiazepine category	Short-acting (%)	**94 (87%)**	48 (91%)	46 (84%)
Exclusively (self-report) hypnotic use	Yes (%)	**65 (60%)**	28 (58%)	37 (67%)
Substance / drug use:				
Caffeine	Yes (%)	**80 (74%)**	39 (74%)	41 (75%)
Nicotine	Yes (%)	**35 (32%)**	18 (34%)	17 (31%)
Alcohol	Yes (%)	**54 (50%)**	23 (43%)	31 (56%)
Problematic alcohol use	Yes (%)	**4 (6%)**	2 (9%)	2 (7%)
Antidepressants	Yes (%)	**21 (19%)**	11 (21%)	10 (18%)
Pain medication	Yes (%)	**47 (44%)**	25 (47%)	22 (40%)
Dutch shortened MMPI:				
Negativism	Mean (S.D)	**10.7 (6.6)**	10 3 (6.4)	11.1 (6 8)
Somatisation	Mean (S D)	**13.9 (7.0)**	13 2 (6.6)	14.6 (7 3)
Shyness	Mean (S D)	**10.4 (7.0)**	10 4 (7 0)	10.5 (7 3)
Psychopathology	Mean (S D)	**2.7 (3.6)**	2 5 (2 5)	3 0 (4 4)
Extraversion	Mean (S D)	**13.0 (5.9)**	13 2 (5.9)	12.8 (5 9)
Profile Of Mood State:				
Depression	Mean (S D)	**11.9 (5.0)**	11 7 (5 2)	12 1 (4 9)
Anger	Mean (S.D)	**10.4 (4.8)**	10 4 (4 8)	10.3 (4.8)
Fatigue	Mean (S.D)	**12.1 (6.0)**	11 3 (5.5)	12 9 (6 4)
Vigour	Mean (S D)	**14.8 (4.6)**	15 0 (4.3)	14.5 (4 9)
Tension	Mean (S D)	**11.4 (5.3)**	11 3 (5 5)	11.4 (5 1)
Short-Form 36 (range 0 - 100):				
Physical functioning	Mean (S D)	**65 (28)**	68 (26)	62 (29)
Role functioning - physical problem	Mean (S D)	**60 (40)**	67 (38)	54 (42)
Pain	Mean (S D)	**63 (25)**	63 (24)	64 (26)
General health perception	Mean (S D)	**58 (20)**	62 (16)	54 (23)
Vitality	Mean (S D)	**56 (22)**	60 (21)	53 (23)
Social functioning	Mean (S D)	**65 (23)**	68 (23)	63 (22)
Role functioning - emotional problem	Mean (S D)	**70 (40)**	72 (38)	68 (42)
Mental health	Mean (S D)	**71 (18)**	73 (16)	69 (19)
General Health Questionnaire – 12	Mean (S D)	**1.7 (3.0)**	1.8 (3 3)	1 6 (2 7)

* Self-reported daily benzodiazepine dosage at baseline was 6.6 ±4 3 mg diazepam equivalence

Recruitment, participation and drop-outs

Figure 1 shows the progress of the total population during the trial 2964 long-term users were identified, the GP advised 2004 persons to stop their benzodiazepine use, 1321/2004 (66%) visited their GP in order to evaluate the effect of the letter Of those patients, 285/1321 (22%) had successfully stopped their use and of the stoppers 109/285 gave informed consent (figure 1) Participants (n=109) and non-participants (n=176) did not differ with respect to age (63 ±4 3 years) and gender (69% female sex) However, participants had been using significantly higher benzodiazepine dosages before receiving the discontinuation letter (6 6 ±4 3 versus 5 1 ±4 5 mg diazepam equivalent, p<0 01) Based on the prescription records the year prior to the study, 94 (87%) patients received prescriptions for daily use, while 15 patients intermittently received prescriptions for periods of less than 60 (n=5) or 90 (n=10) days One patient was lost to follow-up from the medical records, which left 108 evaluable patients In five patients, the duration of follow-up was limited to an average of 488 days (range 183 - 671) (two moved, three died) Eighteen (17%) patients did not complete the follow-up assessment (see figure 1) The rate of relapse did not differ between patients who completed the follow-up assessment and those who did not (p = 0 16)

Characteristics of the study participants

Psychopathological dysfunction was relatively mild Based on a cut-off score of 2/3 on the General Health Questionnaire 12-item version, 23% of the patients were classified as psychiatric cases The scores on other questionnaires showed no or only small deviations from norm scores (see table 1) Half of the patients (50%) used alcohol, 32% used nicotine and 74% drank caffeine

Long-term outcomes

After quitting benzodiazepine use of their own accord, 53/108 (49%) patients remained completely abstinent during the 2-year follow-up, while 55/108 patients relapsed after a median period of abstinence of 243 days (P_{25} = 97 days, P_{75} = 459 days) Based on the classification of Couvée *et al* (2002)[17], 79 (73%) patients were classified as success, 4 (4%) as partial success, 5 (5%) as minor success, and only 20 (19%) as failure Of the 15 patients who received prescriptions for intermittent usage before sending the letter, 14 (93%) ended up in category A (success) Table 2 presents a more detailed overview of this classification.

Table 2

BZ prescription patterns according to Couvée *et al* (2001) during follow-up

	Outcome categories	Total group n	(%)	Totals	(%)
A	**Success**			**79**	**(73%)**
1	Benzodiazepine-free	53	(49%)		
2	Benzodiazepine use one episode ≤ 15 days	10	(9%)		
3	Benzodiazepine use > one episode ≤ 15 days	3	(3%)		
4	Benzodiazepine use one episode > 15 days and ≤ 30 days	6	(6%)		
5	Benzodiazepine use > one episode > 15 days and ≤ 30 days	7	(6%)		
B	**Partial success**			**4**	**(4%)**
6	Benzodiazepine use one episode > 30 days and ≤ 60 days	2	(2%)		
7	Benzodiazepine use > one episode > 30 days and ≤ 60 days	1	(1%)		
8	Benzodiazepine use one episode > 60 days and ≤ 90 days	1	(1%)		
9	Benzodiazepine use > one episode > 60 days and ≤ 90 days	-			
C	**Minor success**			**5**	**(5%)**
10	Benzodiazepine use > 90 days no use at time of follow-up	4	(4%)		
11	Benzodiazepine use > 95% of follow-up time, lower dose	1	(1%)		
D	**Failure**			**20**	**(19%)**
12	Benzodiazepine use > 90 days and use at time of follow-up	12	(11%)		
13	Benzodiazepine use > 95% of follow-up time, same dose	3	(3%)		
14	Benzodiazepine use > 95% of follow-up time, higher dose	5	(5%)		
		108			

Predictors of benzodiazepine use during follow-up

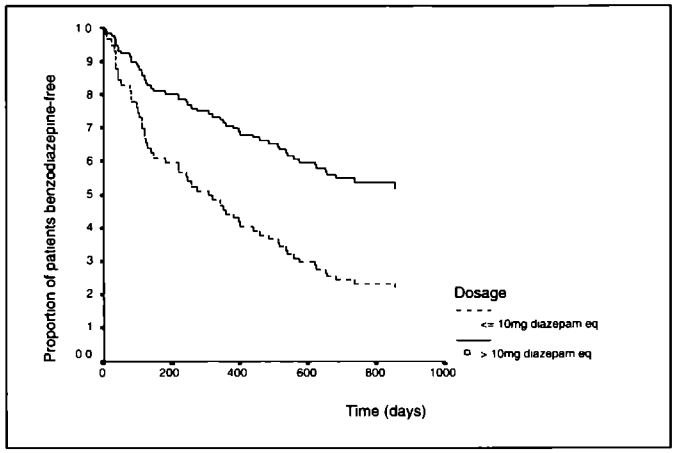
Four variables were related univariately to relapse: baseline benzodiazepine dosage, and three dimensions of the SF-36: general health perception, vitality and mental health. The multivariate Cox regression analyses (model: chi-square = 8.8. df=2, p=0.01) yielded daily benzodiazepine dosage as the strongest independent predictor (RR 2.4 [1.2 - 4.7], p = 0.02). Figure 2 shows the survival curves of patients using 10 mg diazepam equivalent or less versus those using more than 10 mg of diazepam. General health perception (range 0 - 100) also had independent predictive value, but made only a marginal contribution to the model (RR 0.98 [0.97 - 0.99], p = 0.04).

Secondary outcome measures

Psychological functioning (GHQ-12, POMS, SF-36) showed minor, non-significant improvement at follow-up. Moreover, improvement was independent of benzodiazepine use relapse or benzodiazepine outcome classification according to Couvée *et al*. There was no increase in the use of psycho-active agents (caffeine, nicotine, alcohol). The prescription of antidepressants remained stable (baseline and follow-up 19%), while the prevalence rate of pain medication decreased from 44% at baseline to 36% at follow-up, for those patients who remained abstinent. Patients did not switch from benzodiazepines to other hypnotics; only one success category patient had received a prescription for zolpidem during follow-up.

Figure 2

Survival time until relapse stratified by baseline benzodiazepine dosage



Discussion

This is the first study in which a prospective longitudinal monitoring was employed to evaluate the long-term outcome of a minimal-intervention benzodiazepine discontinuation strategy. Half of the patients who had quit successfully in the short-term after minimal intervention remained abstinent for two years. Only 19% of the patients who relapsed were classified as failures after two years, while the other patients showed better usage patterns than before the intervention. We observed no switches to the use of alternative hypnotic drugs (zolplicon, zolpidem), antidepressants or pain medication. These good long-term results contribute positively to the proposals of Russell & Lader (1993) and many others (f.e. Oude Voshaar *et al* 2001) to use a minimal intervention strategy as a first step to cut down long-term benzodiazepine use.[1,18]

The major limitation of our study was the low participation rate, which increases the risk of significant selection bias. However, our short-term evaluation three months after sending the letter revealed a success rate of 22% (285/1321). This is fairly comparable with the success rates reported by others and suggests that the patients who responded to this evaluation were representative of all patients who received the discontinuation letter.[6,7] Some selection bias has obviously occurred, as participants in the follow-up study were using significantly higher dosages before receiving the discontinuation letter compared with non-participants. However, as a lower dose level appeared to be the most important predictor of remaining benzodiazepine free, the present results can be considered conservative.

As we did not include a control group we can not compare our results with the natural course of benzodiazepine use. It is not likely that the success rate of 22% can be explained by the natural course of benzodiazepine use after a minimal intervention, because the mean duration of benzodiazepine use in our sample was 6.8 years (see table 1). Moreover, our long-term success rate is substantially higher than the short-term success rate of 6% in the no intervention control group of the minimal intervention study of Cormack *et al* (1994).[6]

In contrast with the literature on the psychological functioning of long-term benzodiazepine users, the patients in our sample were functioning relatively well.[10 19 20] This may be a reflection of the fact that these patients were able to quit successfully of their own accord. The patients who relapsed did not show any deterioration in psychological functioning and there was no relationship between psychological functioning at follow-up and the outcome according to the classification of Couvée *et al* (2002).[17] It is possible that the instruments used to measure changes in psychological functioning were not sensitive enough in our population.

The best predictor of relapse appeared to be high dosage use (>10 mg diazepam equivalent per day). Poor general health perception also predicted relapse, i.e. patients who perceived themselves as being less healthy were at greater risk of relapse. As the latter variable contributed only marginally to the model, we recommend closer monitoring only in high-dose users after they have quit of their own accord.

References

1 Russel J, Lader MH Guidelines for the prevention and treatment of benzodiazepine dependence on behalf of the Substance Abuse Committee of the Mental Health Foundation Edited by Russel J, Lader MH *The Mental Health Foundation* 1993

2 Committee on the Review of Medicines Systematic review of the benzodiazepines *British Medical Journal* 1980 1 910-912

3 Ashton H Guidelines for the rational use of benzodiazepines When and what to use *Drugs* 1994, 48(1) 25 40

4 Zandstra SM, Fuhrer JW, Van de Lisdonk EH, *et al* Different study criteria affect the prevalence of benzodiazepine use *Social Psychiatry and Psychiatric Epidemiology* 2002, 37(3) 139-144

5 College voor zorgverzekeringen Gebruik van benzodiazepinen 1993 - 1998 Edited by Piepenbrink JF *Geneesmiddelen Informatie Project (GIP-signaal)* 2000

6 Cormack MA, Sweeney KG, Hughes Jones H, Foot GA Evaluation of an easy, cost-effective strategy for cutting benzodiazepine use in general practice *British Journal of General Practice* 1994, 44(378) 5-8

7 Cormack MA, Owens RG, Dewey ME The effect of minimal interventions by general practitioners on long- term benzodiazepine use *Journal of the Royal College of General Practitioners* 1989, 39(327) 408 411

8 O'Leary M A novel approach to tackling the benzodiazepine problem in general practice *Psychiatric Bulletin* 1989, 13 180 181

9 Jones D Weaning elderly patients off psychotropic drugs in general practice a randomised controlled trial *Health Trends* 1990, 22 164-166

10 Bashir K, King M, Ashworth M Controlled evaluation of brief intervention by general practitioners to reduce chronic use of benzodiazepines *British Journal of General Practice* 1994, 44(386) 408-412

11 Oude Voshaar RC, Couvee JE, Van Balkom AJLM, Zitman FG Strategies to discontinue long-term benzodiazepine use A systematic review *Submitted for publication*

12 Cornel, M , Knibbe, RA, Van Zutphen, WM, Drop MJ Problem drinking in a general practice population the construction of an interval scale for severity of problem drinking *Journal of Studies on Alcohol* 1994, 55 466-470

13 Goldberg DP, Blackwell B Psychiatric illness in general practice A detailed study using a new method of case identification *British Medical Journal* 1970, 1 439 443

14 Wald FDM, Mellenbergh GJ De verkorte versie van de Nederlandse vertaling van de Profile of Mood States (POMS) *Nederlands Tijdschrift voor de Psychologie* 1990, 45 86 90

15 Ware JE Jr , Sherbourne CD The MOS 36-item short-form health survey (SF-36) I Conceptual framework and item selection *Medical Care* 1992, 30(6) 473 483

16 Luteijn F, Kok AR NVM Nederlands Verkorte MMPI (NVM Dutch Shortened MMPI) Edited by Luteijn F, Kok AR *Swets & Zeitlinger* 1985

17 Couvee JE, Timmermans EAY, Zitman FG The long term outcome of a benzodiazepine discontinuation programme in depressed outpatients *Journal of Affective Disorders* 2002, 70(2) 133-141

18 Oude Voshaar RC, Gorgels WJMJ, Mol AJJ, *et al* Behandelmethoden om langdurig benzodiazepine gebruik te staken *Nederlands Tijdschrift voor Geneeskunde* 2001, 145(356) 1347-1350

19 Ashton H, Golding JF Tranquillizers prevalence, predictors and possible consequences Data from a large United Kingdom survey *British Journal of Addiction* 1989, 84 541-546

20 Nicholas D, Hammond SM Personality characteristics of long term benzodiazepine users *Personality and Individual Differences* 1992, 13(2) 221-223

Appendix[1]

Dear {*Mr Mrs – Miss*},

For some time now I have been prescribing {*name(s) of the benzodiazepine(s) used*} for you This medication belongs to the group of benzodiazepines By means of this letter, I would like to see whether we can alter the routine of prescribing this medication and taking it

Many general practitioners are worried about the long-term use of this medication, because the body can become accustomed to it, which means that it no longer has the desired effect Some people become addicted to the tablets or capsules, which leads to anxiety or sleeping problems if they forget to take a dose These anxiety and/or sleeping problems are not usually the original problems for which the medication was prescribed Instead they are temporary withdrawal symptoms Benzodiazepines also have other drawbacks For example, users run a higher risk of having accidents and tests have shown that the medication can affect a person's memory

In view of the above, I would like to advise you to gradually cut down your use of {*name(s) of the benzodiazepine(s) used*} and if possible to stop using the medication altogether When you do so, your body will have to adjust to the new situation, which means that you may suffer temporarily from agitation, tenseness and sleeping problems If you find that these symptoms occur, please try to persevere, because before long they will disappear and you will feel better Gradually (step-by-step) cutting down the dose involves the least risk of these symptoms Therefore, try to take a little less each week and only take a tablet or capsule if you have to do something that you are very apprehensive about Once you have managed to cut down, you will probably be able to stop altogether Many people who managed to stop taking the medication informed us that it made them feel much better than before they started taking it

I hope that this letter will encourage you to cut down In about three months time, you will receive an invitation to make an appointment to visit me at the surgery Then, if you wish, we can talk about this issue at greater length

Yours sincerely,

{Name – GP}

[1] The text of this letter is based on a letter used by M A Cormack et al (British Journal of General Practice 1994 44 5 8)

PART III

SHORT-TERM RESULTS OF TAPER-OFF STRATEGIES

Chapter 6

Tapering off long-term benzodiazepine use with or without group CBT: three-condition, randomised controlled trial

Richard C Oude Voshaar, Wim J M J Gorgels, Audrey J J Mol, Anton J L M van Balkom, Eloy H van de Lisdonk, Mannus H M. Breteler, Henk J M. van den Hoogen, Frans G Zitman
(British Journal of Psychiatry 2003, 182 498-503)

Abstract

Background - Benzodiazepine withdrawal programmes have never been experimentally compared with a non-intervention control condition

Aims - To evaluate the efficacy and feasibility of tapering off long-term benzodiazepine use in general practice, and to evaluate the value of additional group cognitive-behavioural therapy (CBT)

Method - A 3-month randomised, controlled trial was conducted in which 180 people attempting to discontinue long-term benzodiazepine use were assigned to tapering off plus group CBT, tapering off alone or usual care

Results - Tapering off led to a significant higher proportion of successful discontinuations than usual care (62% v 21%) Adding group CBT did not increase the success rate (58% v 62%) Neither successful discontinuation nor intervention type affected psychological functioning Both tapering strategies showed good feasibility in general practice

Conclusions - Tapering off is a feasible and effective way of discontinuing long-term benzodiazepine use in general practice The addition of group CBT is of limited value

Introduction

The evaluation of withdrawal programmes of long-term benzodiazepine use has been limited, as none of the reported studies included a control condition to correct for the number of people able to discontinue those drugs without any support, and none of them identified all long-term users before starting recruitment, limiting generalisibility (see chapter 3) [1] In this study, we recruited participants known to their GP to be long-term benzodiazepine users, and included a control group receiving usual care Because Cormack *et al* (1994) found that after written advice from their general practitioner 18% of people using benzodiazepines quit by themselves, this intervention was used as a pre-selection [2] Our objectives were to investigate the effects of tapering off long-term benzodiazepine use in patients who did not quit after written personal advice to do so, the value of additional group cognitive-behavioural therapy (CBT), and the feasibility of using both taper programmes in general practice

Method

Design

The study was a randomised, controlled trial comparing tapering off long-term benzodiazepine use alone with tapering off combined with group CBT and with a control group receiving usual care In order to include only those who were unable to quit of their own accord, all who were long-term users were sent a letter by the participating general practitioner in which they were advised to discontinue their benzodiazepine use The study received ethical approval from the University Medical Centre, Nijmegen, and took place from 1998 to 2001

Retirement

Long-term benzodiazepine use was identified by means of a computerised search for benzodiazepine prescriptions at 30 general practices (58 doctors, 118 082 patients) The practices were chosen to maximise the variety of locations throughout the Netherlands - 12 were urban (Amsterdam, Nijmegen and Almere) and 18 rural (villages nearby Nijmegen) - and of organisation type (4 health centres, 11 group practices and 15 solo practices) 'Long-term use' was defined as benzodiazepine use for at least three months with an prescribed amount sufficient for at least 60 days of consumption in accordance with the recommended dosage Exclusion criteria were current psychiatric treatment, current treatment for drug or alcohol dependence, medical history of psychosis, epilepsy, insufficient mastery of the Dutch language, or terminal illness Furthermore, some people were excluded specifically at the general practitioner's request because of severe co-morbidity or for psychosocial reasons People who met this definition of long-term benzodiazepine use were sent a letter by their GP advising them to

quit gradually and inviting them to the surgery three months later to evaluate the effect of the letter. At this consultation the doctor enquired whether the patient had been able to achieve complete abstinence and if not, whether the patient would participate in this study. All participants provided written informed consent.

Sample size and randomisation

The aim was to increase the success rate after the pre-selection procedure (i.e. the letter from the general practitioner) from an expected 55% through tapering off alone, to 80% by combining tapering off with group CBT.[3] Based on a chi-squared test, this effect size required a sample size (two sided $\alpha = 0.05$, $\beta = 0.20$) of 52 participants in each experimental group, or 62 participants based on a corrected chi-squared or Fisher's exact test.[4] Participants were randomised in a ratio of 2 :2 :1 to achieve maximum discriminative power between the two experimental groups. Computerised randomisation took place after at least ten participants within a geographic cluster had given informed consent, in order to form CBT groups with a minimum of four participants at a location near to the participants' homes.

Intervention

Tapering off - Participants who were not using diazepam were transferred to an equivalent dose of diazepam for two weeks by their own doctor using the conversion table of Zitman & Couvée (2001).[5] For participants taking more than one benzodiazepine, the dosages were added together. The daily dose of diazepam was reduced by 25% a week during four weekly visits. In accordance with Schweizer *et al* (1990) participants had the opportunity to divide the last step into two steps of 12½% for four days.[6] The last visit took place two weeks after the last reduction step. The general practitioner filled in a case record form to monitor progress and any adverse events during the intervention period. Two months later, we evaluated participant and doctor satisfaction and the feasibility of the withdrawal programme by means of a postal questionnaire.

Group cognitive-behavioural therapy - The participants who were randomised to tapering off combined with group CBT attended five weekly 2-h sessions of group CBT in addition to the dose reduction visits to their general practitioner. The sessions started halfway through the tapering-off period and finished two weeks after the conclusion of the withdrawal programme. The aim of the group therapy was to support the participants during the tapering-off proces and to prevent relapse thereafter.

The therapy programme included:

(a) psycho-education concerning the advantages and disadvantages of long-term benzodiazepine use;

(b) teaching and practising relaxation exercises by means of progressive relaxation,

(c) cognitive restructuring of the interpretation of withdrawal symptoms

The sessions were led by registered psychologists, experienced in CBT, who received training and a detailed manual of the therapy The therapists documented participation and reasons for non-participation at each session Tape recordings of a random sample of sessions 3 and 5 were judged by an independent assessor using previously defined criteria, and did not show any protocol violations Two months later, we evaluated patient satisfaction with the group therapy by means of a postal questionnaire

Usual care - Participants in the usual care control group were informed about the randomisation by letter They did not receive any help with benzodiazepine reduction

Measurements

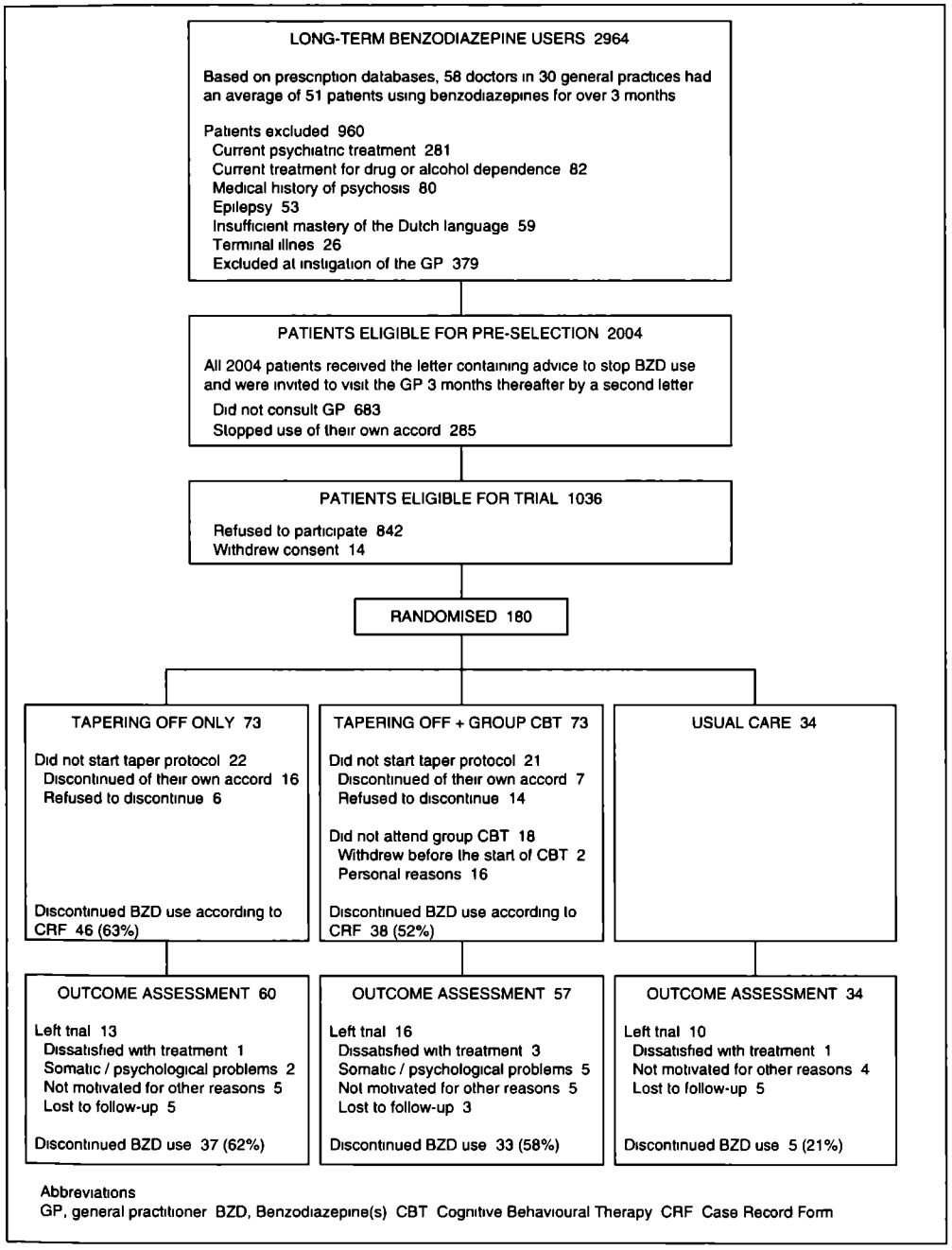
Participants received a baseline assessment after giving informed consent, and they received an outcome assessment three months after the start of the intervention Structured interview assessments were carried out at the participants' homes by a trained research assistant, who explored the self-reported use of benzodiazepines, administered the 15-words test, and assessed the circumstances of filling in the self-report questionnaires

Primary outcome measure - The primary outcome measure was the proportion of participants who successfully discontinued long-term benzodiazepine use, defined as no benzodiazepine use at the outcome self-report assessment We checked self-reported discontinuation of benzodiazepine use in the general practitioner's prescription database, which showed that less than 5% of the participants who reported successful discontinuation had received a benzodiazepine prescription in the month before the outcome assessment

Secondary outcome measures - Secondary outcome measures were the reduction in daily benzodiazepine dosage by participants who did not successfully discontinue drug use, the use of alcohol (including the number of problematic drinkers, based on the 18-item list of Cornel *et al*, 1994)[7], psychological well-being assessed by the General Health Questionnaire 12-item version (GHQ-12)[8], memory (delayed recall of the 15-words test)[9], mood (the scales of depression, anger, fatigue, vigour and tension of the 32-item shortened Profile of Mood States, POMS)[10], and the number and severity of benzodiazepine withdrawal symptoms (Benzodiazepine Withdrawal Symptom Questionnaire)[11]

Figure 1

CONSORT diagram



Abbreviations
GP, general practitioner BZD, Benzodiazepine(s) CBT Cognitive Behavioural Therapy CRF Case Record Form

Statistical analysis

To check for baseline differences between the three groups, a series of univariate analyses of variance (ANOVAs) or non-parametric equivalents were performed on psychiatric status and demographic variables. The primary outcome measurements were analysed with a chi-squared test (number of participants who discontinued successfully). A forward logistic regression analysis with correction for treatment group was performed to identify independent predictors (all baseline characteristics) of discontinuation success.

The dosage reduction in participants who failed to discontinue diazepam was analysed with one-way ANOVA (dosage quotient at outcome and baseline after natural log-transformation). Repeated measures ANOVAs were performed on the other secondary outcome variables for continuous variables and chi-squared tests for dichotomous variables. Significant main effects were further analysed with pairwise comparisons.

Analyses were performed on an intent-to-treat basis. In the case of a missing outcome value, the last observation was carried forward to serve as the outcome measurement (whole sample, n=180). The analyses were repeated after excluding all those who had left the study at the outcome assessment (completers sample, n=141). A substantial number of participants had discontinued their use of benzodiazepines before the intervention started. For this reason, we also carried out a per protocol analysis on the participants who had been fully compliant with both the treatment programme and the outcome measurement (per protocol sample, n=78). We excluded the control group from this analysis, because only data on the experimental groups were available at the start of the intervention.

Results

Study profile

Of the 2964 persons identified as long-term users of benzodiazepines, 2004 were advised to stop their benzodiazepine use; 1036 were eligible for the trial (figure 1). The participation rate was low: 180 out of 1036 (17.4%). Participants (n=180) and non-participants (n=876) did not differ with respect to age, gender or benzodiazepine dosage used. Of the 146 participants assigned to one of the withdrawal programmes, 23 discontinued their benzodiazepine use while waiting for the intervention to begin. In order to start therapy groups with at least 4 participants, the mean (±sd) delay between baseline assessment and intervention was 71 (±45) days (range 0 - 223 days). Thirty-nine participants refused to take part in the outcome assessment. The numbers leaving the study at this stage did not differ significantly across the three groups (χ^2=1.85; df=2; p=0.40). Of the 85 participants compliant with the entire intervention programme (tapering off alone or tapering off with group CBT), 78 were assessed at outcome.

Characteristics of the study participants

Comparisons of the three groups did not reveal any significant differences in baseline characteristics (table 1). In addition, no significant difference in baseline characteristics was observed between those leaving the study and those completing the study. In the sample as a whole, the decile scores on the 15-words test did not differ from the norm. Subanalyses revealed that participants who were using 10 mg diazepam equivalent or more per day (n=35) had significantly worse scores than the participants who were using less than 10 mg per day (t=2.25; df=178; p=0.03) and the norm population (t=5.93; df=34; p<0.001).

Table 1

Characteristics of the study participants (n=180) at baseline assessment

	Tapering off only (n=73)	Tapering off + CBT (n=73)	Usual care (n=34)	P value
Background characteristics:				
Age (years) mean (s d)	61 8 (12 5)	63 7 (12 7)	64 6 (11 0)	0 47
Gender (female)· n (%)	53 (73)	50 (69)	23 (68)	0 82
Marital status: n (%)				0 98
No relationship	3 (4)	3 (4)	2 (6)	
Married	50 (69)	48 (66)	22 (65)	
Divorced	3 (4)	5 (7)	3 (9)	
Widowed	17 (23)	17 (23)	7 (21)	
Living alone· n (%)	21 (29)	22 (30)	11 (32)	0 93
Highest level of eduction· n (%)				0 28
Primary education	27 (37)	19 (26)	16 (47)	
Secondary education	42 (58)	49 (67)	17 (50)	
University	4 (6)	5 (7)	1 (3)	
Benzodiazepine use				
Dosage (mg diazepam eq)· mean (s d)	6 1 (9.8)	7 1 (9 5)	5 3 (5 0)	0 54
Patients using ≥ 10 mg diazepam eq · n (%)	12 (16)	17 (23)	6 (18)	0 55
Duration of use (months): mean (s d.)	160 (116)	157 (120)	178 (106)	0.43
Secondary outcomes				
GHQ-12 score. mean (s d)	2 4 (3 2)	2 6 (3 4)	2 2 (2 9)	0 91
Profile Of Mood States score n (%)				
Depression	12 8 (5 8)	14.1 (6 2)	13 7 (6.7)	0 44
Anger	11 1 (5 1)	12 3 (5 7)	11 9 (5 4)	0 40
Fatigue	12 4 (6 3)	12 4 (5 3)	12 4 (5 5)	0 99
Vigour	15 0 (4 3)	15 0 (4 6)	14 1 (4 5)	0 61
Tension	12.0 (5 4)	12 5 (4 8)	11 9 (5 1)	0 78
Delayed recall (15-words test) mean (s d)	6 7 (3 0)	7 4 (3.2)	6 8 (2 8)	0 31
BWSQ score· mean (s d)	7 0 (7 0)	6 3 (6.5)	5 8 (6 0)	0 76
Patients using alcohol				
n (%)	42 (58)	38 (52)	17 (50)	0 71
Units of alcohol/ week mean (s d)	9 2 (8 3)	9 3 (6 8)	6 9 (6 0)	0 45
Problem drinkers[1] n (%)	5 (12)	8 (21)	3 (9)	0 68

Abbreviations CBT, cognitive-behavioural therapy, BWSQ, Benzodiazepine Withdrawal Symptom Questionnaire[7]; GHQ-12, General Health Questionnaire 12-item version[4]

[1] Based on the sum score of the list of Cornel et al (1994)[3] Percentages are of those using alcohol in their group

Benzodiazepine usage

The proportions of participants who successfully discontinued benzodiazepine use differed significantly between the three groups in the intent-to-treat analysis (table 2). Subsequent pairwise comparisons revealed that the two experimental groups did not differ significantly from each other in the intent-to-treat analysis (whole sample p=0.51; completers sample p=0.68). However, the two experimental groups were significantly more successful than the control group: tapering off alone (whole sample p<0.001; completers sample p=0.001) and tapering off combined with group CBT (whole sample p=0.002; completers sample p=0.002). Corroborating these findings, the per protocol analysis did not show any significant difference between the two experimental conditions (p=0.53). Logistic regression analysis yielded benzodiazepine dosage as the only independent predictor of successful discontinuation (OR=4.5, [95% CI 2.0-10.2]). Patients who used 10 mg diazepam equivalents or more had a significantly lower chance of successful discontinuations than patients using less than 10 mg (35% v. 64%, p=0.009).

Among those failing to quit, dose reduction differed significantly across the three groups (whole sample $F_{2,102}$=3.33, p=0.04; completers sample $F_{2,62}$=3.98, p=0.02). Tukey HSD *post hoc* tests showed a significant difference in dosage reduction between tapering off combined with group CBT and usual care (whole sample p=0.03; completers sample p=0.02).

Table 2

Benzodiazepine use at 3-months' follow-up

	Tapering off only	Tapering off + CBT	Usual care	P value
Successful discontinuation: n (%)				
Intent to treat sample				
Whole sample with LOCF (n=180)	37 (51%)	33 (45%)	5 (15%)	p = 0 002
Completers sample (n=141)	37 (62%)	33 (58%)	5 (21%)	p = 0 002
Per protocol sample				
Completers sample (n=78)	27 (57%)	20 (65%)	-	p = 0 53
Failure to discontinue: median % dose reduction				
Intent to treat sample:				
Whole sample with LOCF (n=105)	23%	37%	- 3%	p = 0 04
Completers sample (n=66)	35%	53%	- 5%	p = 0 02
Per protocol sample.				
Completers sample (n=31)	40%	72%	-	p = 0 02

Abbreviations: CBT, cognitive-behavioural therapy; LOCF, last observation carried forward

Secondary outcome measures

We used repeated measure ANOVAs across the three groups to evaluate the effects of the severity of withdrawal symptoms, psychological distress, mood, memory and problem alcohol use. There was a significant time-effect only for the delayed recall of the 15-words test, which indicated an

improvement. However, no significant interaction effects emerged for any of the secondary outcome measures, thus these measures were fairly comparable in the three groups (table 3). Moreover, comparing participants who successfully discontinued benzodiazepine use with those who failed to do so did not result in significant time x outcome interaction effects for any of the secondary outcome measures. Neither the prevalence of alcohol use, nor the amount consumed by alcohol users, changed.

Table 3

Secondary outcome measures at 3 months' follow-up in the intent-to-treat sample (LOCF, n=180)

	Tapering off only	Tapering off +CBT	Usual care	P value
GHQ-12 score mean (s d)	1 8 (2 5)	2 4 (3 0)	1 8 (3 0)	p = 0 83
Profile Of Mood States mean (s d)				
Depression	12 6 (5.2)	13 8 (6 9)	13.0 (7.5)	p = 0 86
Anger	11 5 (5 5)	12 0 (6 2)	10 7 (5 1)	p = 0 22
Fatigue	12 7 (6 4)	12 7 (5 9)	11 7 (7 0)	p = 0.68
Vigour	14 9 (4 9)	15 0 (4 7)	15 3 (5.9)	p = 0 39
Tension	11 4 (4 9)	12 6 (5 8)	11 1 (5 6)	p = 0 46
Delayed recall (15-words test) mean (s d)	7 2 (2 9)	8 1 (3 4)	7.6 (2 5)	p = 0 83
BWSQ score: mean (s.d.)	6 2 (6 8)	6 8 (7 5)	5 8 (7.3)	p = 0 57
Patients using alcohol				
n (%)	42 (58)	40 (55)	18 (53)	p = 0 81
Units of alcohol / week mean (s d)	10 0 (11 0)	8 3 (6 4)	7 3 (6 4)	p = 0 63
Problem drinkers n (%)[1]	5 (12)	10 (14)	5 (15)	p = 0 71

Abbreviations CBT, cognitive-behavioural therapy, GHQ-12, General Health Questionnaire 12-item version[4], BWSQ, Benzodiazepine Withdrawal Symptom Questionnaire[7],

[1] Based on the sum score of the list of Comel[3]

Doctor and patient views of the tapering-off strategy

Participants (n=103) who entered the withdrawal programme visited their general practitioner an average of 5.6 times (sd 1.4, range 1 - 9). The average number of visits did not differ between the participants assigned to tapering off alone and those assigned to tapering off combined with group CBT, and there was no difference between the participants who successfully discontinued benzodiazepine use and those who did not.

A total of 43 out of the 58 participating doctors actually supervised the patients during the tapering off proces; 42 of them returned the postal evaluation questionnaire. Analyses of these questionnaires showed that 37 doctors (88%) found the protocol feasible at their own practice, 35 (83%) would encourage other general practitioners to taper off long-term benzodiazepine use with the aid of the withdrawal protocol, and 22 (52%) had already started using this protocol for patients not included in the trial. No major adverse event during the reduction period (such as epileptic seizures or psychotic episodes) was reported in the case record forms.

A total of 91 (88%) of the 103 participants who entered the withdrawal programme returned the postal evaluation questionnaire. The results showed that 78 (86%) of those who responded were satisfied with the 'treatment' received; 66 (73%) would be willing to follow the same treatment again if necessary. With respect to their supervision, 65 (76%) preferred treatment by their own GP, 6 (7%) preferred referral to a specialised treatment setting, 12 (14%) preferred no support with tapering-off and 3 (3%) had no preference.

Attrition rates and participant's views on group CBT

Seven (10%) of the 73 participants assigned to CBT discontinued their benzodiazepine use before the start of the intervention. In order to prevent relapse, we invited these participants to the therapy sessions; however, only two actually participated. Of the participants who began the tapering-off proces combined with group CBT, only 34 (65%) attended three or more sessions (figure 1). The discontinuation success rates did not differ significantly between the patients who were compliant with CBT and those who were not: 20/31 (65%) v. 6/15 (40%), p=0.12. The postal evaluation questionnaire was returned by 30 (88%) of the 34 compliant participants: 14 (47%) of them would have preferred more sessions; 28 (93%) were satisfied with the group therapy in general. The degree of satisfaction with group CBT was not related to taper success.

Discussion

Tapering off was an effective strategy for the discontinuation of long-term benzodiazepine use, even after pre-selection with a letter containing advice to stop, achieving its highest success rates in patients using less than 10 mg diazepam equivalents. Adding group CBT did not increase the proportion of those who successfully discontinued. Although the study was marginally lacking power for some analyses, this is irrelevant since the success rate for patients receiving group CBT was numerically lower than that for the group assigned to tapering off alone. Of those who failed to discontinue benzodiazepine use, those assigned to additional group CBT reduced their dosage significantly more than the participants in the control group. Both withdrawal programmes proved to be feasible in general practice. After the intervention, we did not find any significant differences between the three groups in the presence and severity of withdrawal symptoms, symptoms reflecting psychological distress and mood disturbances between the three groups. Neither the prevalence of problem drinking or alcohol use, nor the amount of alcohol consumed, was influenced by the intervention type or tapering off, which indicates that none of our participants replaced their benzodiazepine use with alcohol.

Efficacy of tapering off

This was the first study to show the efficacy of tapering off long-term benzodiazepine use by including a 'usual care' control condition Although we pre-selected patients by sending a letter advising them to stop their use, our success rates were comparable with those of other benzodiazepine withdrawal studies [5,6] In the control group, 21% of the participants stopped their benzodiazepine use spontaneously In addition, 23 (16%) of the 146 participants assigned to the experimental groups discontinued benzodiazepine use without any professional help while waiting for the interventions to start At first we considered this to be a methodological, but inevitable problem of our study, because it took some time to fill the therapy groups However, it appeared to be a cost-effective strategy in view of the 60% success rate among those still using benzodiazepines, as was shown by the per protocol analysis The proportions of participants who stopped spontaneously were much higher than the estimated 6% Several explanations can be put forward First, actually taking part in a discontinuation trial could provide an extra incentive to discontinue benzodiazepine use independently, even if a previous attempt was not successful Second, owing to selection processes, the proportion of participants in discontinuation trials who are able to stop their use without any professional help might be higher than in long-term users in general

Generalisibility

A participation rate of 17 4% presumes significant selection processes Although the people gave a variety of reasons for non-participation, dependence on benzodiazepines might have played an important part Kan *et al* (1997) found that 40% of all those prescribed benzodiazepines in general practice were dependent on benzodiazepines according to DSM-III-R criteria, and Linden *et al* (1998) found that two- thirds of those who were long-term benzodiazepine users rejected a drug 'holiday' [12,13] Reluctance to enter group therapy as well as reluctance to hold interview sessions at home might have also contributed to the small number of participants In clinical practice a higher recruitment rate might be achieved if the patients are not asked to participate in a randomised controlled trial As participants were representative with respect to not only age and gender, but also to the (only) independent predictor of success, benzodiazepine dosage, it is unlikely that we excluded treatment-resistant patients As we identified all patients who were long-term users before we recruited participants, it is not possible to compare our attrition rate with that of other studies that recruited referred participants from specialised settings or by advertisement

Efficacy of group CBT

In our study, adjunctive group CBT focused on the management of withdrawal symptoms did not have any additional value Previous studies evaluating simultaneous psychological treatment to improve these success rates have considerable methodological problems Two studies did not compare the

efficacy of additional CBT v tapering off alone[14 15], the other studies did not use a controlled design[16 19], did not randomise participants over the conditions[20] or studied a sample of fewer than 10 participants[21 22] The two studies without these methodological problems were restricted to participants who met the criteria for panic disorder, here the addition of CBT to tapering off significantly increased the proportion who successfully discontinued benzodiazepine use[3 23] These results are difficult to generalise, as the prevalence of panic disorder among those who are long-term benzodiazepine users has been estimated to be at most 27%[24] Our success rate for CBT might have been increased by *a priori* selection on psychiatric morbidity and by introducing disorder-specific elements A disadvantage of this strategy is that the programme cannot then be used easily in general practice

The lack of additional value might also be due to the limited number of sessions provided However, the efficacy of brief psychotherapy in alcohol dependence and somatisation disorder in general practice has been supported by the results of randomised controlled trials[25 26] In view of the relapse rate in the benzodiazepine withdrawal study by Zitman & Couvée (2001), and the delayed effects of psychotherapy in the treatment of cocaine dependence and in the tapering off of alprazolam in panic disorder, a long-term follow-up study is planned[3 5 27] Another possibility is to give CBT after instead of during tapering-off In our opinion, however, this strategy is of limited value in clinical practice only two of the seven participants who stopped their use before the intervention could be motivated to attend the therapy sessions to help them remain benzodiazepine-free in the future

Adherence to group CBT

Adherence to group therapy was poor, which may reflect an overall resistance to group therapy among people who are long-term benzodiazepine users This is in line with findings in other studies and with our interpretation of the personal reasons why patients refused to attend group therapy sessions[18 23] Moreover, individual CBT sessions to restructure dysfunctional cognition might be more successful However, the poor adherence cannot explain the lack of success, as the success rate of patients who were compliant to CBT (n=34) was 65% Although sub-analyses lack statistical power, it is unlikely that this would be superior to the 57% success rate of tapering off alone

Feasibility in general practice

Tapering off was tolerated well in general practice the general practitioners did not report any major adverse event during or after the tapering-off process The good compliance and high level of satisfaction with the programme among both doctors and participants further strengthen the feasibility of tapering off as a strategy to discontinue long-term benzodiazepine use in general practice

Clinical implications:

- This study is the first to evaluate additional psychotherapy in a randomised, controlled fashion.
- Gradual tapering off is an effective way of discontinuing benzodiazepine use.
- Additional psychotherapy does not seem to increase the success rate of the gradual tapering-off approach.

Limitations:

- Only one in six patients in this study were willing to take part in a withdrawal programme.
- Treatment adherence in psychotherapy was limited.
- Patients received no diagnostic psychiatric screening, which made sub-analyses in specific diagnostic groups impossible.

References

1 Oude Voshaar RC, Gorgels WJMJ, Mol AJJ, *et al.* Behandelmethoden om langdurig benzodiazepinegebruik te staken (Treatment modalities for discontinuation of long-term benzodiazepine use] *Nederlands Tijdschrift voor Geneeskunde* 2001; 145. 1347-1350

2 Cormack MA, Sweeney KG, Hughes-Jones H, *et al.* Evaluation of an easy, cost-effective strategy for cutting benzodiazepine use in general practice *British Journal of General Practice* 1994, 44. 5-8

3. Otto MW, Pollack MH, Sachs GS, *et al* Discontinuation of benzodiazepine treatment efficacy of cognitive-behavioral therapy for patients with panic disorder. *American Journal of Psychiatry* 1993, 150: 1485-1490

4 Dupont WD and Plummer WD. Power and sample size calculations A review and computer program. *Controlled Clinical Trials* 1990, 11 116-128.

5 Zitman FG, and Couvee JE Chronic benzodiazepine use in general practice patients with depression an evaluation of controlled treatment and taper-off Report on behalf of the Dutch Chronic Benzodiazepine Working Group *British Journal of Psychiatry* 2001, 178. 317-324.

6 Schweizer E, Rickels K, Case WG, *et al* Long-term therapeutic use of benzodiazepines II. Effects of gradual taper *Archives of General Psychiatry* 1990, 47· 908-915

7. Cornel M, Knibbe RA, Van Zutphen WM, *et al* Problem drinking in a general practice population the construction of an interval scale for severity of problem drinking *Journal of Studies on Alcohol* 1994, 55 466-470.

8. Goldberg DP and Blackwell B Psychiatric illness in general practice A detailed study using a new method of case identification. *British Medical Journal* 1970, 1 439-443.

9. Saan RJ and Deelman BG De nieuwe 15-woordentest (A en B) Een handleiding Lisse Swets & Zeitlinger 1996

10 Wald FDM and Mellenbergh GJ De verkorte versie van de Nederlandse vertaling van de Profile of Mood States (POMS) *Nederlands Tijdschrift voor de Psychologie* 1990, 45 86-90

11. Tyrer P, Murphy S, and Riley P. The Benzodiazepine Withdrawal Symptom Questionnaire *Journal of Affective Disorders* 1990, 19. 53-61

12 Kan CC, Breteler MHM, and Zitman FG High prevalence of benzodiazepine dependence in out-patient users, based on the DSM-III-R and ICD-10 criteria. *Acta Psychiatrica Scandinavica* 1997, 96. 85-93

13 Linden M, Bar T, and Geiselmann B Patient treatment insistence and medication craving in long-term low- dosage benzodiazepine prescriptions. *Psychological Medicine* 1998; 28 721-729.

14 Elsesser K, Sartory G, Maurer J The efficacy of complaints management training in facilitating benzodiazepine withdrawal *Behavioural Research and Therapies* 1996; 34 149-156.

15 Sanchez-Craig M, Cappell H, Busto U, *et al.* Cognitive-behavioural treatment for benzodiazepine dependence a comparison of gradual versus abrupt cessation of drug intake *British Journal of Addiction* 1987, 82 1317-1327

16 Cormack MA and Sinnott A Psychological alternatives to long-term benzodiazepine use *Journal of the Royal College of Geneneral Practitioners* 1983; 33: 279-281

17 Schmauss C, Apelt S, and Emrich HM Characterization of benzodiazepine withdrawal in high- and low-dose dependent psychiatric inpatients *Brain Research Bulletin* 1987, 19 393-400

18. Crouch G, Robson M, Hallstrom C. Benzodiazepine dependent patients and their psychological treatment *Progresive Neuropsychopharmacology in Biological Psychiatry* 1998, 12. 503-510

19. Joughin N, Tata P, Collins M, *et al* In-patient withdrawal from long-term benzodiazepine use. *British Journal of Addiction* 1991, 86 449-455.

20. Higgitt A, Golombok S, Fonagy P, *et al* Group treatment of benzodiazepine dependence. *British Journal of Addiction* 1987, 82. 517-532

21. Nathan RG, Robinson D, Cherek DR, *et al.* Alternative treatments for withdrawing the long-term benzodiazepine user a pilot study. *Internation Journal of Addiction* 1986, 21. 195-211.

22. Tyrer P, Murphy S, Oates G, *et al* Psychological treatment for benzodiazepine dependence. *Lancet*, 1985, 1. 1042-1043

23. Spiegel DA, Bruce TJ, Gregg SF, *et al.* Does cognitive behavior therapy assist slow-taper alprazolam discontinuation in panic disorder? *American Journal of Psychiatry* 1994, 151: 876-881

24 Rickels K, Case WG, Schweizer EE, *et al.* Low-dose dependence in chronic benzodiazepine users: a preliminary report on 119 patients *Psychopharmacology Bulletin* 1986, 22· 407-415

25. Lidbeck J. Group therapy for somatization disorders in general practice effectiveness of a short cognitive-behavioural treatment model. *Acta Psychiatrica Scandinavica* 1997, 96 14-24

26 Sandahl C, and Ronnberg S. Brief group psychotherapy in relapse prevention for alcohol dependent patients. *International Journal of Group Psychotherapy* 1990, 40 453-476

27. Carroll KM, Rounsaville BJ, Nich C, *et al.* One-year follow-up of psychotherapy and pharmacotherapy for cocaine dependence Delayed emergence of psychotherapy effects. *Archives of General Psychiatry* 1994; 51: 989-997.

Chapter 7

Cross-validation, predictive validity and time course of the Bendep-SRQ in a benzodiazepine discontinuation trial

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Abstract

The Benzodiazepine Dependence Self-Report Questionnaire (Bendep-SRQ) measures the severity of benzodiazepine dependence on four domains awareness of problematic use, preoccupation with the availability of benzodiazepines, lack of compliance with the therapeutic regimen, and withdrawal

Although promising results of the Bendep-SRQ have been obtained in cross-sectional studies, no attention has been paid to its clinical relevance during benzodiazepine withdrawal, i e , predictive validity and time course We performed cross-validation and evaluated the predictive validity and time course on 180 long-term benzodiazepine users who were taking part in a general practice benzodiazepine discontinuation trial

Three of the four domains had good scalability Some concerns arose about the preoccupation scale, which emphasizes the need for cross-validation in clinically relevant populations All scales showed excellent reliability (subject discriminability, item discriminability), while construct and discriminant validity were adequate

All four scales contributed significantly to the prediction of whether complete abstinence would be achieved directly after taking part in the discontinuation programme This prediction was independent of the other prognostic variables, except for those in the domain problematic use The scales problematic use and preoccupation showed good sensitivity to changes during follow-up The insensitivity of the scale lack of compliance can be explained by low baseline scores in our population, while the insensitivity of the withdrawal scale was probably the result of the study design In conclusion, our study indicated the clinical relevance of the Bendep-SRQ before and during a benzodiazepine discontinuation trial We recommend the use of the Bendep-SRQ in discontinuation therapy and research into the field of benzodiazepine addiction

Introduction

Although people have been aware that withdrawal symptoms occur following discontinuation of benzodiazepines since their introduction in the early 1960s[1-3], it took until the early 1980s to develop symptom-rating scales to measure the nature and severity of the benzodiazepine withdrawal syndrome[4-10] Unfortunately, most of these scales have only been tested in small patient populations, without evaluating their psychometric properties or their predictive validity in benzodiazepine withdrawal Recently, the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) developed by Tyrer *et al* (1990)[11], was evaluated psychometrically within a benzodiazepine discontinuation programme [12] This study design enabled evaluation of its clinical utility, i e , predictive validity The mean scores could differentiate between "successes" and "failures", while lower scores in the last phase of tapering-off predicted no or limited use of benzodiazepines at follow-up, which increased the percentage of correct predictions from 56% to 65%

It has been shown that benzodiazepine dependence may not be reduced to a withdrawal syndrome on the basis of discontinuation alone [13] The BZ dependence criteria of the DSM-III-R and ICD-10 only met the requirements of the Rasch model after the removal of particular items The remaining items were considered to probe BZ dependence at its general core, but not reflect BZ dependence comprehensively, because criteria related to BZ withdrawal were omitted It is possible that these withdrawal criteria reflected a separate dimension, which means that BZ dependence might be a multidimensional concept These findings are in line with the results of a factor analysis reported by Baillie and Mattick (1996) that yielded three factors during the development of the Benzodiazepine Dependence Questionnaire (BDEPQ) general dependence, pleasant effects and perceived need[9] However, these researchers did not adopt multidimensionality, as they considered the BDEPQ total sum score to be a proper measure to reflect the severity of BZ dependence comprehensively

In contrast with Baillie and Mattick (1996), Kan *et al* (1999) adopted a multidimensional approach to develop the Benzodiazepine Dependence Self-Report Questionnaire (Bendep-SRQ) [14] In order to construct adequate scales, Rasch modelling was applied to the dimensions suggested by factor analyses The scalability, reliability and validity of the four resulting Bendep-SRQ scales (problematic use, preoccupation, lack of compliance and withdrawal) proved promising in a subsequent cross-validation study on outpatient benzodiazepine users [14,15] However, it remains unclear whether these results can be generalised to long-term benzodiazepine users who are taking part in a discontinuation programme Moreover, as a result of the cross-sectional designs of these studies, predictive validity and time course during benzodiazepine withdrawal have not been evaluated yet It can be expected that users with higher scores on any of the four dependence scales will be less successful in their tapering-off attempts than users with low scores

The aim of the present study was to cross-validate the Bendep-SRQ in a group of long-term benzodiazepine users who were taking part in a general practice benzodiazepine discontinuation

programme The following questions were adressed (a) Can previously found psychometric results be generalised to long-term benzodiazepine users who are seeking discontinuation treatment?, (b) What is the predictive value of the Bendep-SRQ regarding the achievement of complete abstinence by tapering-off benzodiazepine use? and (c) Can the Bendep-SRQ monitor the time course of benzodiazepine dependence?

Method

Setting and design

This study was conducted as part of a benzodiazepine discontinuation trial at 30 general practices throughout the Netherlands The Bendep-SRQ (and other measures) were administered at baseline and outcome to 180 subjects randomised over three conditions gradual tapering-off (n=73), gradual tapering-off combined with group therapy (n=73) and a control condition consisting of usual care (n=34) In the two tapering-off conditions, subjects were tapered-off by 25% a week after being transferred to an equivalent dose of diazepam, in the control condition, no attention was paid to the use of benzodiazepines The outcome of this programme has been reported elsewhere [16]

Subjects

Subjects were at least 18 years of age, fulfilled the criteria for chronic use (i e , benzodiazepine use for at least three months with an amount sufficient for at least 60 days of consumption according to the prescription rules) and were not able to discontinue their use of their own accord having received written advice from their general practitioner Exclusion criteria were current psychiatric treatment, current treatment for drug or alcohol dependence, psychosis, epilepsy, insufficient mastery of the Dutch language, or suffering from a terminal illness

The Bendep-SRQ

The Bendep-SRQ is a 20-item self-report questionnaire that measures the severity of benzodiazepine dependence [14] All of the items are rated on a five-point scale The items of the scales problematic use, preoccupation and lack of compliance are rated according to the degree to which they applied over the past three months, while the items of the withdrawal scale are rated according to the subject's latest attempt to reduce or discontinue their benzodiazepine use Analogously to earlier reports, the items were dichotomized between response options 2 (this is not true for me) and 3 (this is partly true, partly false for me), in order to apply Rasch analysis

Analysis

Data gathered at the baseline assessment were used to cross-validate the Bendep-SRQ, while data

gathered at the outcome assessment three months after the start of discontinuation treatment were used to assess the predictive validity and time course

Scalability of the Bendep-SRQ scales - Rasch analysis was applied to the items in the four Bendep-SRQ scales Problematic use, Preoccupation, Lack of Compliance, and Withdrawal The surplus of Rasch modelling to the 'classical test theory' is the justification of the use of the sum score as a sufficient statistic for the underlying construct (i e the latent trait) by means of goodness of fit tests derived from the Rasch scaling model Although the use of sum scores is generally accepted in psychiatric research, this is only justified if the Rasch model holds true, as reflected by the goodness of fit statistics R1 and R2 [17] If R1 is not significant at the 1% significance level (P>0 01) the null hypothesis that all items have equal discriminative power cannot be rejected and equi-discriminability can be assumed Similarly, unidimensionality and local stochastic independence hold true when R2 is not significant (P>0 01) Rasch homogeneity holds true when both statistics are non-significant Kan *et al* (2001) reported that the latent trait for three of the four scales had a normal distribution [18] Therefore, we applied the Rasch model under the assumption that the latent trait has a normal distribution by including the R0 statistic (marginal maximum likelihood method) [17 19] Nonrejection of this additional assumption implies that standard scores can be derived that correspond with estimates of the latent subject trait instead of the observed scores This is preferable, because the primary aim of a scale is to reflect the latent subject trait as accurately as possible The statistics R1 and R2 can then be computed on the basis of a normally distributed latent trait For more detailed information on the assumptions from which the Rasch model can be derived and the required additive structure underlying the observed data, we refer to Fischer *et al* (1995) and Kan *et al* (2001) [18 20]

Reliability - Reliability is the degree to which a measurement can be repeated and the same values can be obtained To evaluate the reliability of the Bendep-SRQ scales we assessed subject discriminability and item discriminability

Subject discriminability (Internal Consistency) Subject discriminability implies that the subjects differ systematically, i e , the variation between subjects is larger than the variation due to random error Subject discriminability of the Bendep-SRQ scales was evaluated by means of the KR-20 coefficient, analogous to Cronbach's alpha for continuous variables

Item discriminability Item discriminability implies that the items differ systematically, i e , the variation between items is larger than the variation due to random error This was tested by Cochran's Q test If the Q value is significant, items can be considered to occupy distinct points on the scale Additionally, analogous to the concept of reliability as described by Hoyt (1941), which is a measure of intersubject discriminability, a measure of interitem discriminability has recently been developed the item discriminability coefficient (IDC) [14 21] On the premises that the underlying item response

model holds true, the IDC will show the extent to which the differences between items are systematic The higher the IDC (range, 0 to 1), the more powerful the predictions about the item scale

Validity - A measurement is valid when the scale measures what it is intended to measure The validity of the Bendep-SRQ scales was assessed in terms of construct, discriminant, and predictive validity

Construct validity Construct validity refers to the degree to which inferences can legitimately be made from the operationalizations in the questionnaire regarding the theoretical constructs on which the operationalizations were based To establish the construct validity of the Bendep-SRQ scales, theoretical rationales have been formulated to explain the specific item orders based on increasing Rasch scale values, which reflects increasing severity levels of the constructs To comply with the postulated theoretical rationales, the estimates of the Rasch scale values in the present study should approximately replicate the specific item orders of the Bendep-SRQ scales in the former study This would confirm the construct validity of the Bendep-SRQ scales

Discriminant validity Discriminant validity means that the measure can discriminate between groups, e g , between subjects with and subjects without a particular disorder To estimate discriminant validity, we factor-analysed the following scale scores The Benzodiazepine Withdrawal Symptom Questionnaire version 2 (BWSQ-v2) that assesses BZ withdrawal symptoms during discontinuation of benzodiazepines in pharmacologically dependent patients[11 12], the Dutch shortened Profile of Mood States (POMS), a 32-item self-report questionnaire that measures five short-term changeable mood states[22], the Short Form-36 that assesses quality of life on eight domains[23 26], and the Dutch Shortened Minesota Multiphasic Personality Inventory (MMPI) that assesses personality characteristics [27] All of these questionnaires have proven to have good reliability and validity

Predictive validity Predictive validity refers to whether a psychological measure is correlated with a particular type of behavior that occurs at a later point in time, in this case, whether or not a subject successfully discontinued their BZ use after participating in our benzodiazepine discontinuation programme This was estimated for each scale separately by logistic regression analysis to predict the outcome (successfully discontinued or failed to discontinue) adjusted first only for treatment condition (tapering-off with or without group cognitive-behavioural therapy or usual care) and second for treatment condition and all baseline characteristics univariately discriminating between subjects who successfully discontinued and those who did not

Longitudinal monitoring - Previous reports on the Bendep-SRQ showed good test-retest reliability To describe treatment effects, an instrument also has to have good sensitivity to change We evaluated sensitivity to change using a repeated measures design with one within-subject factor with two levels (sum score at baseline and sum score at outcome) and one between-subject factor with two levels (treatment success and failure)

Data analysis program - Rasch analyses were conducted using the Rasch Scaling Program.[28] Other data analyses were conducted using SPSS 10.0.5 (SPSS Inc, Chicago, IL).

Results

Sociodemographic features and pattern of BZ use

The baseline characteristics of all the subjects are presented in table 1, because there were no differences between the three conditions. Mean daily benzodiazepine dosage was relatively low (6.4 mg diazepam a day). Sociodemographic and benzodiazepine usage characteristics were comparable with those in the sample studied by Kan *et al* (2001).[18] The scores on the Bendep-SRQ in our sample were the same as those in the previous sample on the problematic use scale (p=0.26), but significantly lower on preoccupation (p=0.01), lack of compliance (p<0.01), and withdrawal (p<0.01) (see table 4).

Table 1

Baseline characteristics

Variables	Study sample (n=180)
Socio-demographic variables.	
Gender (female) n (%)	126 (70%)
Age (years) mean (s d)	63 (12)
Marital status n (%)	
No relationship	8 (4%)
Married / steady relationship	120 (67%)
Divorced	11 (6%)
Widowed	41 (23%)
Living alone n (%)	54 (30%)
Level of eduction n (%)	
Primary level	62 (34%)
Secondary level	108 (60%)
Advanced level	10 (6%)
Benzodiazepine usage characteristics.	
Dosage· mean MDD/DDD (s d)	0.64 (0 90)
Duration of use in months: mean (s d)	162 116

Abbreviations· MDD/DDD, mean daily dose / defined daily dose

Scalability

Table 2 shows that the R0, R1 and R2 test results of the Rasch analyses on the scales problematic use, lack of compliance, and withdrawal were all non-significant (p>0.01). This implies that the latent trait had a normal distribution and that Rasch homogeneity can be assumed. However, the latent trait of the preoccupation scale did not appear to be normally distributed (p=0.013) and removing this

Table 2

Scalability of the Bendep-SRQ scales by means of the Rasch Scaling Program using the Marginal Maximum Likelihood (MML) method

Scale	I	R0	df	p	R1	df	p	g	R2	df	p	n
- Problematic use	5	5 79	3	0 12	7 74	7	0 36	2	9 59	12	0 65	171
- Preoccupation*	5	10 81	3	0 01	17 42	7	0 01	2	12 43	12	0 42	171
*CML method***	-	-	-	-	*7 65*	*4*	*0 11*	*2*	*34 11*	*8*	*<0 01*	*111#*
- Lack of Compliance***	5	-	-	-	-	-	-	1	22 49	12	0 03	171
- Withdrawal	5	1 91	3	0 59	7 92	7	0 34	2	13 43	12	0 34	163##

ABBREVIATIONS R0, test statistic of Rasch analysis with regard to a normal distribution of the latent trait, R1, test statistic of Rasch analysis with regard to equidiscriminability, R2, test statistic of Rasch analysis with regard to unidimensionality and local stochastic independence, I, number of items in the scales, df, degree of freedom, p, p-value, g, number of subgroups formed by Rasch analysis, n, number of subjects left in the analysis, CML, conditional maximum likelihood

* As the statistic R0 reached significance using the marginal maximum likelihood method, the conditional maximum likelihood method was also applied to this scale

** As the conditional maximum likelihood method does not assume a normally distributed latent trait, the R0 is not calculated

*** Due to the small proportion of subjects who loaded on the scale, only the R2 could be computed

\# R1 and R2 statistics were calculated after excluding subjects with the minimum or maximum sum score that did not lead to variance

\#\# Excluding the subjects who had not attempted to reduce or cease their benzodiazepine use before the assessment (n=8)

assumption from the Rasch model by using the conditional maximum likelihood (CML) method showed that the scale was not Rasch homogeneous. Removing one of the items "Just before I take my medication, that is the only thing I can think about" or "I spend a great deal of time thinking about medicine" yielded a Rasch-homogeneous scale by using the CML method. The MML method, however, yielded a highly significant R0-statistic.

Reliability

Subject discriminability and item discriminability (table 3) indicated good reliability of the preoccupation, lack of compliance, and withdrawal scales. The problematic use scale yielded a moderate to good KR-20 value. Very good Cochran's Q and IDC results were found.

Table 3

Reliability of the Bendep-SRQ scales in terms of subject and item discriminability

Parameter	Problematic use	Preoccupation	Lack of Compliance	Withdrawal*
KR-20	56	74	73	76
CQ**	235	151	30	36
IDC	99	98	87	89

ABBREVIATIONS KR-20, Kuder-Richardson-20 coefficient of internal consistency, CQ, Cochran's Q (in rounded figures), IDC, item discriminability coefficient.

* Excluding all subjects who had not attempted to reduce or discontinue their BZ use before the assessment

** All CQ p-values $p < 0.001$

Construct validity

The item orders based on increasing scale value estimates yielded by the Rasch analyses were only identical to the item orders found in the original study on the development of the Bendep-SRQ for the preoccupation scale (table 4).[14] The item order in the other three scales differed from the original study by 1 item. In our sample the item 'Other people have urged me to use less medication' had a lower rank order on the problematic use scale, while the item "tiredness" had a lower rank order on the withdrawal scale. In the lack of compliance scale, the item 'I take more medication than is written on the label' had a higher rank order. The Rasch scale estimate of the 'deviating' item only exceeded twice the standard error of the Rasch scale estimate of the preceding and following item in the problematic use scale.

Discriminant validity

The results of the principal axis factor analyses with varimax rotation are shown in table 5. A three-factor solution was recommended by the scree plot, showing a substantial decrease and a gradual decline in the eigenvalue of additional factors. Moreover, two- and four-factor solutions were less interpretable. The interpretation of the factor solution given below is not necessarily the best one, but

Table 4

Construct validity (item order based on the Rasch scale values)

Bendep-SRQ scale (item)	Original study[14]	Trial sample
Problematic use:		
I have been thinking about giving up the medication	-1 41 (0 15)	-2 67 (0 24)
At present, the medication is less effective than it used to be	0 01 (0 14)	-0 04 (0 19)
Other people have urged me to use less medication	0 11 (0 14)	-0 67 (0 19)
I think the medication is destroying my life	0 64 (0 15)	1 40 (0 25)
The medication is getting me into trouble	0 66 (0 15)	2 00 (0 29)
Sum score PROBLEMATIC USE mean (s d)	1 5 (1 3)	1 5 (1 2)
Preoccupation:		
I take another dose of medication on time because otherwise I would suffer from complaints	-1 63 (0 18)	-1 80 (0 25)
I feel safe when I have my medication with me	-0 97 (0 16)	-1 08 (0 22)
I get nervous if my medication is out of reach	-0 40 (0 15)	-0 34 (0 23)
Just before I take my medication, that is the only thing I can think about	1 47 (0 16)	1 15 (0 24)
I spend a great deal of time thinking about medication	1 53 (0 16)	2 06 (0 52)
Sum score PREOCCUPATION mean (s d)	2 4 (1 5)	2 0 (1 6)
Lack of Compliance:		
I take more medication than is written on the label	-1 12 (0 19)	-0 73 (0 39)
My medication is gone too quickly	-0 72 (0 19)	-1 60 (0 39)
I go and get a new prescription before the appointed time	-0 49 (0 19)	-1 21 (0 36)
I take a lot of medication in one go	0 18 (0 20)	1 60 (0 36)
I alter what is written on the prescription	2 15 (0 33)	1 95 (0 52)
Sum score LACK OF COMPLIANCE mean (s d)	0 6 (1 6)	0 4 (0 9)
Withdrawal:		
Restlessness	-0 88 (0 19)	-0 50 (0 19)
Feeling depressed	-0 29 (0 18)	-0 04 (0 21)
Tiredness	-0 21 (0 18)	-0 74 (0 20)
Irritability	0 38 (0 18)	0 01 (0 21)
Shaking	1 00 (0 18)	1 27 (0 25)
Sum score WITHDRAWAL mean (s d)	2 0 (1 9)	1 4 (1 6)

it is the most plausible The first factor appeared to be a dimension of the psychopathological status, as four of the five scales of the POMS and three of the five scales of the MMPI showed the highest loadings on this factor However, the Bendep-SRQ scale 'lack of compliance' and the BWSQ-v2 also loaded moderately on this factor The 'vigour' scale of the POMS and all scales of the Short-Form 36 loaded highest on the second factor, representing quality of life The highest loadings of the Bendep-SRQ scales were observed on the third factor that reflected a dimension of benzodiazepine dependence. No other scale loaded substantially on this factor, which indicated good discriminant validity

Table 5

Discriminant Validity of the Bendep-SRQ

	Factor*		
Scale	I	II	III
Bendep-SRQ**			
Problematic use			74
Preoccupation			66
Lack of Compliance	41		45
BWSQ-v2	41		
Profile of Mood States			
Depression	80		
Anger	85		
Fatigue	54		
Vigour		-/- 49	
Tension	80	47	
Dutch Shortened MMPI			
Negativism	70		
Somatisation	47	-/- 47	
Shyness			
Severe psychopathology	42		
Extraversion			
SF-36			
Physical functioning		75	
Role functioning (Physical)		61	
Pain		64	
General health perception	-/- 32	63	
Vitality		78	
Social functioning	-/- 37	48	
Role functioning (Emotional)	-/- 40	42	
Mental Health	-/- 68	39	

* Principal axis factor analysis with varimax rotation on a matrix of scale scores of all participants (n=180)
** Withdrawal scale excluded to avoid the selection of patients with previous attempts to discontinue of reduce their use (n=15)

Predictive validity

As shown by the crude odds ratios in table 6, all scales of the Bendep-SRQ showed significant predictive validity in a logistic regression analysis after correcting for treatment condition. The lack of compliance and preoccupation scales appeared to have the highest predictive values: both scales achieved an improvement of the prediction of the model from 63% to 70% correct. To assess the independent predictive value of the scales, we also calculated the odds ratios after correcting for all baseline measurements that univariately discriminated between successfully treated subjects and failures. These were dose ($p = 0.001$), sum score on the BWSQ-2 ($p = 0.003$), use of nicotine ($p = 0.009$), negativism of the Dutch shortened MMPI ($p = 0.043$) and tension of the POMS ($p = 0.048$). To calculate the adjusted odds ratio for 'withdrawal', the BWSQ-2 sum score was a priori left out of the analysis, as the two scales tend to measure the same. Except for the problematic use scale, all of the scales still had significant independent predictive value.

Table 7

Time course of mean benzodiazepine dependence scores during benzodiazepine discontinuation therapy

			1. Problematic use		2. Preoccupation		3. Lack of Compliance		4. Withdrawal	
			Time of assessment		Time of assessment		Time of assessment		Time of assessment	
			Baseline	*Outcome*	*Baseline*	*Outcome*	*Baseline*	*Outcome*	*Baseline*	*Outcome*
Treatment outcome		*Success*	1 5 ±1 2	0 6 ±0.8	1 6 ±1 5	0 5 ±0 9	0 1 ±0 4	0 0 ±0 2	1 1 ±1.5	0 9 ±1 3
		Failure	1 9 ±1.3	1.7 ±1.3	2.7 ±1 7	2 4 ±1 4	0.7 ±1 3	0 6 ±1.1	2.1 ±1.7	1 8 ±1 7
p-value (statistics)	Time		0 000		0.000		0.302		0.047	
	Outcome		0.000		0 000		0.000		0.000	
	Time*outcome		0 003 (F=9 13, df=1,138)		0 002 (F=9 86, df=1,138)		0 769 (F=0 09, df=1,138)		0.963 (F<0 01, df=1,125)	

Table 6

Predictive validity of the Bendep-SRQ scales during benzodiazepine discontinuation therapy

Bendep-SRQ scale	Crude OR [95% C.I.]*	p-value	Adj. OR [95% C.I.]**	p-value
Problematic use	1 39 [1 04 - 1 85]	0 025	1 11 [0 79 - 1 55]	0 540
Preoccupation	1 62 [1 27 - 2.07]	0 000	1 38 [1 04 - 1 84]	0 025
Lack of Compliance	2 89 [1 53 - 5.47]	0 001	2 37 [1 10 - 5 13]	0 028
Withdrawal	1 55 [1 22 - 1.98]	0 000	1 48 [1 06 - 2 05]***	0 020

Abbreviations OR, odds ratio, C I , confidence interval, adj , adjusted
* ORs for the scale score at baseline in successful and unsuccessful subjects, only corrected for treatment condition (n=141)
** Other significant independent predictors were treatment condition (p=0.001), dose (p=0 003) and use of nicotine (p=0 013)
*** Adjusted odds ratio calculated after removing the BWSQ-2 score

Time course

The longitudinal course showed significant time-effects in the scales problematic use, preoccupation, and withdrawal, which indicated a decrease in the severity of dependence after taking part in the benzodiazepine withdrawal program (table 7). Time x treatment outcome interactions were only significant for the scales problematic use and preoccupation, which indicated a greater decrease in dependence severity in subjects who successfully discontinued compared to those who did not.

Discussion

The Bendep-SRQ was cross-validated in primary care patients who were taking part in a benzodiazepine discontinuation programme in order to evaluate the generalisability of previous results to this population and to assess the predictive validity and time course of dependence. In general, our results provide further support for the scalability, reliability and validity of the Bendep-SRQ scales.

The main difference from previous studies was that our population comprised subjects who had the intention to quit their benzodiazepine use. They expressed this intention by giving informed consent to participate in a benzodiazepine discontinuation trial. Our sample was comparable with that studied by Kan *et al* (2001) with respect to the socioeconomic variables, benzodiazepine dosage and duration of use.[18] However, our sample had significantly lower scores on the Bendep-SRQ scales preoccupation, lack of compliance, and withdrawal, which indicated selective recruitment.

In our sample, Rasch homogeneity was confirmed in the problematic use, lack of compliance, and withdrawal scales. In line with a previous report, the latent trait was not normally distributed in the preoccupation scale, but in contrast, the Rasch model did not hold true for this scale.[18] Removing one of the items "Just before I take my medication, that is the only thing I can think about" or "I spend a great deal of time thinking about medicine" yielded a Rasch homogeneous scale. This implies that the assumption of local stochastic independence was threatened for these items and not the unidimensionality. In both cases however, the latent trait was not normally distributed, as indicated by

a highly significant R0 ($p< 0.01$) As the item parameter estimates in the Rasch model are independent of the subject parameters, this finding cannot be explained by recruitment selection Further research is required to shed more light on whether this scale can be properly used during withdrawal Surprisingly, a literature search to find information on the relationship between long-term benzodiazepine use and preoccupation with the availability of benzodiazepines, more specifically craving, revealed a gap in craving research in the field of benzodiazepine addiction, as only two reports were found [29 30]

The KR-20, IDC, and Cochran's Q showed excellent results, even better than those of previously research, which confirms the high reliability of all scales of the Bendep-SRQ The factor analytic results shown in table 5 could be interpretated the same way as those found in earlier studies on the Bendep-SRQ, which also supports discriminant validity In contrast with earlier studies, no information could be provided on concurrent validity, because we did not include any other dependence measurements

The item orders for the scales problematic use, lack of compliance, and withdrawal were different form those in the original study However, the difference between the items based on increasing scale value estimates yielded by the Rasch analysis only exceeded the range of twice the standard error of the scale value estimate in the problematic use scale [14] This suggests that we have found the definitive rank order Following the same reasoning, the item orders found for the scales 'lack of compliance' and 'withdrawal' might be based on coincidence, because these differences did not exceed twice the standard error of the scale value estimate, whereas in the study by Kan *et al* (1999) they did [14] So for these scales, the rank order found by Kan *et al* holds true In conclusion, the approximate replication of previous item-orders supports the construct validity of the Bendep-SRQ scales

As Rasch homogeneity was confirmed for three of the previous established scales, it was justified to use the sum scores for predictive analyses and follow-up measurements Although the 'preoccupation' scale was not Rasch homogeneous, we used the sum score of the original 5-item scale to evaluate the clinical relevance of the previously developed and repeatedly confirmed scale The predictive validity of the Bendep-SRQ scales was supported by significant odds ratios (table 6) Moreover, three out of the four scales had predictive value independent of the daily dose, withdrawal symptoms, smoking status, personality traits and psychopathology, which shows the relevance of the benzodiazepine dependence level in clinical practice

Tapering-off benzodiazepine use significantly reduced the severity of the dependence characteristics problematic use, preoccupation, and withdrawal Patients who discontinued their benzodiazepine use completely had significantly greater decreases of the scale scores problematic use and preoccupation compared to subjects who did not The insensitivity of lack of compliance for stopping benzodiazepine use was probably due to the fact that the subjects who were able to stop had very low scores on this scale at baseline, so a significantly lower score at outcome was almost

impossible. More importantly, it might be argued that a high score on this scale reflects therapy resistance. We expected the sum score of the withdrawal scale to be higher at outcome, with a significant time x treatment outcome interaction, because the experience of more severe withdrawal symptoms has been associated with an inability to achieve complete abstinence.[12] However, we found a small but significant decrease in the sum score and no interaction effects. This could be explained by the study design, because the patients filled out the withdrawal scale four weeks after completing the intervention. The sum score would probably have been more sensitive if the scale had been administered during withdrawal.

The present study on the psychometric properties of the Bendep-SRQ provided further support for the scalability, reliability and validity of the scales problematic use, lack of compliance, and withdrawal. However, some concerns arose about the preoccupation scale. The different rank orders found in the other scales did not threaten Rasch homogeneity, but the rank order of the scale problematic use suggests that we should reconsider the theoretical rationales that underlie the construct validity in long-term benzodiazepine users who seek discontinuation therapy. These results clearly show the limitations of generalizing psychometric properties of questionnaires if they are administered in other populations and thus the need for cross-validation in the different populations of clinical interest. The predictive validity and longitudinal course of the Bendep-SRQ were promising. Therefore we recommend its use in all treatment regimens in the field of benzodiazepine addiction. Further research is recommended to investigate whether particular profiles of the Bendep-SRQ scores reflect an indication for more rigorous treatment.

References

1 Hollister LE, Motzenbecker FP, and Degan RO Withdrawal reactions from chlordiazepoxide (Librium) *Psychopharmacologia* 1961, 2 63-68

2 Slater J Suspected dependence on chlordiazepoxide hydrochloride (Librium) *Journal of the Canadian Medical Association* 1966, 95 416

3 Selig JW, Jr A possible oxazepam abstinence syndrome *Journal of the American Medical Association* 1966, 198 951-952

4 Pecknold JC, McClure DJ, Fleun D, et al Benzodiazepine withdrawal effects *Progressive Neuropsychopharmacology in Biological Psychiatry* 1982, 6 517-522

5 Merz WA and Ballmer U Symptoms of the barbiturate/benzodiazepine withdrawal syndrome in healthy volunteers standardized assessment by a newly developed self rating scale *Journal of Psychoactive Drugs* 1983, 15 71-84

6 Petursson H and Lader M Dependence on tranquilizers Maudsley Monograph no 28 Oxford Oxford University Press, 1984

7 Ashton H Benzodiazepine withdrawal an unfinished story *British Medical Journal (Clinical Research Edition)* 1984, 288 1135 1140

8 Busto UE, Sykora K, and Sellers EM A clinical scale to assess benzodiazepine withdrawal *Journal of Clinical Psychopharmacoogy* 1989, 9 412-416

9 Baillie AJ and Mattick RP The benzodiazepine dependence questionnaire development, reliability and validity *British Journal of Psychiatry* 1996, 169 276-281

10 Rickels K, Schweizer E, Case WG, *et al* Long-term therapeutic use of benzodiazepines I Effects of abrupt discontinuation *Archives of General Psychiatry* 1990, 47 899-907

11 Tyrer P, Murphy S, and Riley P The Benzodiazepine Withdrawal Symptom Questionnaire *Journal of Affective Disorders* 1990, 19 53-61

12 Couvée JE and Zitman FG The Benzodiazepine Withdrawal Questionnaire Psychometric evaluation of BWSQ during a discontinuation program in depressed chronic benzodiazepine users in general practice Journal of Affective Disorders 2002, 70(2) 133 141

13 Kan CC, Breteler MHM, van der Ven AHGS, *et al* An evaluation of DSM-III-R and ICD-10 benzodiazepine dependence criteria using Rasch modelling *Addiction* 1998, 93 349-359

14 Kan CC, Breteler MHM, Timmermans EAY, *et al* Scalability, reliability, and validity of the benzodiazepine dependence self-report questionnaire in outpatient benzodiazepine users *Comprehensive Psychiatry* 1999, 40 283-291

15 Kan CC, Breteler MHM, van der Ven AHGS, *et al* Cross-validation of the benzodiazepine dependence self-report questionnaire in outpatient benzodiazepine users *Comprehensive Psychiatry* 2001, 42 433 439

16 Oude Voshaar RC, Gorgels WJ, Mol AJ, *et al* Tapering off, with or without simultaneous group cognitive behavioural therapy, as a strategy to achieve discontinuation of long-term benzodiazepine use, a three-condition randomised controlled trial *British Journal of Psychiatry* 2003, 182 498-503

17 Glas CAW The derivation of some tests for the Rasch model from the multinomial distribution *Psychometrika* 1988, 53 525-546

18 Kan CC, van der Ven AHGS, Breteler MHM, *et al* Latent trait standardization of the benzodiazepine dependence self- report questionnaire using the Rasch scaling model *Comprehensive Psychiatry* 2001, 42 424-432

19 Duncan-Jones P, Grayson DA, and Moran PA The utility of latent trait models in psychiatric epidemiology *Psychological Medicine* 1986, 16 391 405

20 Fischer GH Derivations of the Rasch model In Fischer GH, Molenaar IW (eds) Rasch models Foundations, Recent Developments and Applications New York Springer Verlag, 1995 15-38

21 Hoyt C Test reliability by analysis of variance *Psychometrika* 1941 6 135-160

22 Wald FD, Mellenbergh GJ De verkorte versie van de Nederlandse vertaling van de Profile of Mood States (POMS) *Nederlands Tijdschrift voor de Psychologie* 1990, 45 86-90

23 McHorney CA, Ware JE, Jr and Raczek AE The MOS 36-Item Short Form Health Survey (SF 36) II Psychometric and clinical tests of validity in measuring physical and mental health constructs *Medical Care* 1993, 31 247-263

24 McHorney CA, Ware JE, Jr , Lu JF, *et al* The MOS 36-item Short-Form Health Survey (SF 36) III Tests of data quality, scaling assumptions, and reliability across diverse patient groups *Medical Care* 1994, 32 40-66

25. McHorney CA and Ware JE, Jr Construction and validation of an alternate form general mental health scale for the Medical Outcomes Study Short-Form 36-Item Health Survey *Medical Care* 1995, 33 15-28

26. Ware JE, Jr and Sherbourne CD The MOS 36-item short-form health survey (SF-36) I. Conceptual framework and item selection *Medical Care* 1992, 30 473-483.

27 Luteijn F and Kok AR NVM. Nederlandse Verkorte MMPI Lisse The Netherlands Swets & Zeitlinger B V., 1985

28. Glas CA RSP· Rasch Scaling Program 1993. Groningen, The Netherlands, IEC ProGAMMA

29 Lucki I, Volpicelli JR, Schweizer E Differential craving between recovering abstinent alcoholic-dependent subjects and therapeutic users of benzodiazepines *NIDA Research Monographs* 1991, 105 322-333.

30. Linden M, Bar T, and Geiselmann B. Patient treatment insistence and medication craving in long-term low-dosage benzodiazepine prescriptions. *Psychological Medicine* 1998, 28. 721-729

PART IV

LONG-TERM RESULTS OF TAPER-OFF STRATEGIES

Chapter 8

Long-term outcome of a three-condition, randomised, usual care controlled benzodiazepine discontinuation study

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Abstract

Background - Long-term studies of benzodiazepine discontinuation are scarce and inconclusive due to the lack of controlled comparisons with non-intervention

Objective - To investigate longitudinally the 18-month outcome of benzodiazepine discontinuation in general practice with respect to benzodiazepine use, psychotropic drug use and psychological functioning

Methods - In an 18-month prospective follow-up study, tapering off with group cognitive-behavioural therapy (CBT) and tapering-off alone were compared with a non-intervention control group in a randomised controlled design as strategies to discontinue long-term benzodiazepine use in 180 patients who were not able to discontinue after receiving a letter from their general practitioner advising cessation by themselves

Results - At follow-up, tapering off alone resulted in higher abstinence rates compared to the control group (36% vs 15%, p=0 03), while simultaneous group CBT had no additional value to tapering off alone Although patients were suffering from mild anxiety and depressive symptoms, neither intervention type nor outcome affected psychological functioning Patients did not switch from benzodiazepines to other psychotropic drugs, nicotine, or alcohol

Conclusion - This is the first long-term outcome study that provides evidence that tapering-off benzodiazepine use is an effective strategy to discontinue benzodiazepine usage in motivated patients who are not able to quit after receiving a letter advising cessation by themselves Moreover, no negative effects were found on psychological functioning or psychotropic drug use Additional psychotherapy during the discontinuation programme did not improve success rates or psychological functioning

Introduction

About 60% of long-term benzodiazepine users who take part in benzodiazepine discontinuation programmes are able to achieve complete abstinence in the short term [1 2] When usage has lasted several years, however, short-term effects cannot be seen the ultimate goal of treatment To the best of our knowledge, five long-term evaluations of benzodiazepine discontinuation programmes have been described with a follow-up period ranging from ten months to five years [3 8] However, none of these studies compared the outcome of the discontinuation programmes with the natural course of long-term benzodiazepine use in a randomised controlled fashion These studies therefore remain inconclusive with respect to discontinuation rates and the effect on psychological functioning

When reviewing these follow-up studies, it appears that outcome largely depends on the type of measurement used With cross-sectional measurements, the studies yielded abstinence rates of 54%[4] and 58%[5] In contrast, studies longitudinally monitoring their patients reported abstinence rates of only 16%[6] or 18%[8] The findings of a fifth study, however, were very different, showing a continued abstinence rate of 82% [3] This study differed from the other four because (a) it was an evaluation of a patient-tailored withdrawal programme leading to taper-off periods up to 15 months, and (b) the specialised setting, which was a third-line Clinical pharmacology Unit

Four long-term outcome studies evaluated psychological functioning at the end of follow-up [3 6] The results were contradictory, probably because of differences and shortcomings in methodology Golombok *et al* (1987) reported significant mental problems after successful discontinuation, while Ashton (1987) suggested improved functioning of patients remaining benzodiazepine-free [3 4] However, both studies did not report baseline functioning nor made a comparison between abstinent and non-abstinent patients Holton *et al* (1992) and Rickels *et al* (1991) differentiated between abstinent and non-abstinent patients The former did not find significant differences between these two groups, while the latter found better functioning in abstinent patients [5 6] This difference may be due to the fact that Rickels *et al* (1991), contrary to Holton *et al* (1992), corrected for baseline values and used another assessment period (one month before follow-up versus the last year of follow-up) [5] Interpretation is also hampered by the fact that, as mentioned before, all these studies lacked a non-intervention control group

This study deals with the above mentioned issues, because it presents an 18-month follow-up of a randomised controlled trial (RCT) comparing tapering off long-term benzodiazepine use, with or without cognitive-behavioural therapy (CBT), with a non-intervention control group [9] We aimed to answer the following questions (a) what are the longitudinal effects of the two tapering-off programmes on benzodiazepine usage and the use of other psychotropic drugs and (b) what long-term effects can be expected for psychological functioning? We hypothesised that tapering off with group

CBT would be superior to tapering off alone, which would be superior to the control group, with higher continued abstinence rates and better psychological functioning at the end of follow-up

Methods

Design and short-term results of the randomised controlled trial

The results of the RCT are described in detail elsewhere[9], but they can be briefly summarised as follows of the 2964 identified long-term benzodiazepine users in primary care (i e , patients who had used benzodiazepines for over three months), 2004 met the criteria for, and were included in, the minimal intervention (i e , a letter from their GP advising benzodiazepine discontinuation), which was used to select patients unable to stop by themselves [10] All 2004 patients were invited by letter to visit their GP for an evaluation of the effect of the minimal intervention Of the 1321 patients who visited their GP, 1036 were still using benzodiazepines and were asked to participate in the RCT Finally, 180 patients participated and were randomised over tapering off with CBT (n=73), tapering off alone (n=73), and a non-intervention control group (n=34) Patients assigned to one of the two active treatment groups were tapered off by the GP in weekly steps of 25% after being transferred to an equivalent dose of diazepam Patients assigned to tapering-off with CBT attended five 2h weekly sessions of group CBT starting halfway through the taper-off programme Patients in the non-intervention control group did not receive any help with benzodiazepine reduction during the intervention period [9]

Both active treatment groups yielded significantly higher proportions of patients who successfully discontinued their use compared with the control group, based on the intent-to-treat analysis of the RCT self-report outcome assessment tapering-off with CBT, 58% (33/57), tapering-off alone, 62% (37/60), and non-intervention, 21% (5/24) The two active treatment groups did not differ significantly

Design and assessments follow-up study

This 18-month prospective follow-up study consisted of (a) a computerised extract of all drug prescription data from the GP information system (= computerised medical records) of the 30 participating practices, and (b) a self-report follow-up assessment at 18 months identical to the baseline and outcome assessment of the RCT All patients gave written informed consent for the follow-up study The study received ethical approval from the University Medical Centre Nijmegen, and was carried out between 1998 and 2001

Drug prescription data were extracted at a patient level and contained date of issue, Anatomical Therapeutic Chemical classification code (ATC-code)[11] and name of the drug, number of tablets and

dose, and prescription rules Gender, date of birth, and the administration number of individual patients were extracted to link prescription data with the results of the RCT and the 18-month follow-up assessment For patients who left the practice before the end of the follow-up period, the date and reason for leaving the practice were recorded

The primary outcome measure was defined as the proportion of long-term benzodiazepine users who did not receive any benzodiazepine prescriptions after the intervention period of the RCT according to the prescription data records We calculated the daily dosage over predefined periods based on the sum of the total dosage of all issued benzodiazepine prescriptions Dosages were expressed in mg diazepam equivalent according to Zitman & Couvée (2001) [7] The following periods were defined period -1 consisted of the three months before the minimal intervention, i e , the letter from the GP (baseline period) Period 0 was defined as the time between the sending of the letter and the RCT, which varied in length between 5 and 15 months (mean ±sd was 7 6 ± 1 9 months) In this period, the minimal intervention was evaluated and patients were recruited and randomised for the RCT Period 1 consisted of the intervention period, and was defined as the three months after the start of the RCT Periods 2 to 6 were the follow-up periods, each covering a 3-month period As prescriptions for benzodiazepines in the Netherlands have a restricted duration of one month, periods of at least three months provided reliable estimates of the daily dosage

Patients' prescription patterns during follow-up were classified according to Couvée *et al* (2002) to provide detailed information for those patients who could not discontinue or relapsed This classification system is based on general guidelines for the adequate maximum duration of treatment with benzodiazepines It systematically describes 14 prescription patterns, with pattern 1, benzodiazepine-free, to pattern 14, benzodiazepine use during more than 95% of the follow-up period at a higher dosage than at the beginning of the study Based on these prescription patterns, four outcome categories were established A, success, B, partial success, C, minor success, and D, failure (see table 2) [8]

Secondary outcome measures were the use of psychotropic drugs other than benzodiazepines, as extracted from the GP information system, and psychological functioning as measured at the end of follow-up The prevalence rates of psychotropic drug use other than benzodiazepines were analysed over 6-month periods because, in contrast with the prescriptions for benzodiazepines, these prescriptions were for quantities sufficient for three months The following categories were analysed separately (i) antidepressants (N06A), (ii) anxiolytic or hypnotic drugs other than benzodiazepines (N05A and N05C without N05AB and N05CD), (iii) pain medication (N01, N02 and M01A), and (iv) other psychotropic drugs, such as antipsychotics and antiepileptic drugs (N03, N04, N05A, N07 and N06 without N06A) The six-month period before the minimal intervention was defined as the baseline period, while 0-6, 6-12 and 12-18 months after the start of the RCT were defined as the three follow-up periods

The outcome assessment was carried out at the end of the follow-up period by a research assistants who visited the patients at home Self-report questionnaires were used for use of benzodiazepines in the month prior to the assessment (as Rickels *et al*, 1991 and Golombok *et al*, 1987)[4 5], the use of alcohol (including the number of problem drinkers based on the 18-item list of Cornel)[12], psychological well-being (GHQ 12-item version)[13], mood (the scales depression, anger, fatigue, vigour and tension of the 32-item shortened profile of mood states, POMS)[14], the number and severity of benzodiazepine withdrawal symptoms (benzodiazepine withdrawal symptom questionnaire version 2, BWSQ-v2)[15], and the severity of benzodiazepine dependence (the scales problematic use, preoccupation, lack of compliance and withdrawal of the Bendep-SRQ)[16] All questionnaires showed good reliability and validity for the Dutch population

Sample size

Expecting longitudinally measured abstinence rates of 20% in the TOA condition[8] and of 50% in the TO+CBT condition, the required sample size per group was 44 patients based on a Yates's corrected chi-square test (two-sided α=0 05, β=0 20)

Statistical analysis

All outcome parameters were first analysed for the three groups Significant main effects were further analysed with pairwise comparisons All analyses were performed on an intent-to-treat basis

The prevalence of benzodiazepine use in the predefined follow-up periods and the prescription patterns according to Couvée *et al* (2002)[8] were analysed by chi-square tests In addition, survival analyses (i e , the life table method of Kaplan and Meier and the Breslow test) were applied to receive the time-dependent survival (unrelapse) probabilities of the three groups and to compare their courses

Of those who failed to achieve continued abstinence after the RCT, the daily dosage was compared for the three groups by repeated measures analysis, with condition as between-subjects factor and time as within-subject factor, corrected for baseline dosage and waiting time for the start of the RCT

The secondary outcome measures were analysed by chi-square tests in the case of dichotomous variables and with repeated measure ANOVA's in the case of continuous variables All secondary outcome measures were analysed for the three groups as well as for the different benzodiazepine outcome criteria, to evaluate the relationship between psychological functioning and benzodiazepine usage during follow-up Time (baseline vs follow-up assessment) was used as within subject factor and treatment group as a three-level or outcome as a two-level between subject factor in the repeated measure ANOVA's Outcome was analysed twice dichotomised as continued abstinence versus benzodiazepine use during follow-up, and outcome category A2 - B (at least partial success, excluding those achieving continued abstinence) versus category C + D (failure) (see table 2)

Results

Patient flow

The dropout rate differed for the various outcome measures. Prescription data were available for 170 of the 180 patients (94%). Data of 10 patients could not be extracted because 9 moved to another city and 1 patient was lost to follow-up. On the other hand, the 18-month follow-up assessment was completed by 143 patients (dropout 37 patients, 21%). Reasons for dropping out were: dissatisfied with the 'treatment' (n=6), somatic or psychological problems (n=8), and unknown (n=23). The number of dropouts was equally distributed over the three groups (χ^2=1.85; df=2; p=0.40). This dropout rate was not related to benzodiazepine prescription during follow-up (p=0.52). Patients who dropped out had significantly lower benzodiazepine dependence profiles based on their Bendep-SRQ scores (problematic use, p=0.02; preoccupation, p<0 01; withdrawal, p=0.02).

Patient characteristics (n=170) did not differ significantly at baseline between the three groups. Patients were prescribed benzodiazepines for a mean (±sd) duration of 13.5 (±9.6) years in a mean daily dosage of 8.4 mg diazepam equivalent during period -1 before the minimal intervention (P_{25} = 4.1 mg; P_{50} = 6.3 mg; P_{75} = 9.9 mg) and 5.9 mg diazepam equivalent in period 0, the baseline of the RCT (P_{25} = 1.7 mg; P_{50} = 3.8 mg; P_{75} = 6.5 mg). The mean (±sd) age was 63 (±12) and 70% were female. For more detailed information see Oude Voshaar *et al.*[9]

Table 1

Benzodiazepine abstinence rates based on prescriptions per 3-month period

	Period:						
	Recruitment*	RCT	Follow-up				
	0	1	2	3	4	5	6
Condition:	(n=170)	(n=170)	(n=170)	(n=170)	(n=170)	(n=170)	(n=170)
Tapering off + CBT (n=68):							
Point prevalence (%)	6% **	15%	44%#^	40%	38%^	46%#	43%
Continued abstinence rate (%)	-	-	44%#^	37%	32%	31%	29%
Tapering off alone (n=69):							
Point prevalence (%)	10% **	23%	63%#	55%#	55%#	48%#	49%
Continued abstinence rate (%)	-	-	61%#	51%#	42%#	36%#	36%#
No intervention (n=33):							
Point prevalence (%)	3% **	15%	21%	21%	21%	24%	30%
Continued abstinence rate (%)	-	-	21%	18%	15%	15%	15%

* Time between the sending of the letter and the start of the RCT in which the effect of the letter (minimal intervention) was evaluated and patients were recruited for the RCT

** 12 patients received no prescriptions after the minimal intervention while waiting for the RCT, although they reported not to have stopped These patients have stopped usage of their own accord while waiting for the RCT

\# Differed significantly with the non-intervention control group (p<0 05)

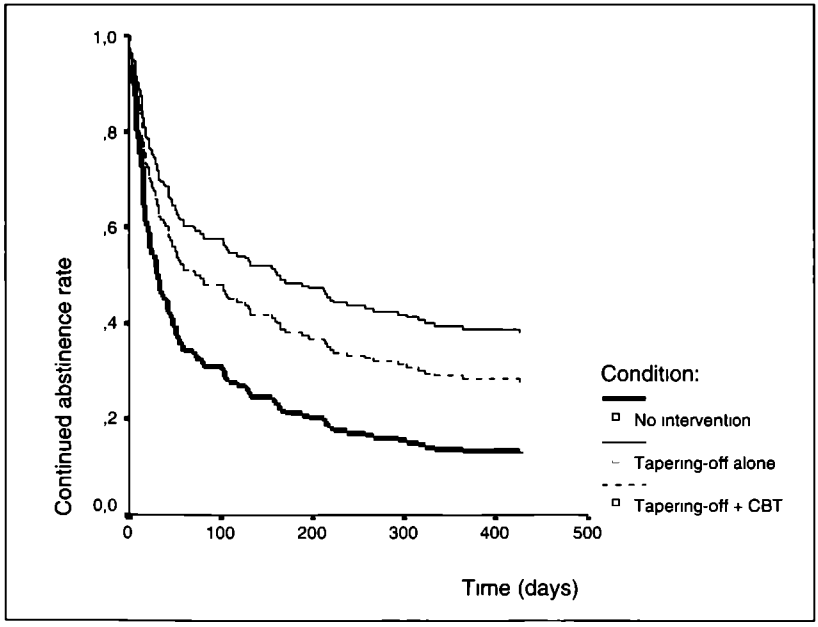
^ Differed significantly with tapering-off alone (p<0 05)

Benzodiazepine use

Table 1 shows the abstinence rates based on the computerised benzodiazepine prescription data. The continued abstinence rate for the tapering off with CBT group was not significantly superior to the non-intervention control group (p=0.12), while the opposite was the case with the tapering off alone group (p=0.03). The two active treatment groups only differed significantly in period 2, i.e., three to six months follow-up (p=0.03), in favour of tapering off alone. Survival function estimates for each group are shown in figure 1. Of those patients restarting benzodiazepine treatment during follow-up, 90% (113/126) restarted within the first 9 months. During follow-up, the three groups differed significantly (Breslow test: 9.31; df=2; p=0.19). Pair-wise comparisons showed that tapering off alone was significantly superior to the non-intervention control group (p=0.003), while tapering off with CBT was not (p=0.12). In line with these findings, tapering off with group CBT did not lead to significantly better prescription patterns during follow-up compared to the non-intervention control group (p = 0.11), while tapering off alone on the other hand did (p=0.03) (table 2).

Figure 1

Survival time until first prescription after the intervention period



Benzodiazepine dosages in failures

The mean (±sd) daily dosage of patients who failed to achieve continued abstinence decreased from 10.3 ±6.6 mg before the minimal intervention (period -1) to 6.9 ±4.5 mg thereafter (period 0) and finally to 5.2 ±6.7 mg diazepam equivalent at the end of follow-up (period 6). The repeated measures ANOVA showed that among patients who did not achieve continued abstinence, those receiving active treatment used significantly lower dosages at follow-up compared to those assigned to the control group ($F=6.5$; $df=1$; $p=0.01$). A significant time x group interaction (active treatment vs. non-intervention; $F=5.3$; $df=1$; $p=0.02$) indicated that this difference was not constant over time, but decreased during follow-up (see figure 2).

Table 2

Benzodiazepine (BZ) prescription patterns according to Couvée *et al* (2002) during follow-up

	Ourcome categories	Tapering off + CBT N (%)	Tapering off alone N (%)	Control group N (%)	Whole sample N (%)
A	**Success**	**31 (46%)**	**35 (51%)**	**7 (21%)**	**73 (43%)**
1	BZ-free	20 (29%)	25 (36%)	5 (15%)	50 (29%)
2	BZ use one episode ≤ 15 days	5 (7%)	2 (3%)		7 (4%)
3	BZ use > one episode ≤ 15 days	1 (2%)	4 (6%)		5 (3%)
4	BZ use one episode > 15 days and ≤ 30 days	2 (3%)	2 (3%)		4 (2%)
5	BZ use > one episode > 15 days and ≤ 30 days	3 (4%)	2 (3%)	2 (6%)	7 (4%)
B	**Partial success**	**1 (2%)**	**3 (4%)**	**1 (3%)**	**5 (3%)**
6	BZ use one episode > 30 days and ≤ 60 days		1 (1%)		1 (1%)
7	BZ use > one episode > 30 days and ≤ 60 days	1 (2%)	1 (1%)		2 (1%)
8	BZ use one episode > 60 days and ≤ 90 days			1 (3%)	1 (1%)
9	BZ use > one episode > 60 days and ≤ 90 days		1 (1%)		1 (1%)
C	**Minor success**	**20 (29%)**	**12 (17%)**	**12 (36%)**	**44 (26%)**
10	BZ use > 90 days no use at time of follow-up		1 (1%)	3 (9%)	4 (2%)
11	BZ use > 95% of follow-up time, lower dose	20 (29%)	10 (15%)	9 (27%)	39 (23%)
D	**Failure**	**16 (24%)**	**19 (28%)**	**13 (40%)**	**48 (28%)**
12	BZ use > 90 days and use at time of follow-up	2 (3%)	8 (12%)		10 (6%)
13	BZ use > 95% of follow-up time, same dose	12 (18%)	11 (16%)	11 (33%)	34 (20%)
14	BZ use > 95% of follow-up time, higher dose	2 (3%)	1 (1%)	2 (6%)	5 (3%)
		68 (100%)	69 (100%)	33 (33%)	170 (100%)

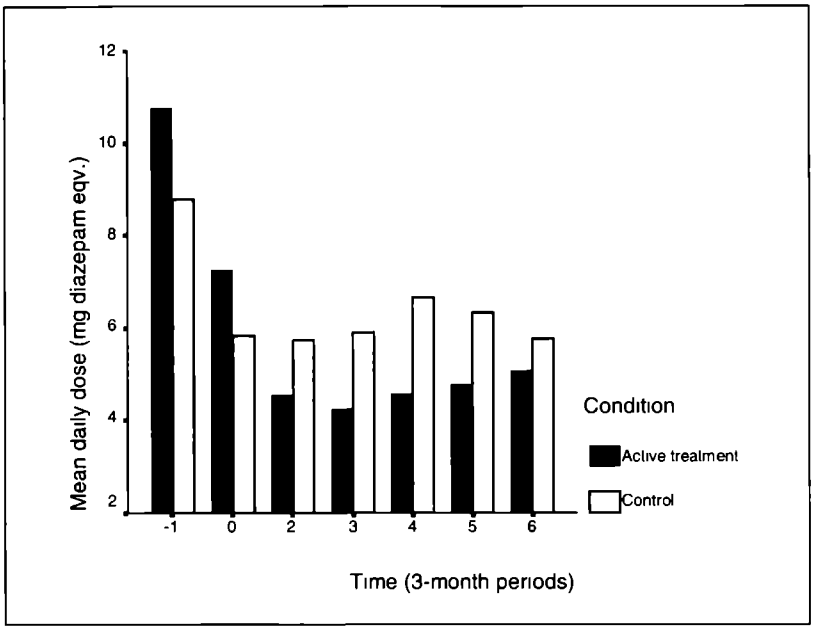
1 Comparison of the four outcome categories A, B, C and D
- TO+CBT versus CC. $\chi^2=6.1$; $df=3$, $p=0.11$
- TOA versus CC $\chi^2=9.2$; $df=3$, $p=0.03$

2 Comparison of outcome after dichotomising between category A versus the categories B, C and D:
- TO+CBT versus CC $\chi^2=5.6$, $df=1$, $p=0.02$
- TOA versus CC $\chi^2=8.0$, $df=1$, $p=0.01$

3 Comparison of outcome after dichotomising between category A and B versus category C and D
- TO+CBT versus CC $\chi^2=4.8$, $df=1$, $p=0.03$
- TOA versus CC $\chi^2=8.6$, $df=1$, $p<0.01$

Figure 2

Mean daily dosages in mg diazepam equivalent for patients not able to achieve continued abstinence



No significant differences between the three groups were found regarding the self-reported abstinence rate the month before the follow-up assessment (χ^2=3.3; df=2; p=0.19). Fifty-two percent (30/58) of the patients assigned to tapering-off with CBT reported no use, 63% (37/59) of those assigned to tapering-off alone, and 42% (11/26) of those assigned to the control group.

Psychotropic drugs and agents

The prevalence of prescribed antidepressants remained stable (baseline 18%; 12-18-month follow-up 20%), and was independent of treatment group or outcome. Among patients who achieved continued benzodiazepine abstinence, the prevalence of pain medication decreased from 52% at baseline to 38% at 12-18-month follow-up, while it remained stable (43% versus 41%) in the other patients. The use of antipsychotic and anticpileptic drugs was negligible at baseline and follow-up. No significant switches to hypnotic or anxiolytic drugs other than benzodiazepines were observed in patients who remained abstinent: one patient received zopiclone 7.5 mg for daily use during follow-up; another patient received 30 tablets valerian extract 45 mg once, and finally a third patient was prescribed 10 tablets of hydroxyzine 25 mg once At baseline, 67% of the patients consumed caffeine, 47% nicotine, and 54% alcohol. These prevalence rates and the mean amount consumed per user remained stable during follow-up independent of treatment group or outcome

Psychological functioning

At baseline, the mean (±sd) score on the GHQ-12 was 2.6 ±3.3. Based on a cut-off rate of 2/3, 34% of the patients could be classified as 'psychiatric cases'. Based on the sex-adjusted norm scores of the POMS for the Dutch population, the proportion of patients in the fifth quintile was 46% for depression, 27% for anger, 41% for fatigue, 36% for having no vigour, and 29% for anxiety. The repeated measures ANOVA's yielded significant time factors for the scores regarding psychological well-being (GHQ-12, $p<0.01$), problematic use (Bendep-SRQ, $p<0.01$), preoccupation (Bendep-SRQ, $p<0.01$), withdrawal (Bendep-SRQ, $p<0.01$), depression (POMS, $p=0.02$), anger (POMS, $p<0.01$), shyness (POMS, $p=0.01$), and tension (POMS, $p<0.01$). All time effects showed an improvement in functioning at follow-up. No significant time x group interactions for any of the secondary outcome measures were found (severity of withdrawal symptoms (BWSQ-v2), profile of benzodiazepine dependence (Bendep-SRQ), psychological well-being (GHQ-12), mood (POMS), and problematic alcohol use (Cornel)). This indicated that for all parameters the change from baseline to end of follow-up was comparable over the three groups.

Comparing patients who achieved continued abstinence with those who did not resulted in significant time x outcome interactions for the dimensions problematic use ($p=0.05$) and preoccupation ($p=0.02$) of the Bendep-SRQ. This indicated that the severity of benzodiazepine dependence decreased more for patients achieving continued abstinence compared with those who did not. Using the outcome criteria of Couvée *et al* (2002) no significant time x outcome interactions were found for any of the variables, including the dimensions of the Bendep-SRQ.

Discussion

Long-term efficacy of tapering-off

Our main result is that at 18-month follow-up, 29% of those assigned to tapering off with group CBT, and 36% of those assigned to tapering off alone, were still benzodiazepine-free. Only tapering off alone differed significantly from the non-intervention control group, in which 15% remained benzodiazepine-free. Actively treated patients who failed to achieve continued abstinence lowered their dosage significantly more than patients in the non-intervention control group. The average dose reduction is partly explained by intermittent usage, since prescription patterns showed that 47% percent of the patients receiving additional CBT, and 54% of those receiving tapering off alone used benzodiazepine intermittently for periods shorter than 60 days. Similar to the short-term results, which have been discussed elsewhere[10], simultaneous group CBT had no additional value to tapering off alone for the effects during long-term follow-up. During the first 3-6-month follow-up, the combination with group CBT was even inferior to tapering off alone.

Contrary to Holton *et al* (1992) and Zitman & Couvée (2001)[6 7], we included patients with an intervention immediately before tapering-off Nevertheless, our abstinence rates were higher It is unlikely that this is due to a shorter follow-up period, because it is shown that most relapses (>90%) occurred within the first nine months [6] Two feasible explanations can be put forward Firstly, differences in the populations studied, as Holton *et al* (1992) included referred patients in a psychiatric setting, and Zitman & Couvee exclusively included a subgroup of depressed long-term benzodiazepine users in primary care [6 7] Several publications suggested that depressive patients have greater difficulty in stopping benzodiazepine use [17] Secondly, due to the prospective nature of our study, both GPs and patients were aware that they would be followed up, while the follow-up in the other studies was performed retrospectively This suggests that a closer monitoring of patients after tapering-off might prevent relapse

The *self-reported* abstinence rate over the last month of follow-up yielded success rates of 52% for tapering off with CBT, and 63% for tapering off alone These success rates replicate the findings of Rickels *et al* (1991) and Golombok *et al* (1987), who found self-reported cross-sectional success rates of 58% and 54% [4 5] Due to the intermittent usage of benzodiazepines during follow-up, cross-sectional success rates overestimate the longitudinal effects Moreover, the significance of self-reported cross-sectional success rates is questionable, since we, having included a control group (contrary to Rickels *et al* 1991 and Golombok *et al* 1987), did not find significant differences in success rate with the control group

Psychotropic drugs and agents

In line with Couvée *et al* (2002), patients were not prescribed more antidepressants or other psychotropic drugs by their GP [8] This contrasts with the results of Rickels *et al* (1991), who found an increase in the use of antidepressants by those taking part in their tapering-off programme [5] This might reflect a difference in the settings because their study was conducted in a psychiatric department where more diagnostic and alternative treatment strategies were available Neither the prevalence of caffeine, nicotine, or alcohol consumption, nor the amount of these agents taken by consumers, were influenced by intervention type or outcome, which indicates that none of our long-term users switched from benzodiazepine use to one of these agents

Psychological functioning

No increase in the presence or severity of withdrawal symptoms was found during follow-up The risk of a prolonged withdrawal syndrome is therefore not a critical issue [18] The severity of benzodiazepine dependence declined significantly in patients who achieved continued abstinence, but not in patients who shifted to better prescription patterns during follow-up This suggests that for low-dose

benzodiazepine dependence, prescription patterns or dosage levels have little influence on the severity of dependence

We did not find significant differences in symptoms for psychological distress and mood disturbances between the three groups or between patients who achieved continued abstinence and those who continued their use Thus, our patients did not deteriorate during follow-up after tapering-off their benzodiazepine use This finding contrasts with Rickels *et al* (1991)[5], who found improved functioning in abstinent patients This discrepancy can be explained by the increase in the use of antidepressants by abstinent patients in the study of Rickels *et al* (1991), and by the low benzodiazepine dosages used by patients in our study Patients who achieved continued abstinence used a mean dosage of 6 0 mg diazepam equivalent before the minimal intervention (period –1) and 3 3 mg at the start of the RCT (period 0), while successful patients in the study of Rickels *et al* (1991) used a mean dosage of 8 3 mg diazepam equivalent Nonetheless, it was somewhat disappointing to find that because tapering-off long-term benzodiazepine use does not significantly improve psychological functioning, our patients still suffered from mild mixed affective symptoms that might require medical treatment Moreover, adequate treatment after tapering-off might also prevent restart of benzodiazepine use

Critical remarks

Prescription data should be interpreted with caution Firstly, not all patients fill their prescription, secondly, there is no guarantee that the patient actually takes the filled prescription, thirdly, a doctor might write a prescription but fail to enter it in the medical records, and finally, there is a possibility that patients may obtain benzodiazepines from other sources However, we measured the self-reported benzodiazepine usage as well, while previous studies have been limited to either prescription data or self-reported use Consequently, reliable comparisons can be made with previous studies

Conclusion

Although a substantial number of patients restart benzodiazepine therapy during follow-up, tapering-off benzodiazepine use effectively reduces long-term benzodiazepine consumption compared with a non-intervention control group Moreover, the psychological functioning of patients did not deteriorate after tapering-off, which might indicate a history of non-effective treatment Despite the fact that the dosages used by our patients appear rather low, these patients were not able to stop their use by themselves after a minimal intervention, and thus really needed more support The identification of all long-term benzodiazepine users and the consecutive pre-selection used in this study show the difficulty of motivating patients (and doctors?) to taper-off benzodiazepine use Further research should therefore not only focus on optimising taper-off strategies, but also on prevention of long-term benzodiazepine use

References

1 Oude Voshaar RC, Couvée JE, Van Balkom AJLM, *et al* Strategies to discontinue long-term benzodiazepine use A systematic review *Submitted for publication*

2 Oude Voshaar RC, Gorgels WJMJ, Mol AJJ, *et al* Behandelmethoden om langdurig benzodiazepine gebruik te staken *Nederlands Tijdschrift voor Geneeskunde* 2001, 145(356) 1347-1350

3 Ashton H Benzodiazepine withdrawal outcome in 50 patients *British Journal of Addiction* 1987, 82(6) 665-671

4 Golombok S, Higgitt A, Fonagy P, Dodds S, Saper J, Lader M A follow up study of patients treated for benzodiazepine dependence *British Journal of Medical Psychology* 1987, 60 (Pt 2) 141 149

5 Rickels K, Case WG, Schweizer E, Garcia Espana F, Fridman R Long-term benzodiazepine users 3 years after participation in a discontinuation program *American Journal of Psychiatry* 1991, 148(6) 757-761

6 Holton A, Riley P, Tyrer P Factors predicting long term outcome after chronic benzodiazepine therapy *Journal of Affective Disorders* 1992, 24(4) 245-252

7 Zitman, F G & Couvee, J E Chronic benzodiazepine use in general practice patients with depression an evaluation of controlled treatment and taper-off Report on behalf of the Dutch Chronic Benzodiazepine Working Group *British Journal of Psychiatry* 2001, 178 317 324

8 Couvée JE, Timmermans EAY, Zitman FG The long-term outcome of a benzodiazepine discontinuation programme in depressed outpatients *Journal of Affective Disorders* 2002, 70(2) 133-141

9 Oude Voshaar RC, Gorgels WJMJ, Mol AJJ, *et al* Tapering off long-term benzodiazepine use with or without simultaneous group cognitive behavioural therapy a three-condition randomised controlled trial *British Journal of Psychiatry* 2003, 182 498-504

10 Cormack MA, Sweeney KG, Hughes-Jones H, *et al* Evaluation of an easy, cost effective strategy for cutting benzodiazepine use in general practice *British Journal of General Practice* 1994, 44(378) 5 8

11 WHO Collaborating Centre for Drugs Statistics Methodology Guidelines ATC classification and DDD assignment 1st edition 1996 Oslo, WHO/NCM

12 Cornel, M , Knibbe, R A , Van Zutphen, W M , *et al,* Problem drinking in a general practice population the construction of an interval scale for severity of problem drinking *Journal on the Studies of Alcohol* 1994, 55 466 470

13 Goldberg DP, Blackwell B Psychiatric illness in general practice A detailed study using a new method of case identification *British Medical Journal* 1970, 1 439-443

14 Wald FDM, Mellenbergh GJ De verkorte versie van de Nederlandse vertaling van de Profile of Mood States (POMS) *Nederlands Tijdschrift voor de Psychologie* 1990, 45 86-90

15 Tyrer, P , Murphy, S , Riley, P The Benzodiazepine Withdrawal Symptom Questionnaire *Journal of Affective Disorders* 1990, (19) 53 61

16 Oude Voshaar RC, Mol AJJ, Gorgels WJMJ, *et al* Cross-validation, time course and predictive validity of the Benzodiazepine Dependence Self Report Questionnaire in a benzodiazepine discontinuation trial *Comprehensive Psychiatry* 2003, 44(3) 247-255

17 Lader M Anxiety or depression during withdrawal of hypnotic treatments *Journal of Psychosomatic Research* 1994, (38) 113-123

18 Higgitt A, Fonagy P, Toone B, *et al* The prolonged benzodiazepine withdrawal syndrome anxiety of hysteria? *Acta Psychiatrica Scandinavica* 1990 , 82(2) 165 168

Chapter 9

Predictors of long-term taper success after a benzodiazepine withdrawal programme in general practice

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Abstract

Objective - To identify predictors of long-term taper success in chronic benzodiazepine users unable to stop after written advice who participated in a benzodiazepine discontinuation programme in general practice.

Methods - One hundred and eighty benzodiazepine users were prospectively followed-up for 18 months through their medical records after they had participated in a randomised controlled trial comparing two tapering-off strategies and a non-intervention control group. Cox-regression analyses was performed to correct for the time until relapse. Potential predictors included benzodiazepine (usage) characteristics, psychopathological symptoms, personality traits, and characteristics of (benzodiazepine) dependence.

Results - A complete follow-up was achieved for 170 (94%) patients, of whom 50 (29%) achieved long-term success, defined as no use of benzodiazepines during the whole follow-up period. Independent predictors of success were: offering a taper-off programme with group therapy (RR=2.4; 95% CI: 1.5-3.9) or without group therapy (RR=2.9; 95% CI: 1.8-4.8), a lower daily dosage at the start of tapering-off (RR=1.5; 95% CI: 1.2-1.9), a substantial dose reduction by themselves immediately before the start of tapering-off (RR=2.1; 95% CI: 1.4-3.3), a low score on 'lack of compliance' of the benzodiazepine dependence self-report questionnaire (RR=2.4; 95% CI: 1.1-5.2), and no use of alcohol (RR=1.7; 95% CI: 1.2-2.5). Patients who used over 10 mg of diazepam equivalent, who had a score of three or more on the scale Lack of compliance of the Bendep-SRQ, or drank more than 2 units of alcohol per day failed to achieve long-term abstinence.

Conclusion - Long-term tapering-off outcome appears to be influenced by non-specific addictive characteristics. A subgroup of chronic benzodiazepine users could be identified that was not *a priori* able to achieve long-term taper success in general practice.

Introduction

Although benzodiazepines are effective drugs for the short-term treatment of insomnia and anxiety, their long-term efficacy remains questionable [1-7] Adverse effects of long-term use are becoming increasingly clear, such as development of dependence[3], increased risk of falls (leading to injuries) and traffic accidents[4,5], and cognitive decline[6-9] The majority of chronic benzodiazepine users receive their prescriptions in general practice [10] Therefore, the general practitioner (GP) is the first physician to make decisions about rational use and reduction of unwarranted chronic use Chronic benzodiazepine use can effectively be discontinued by tapering-off strategies [11-17] Identifying predictors of long-term taper-off outcome would make the management of chronic use more efficient

Several factors have been related to successful benzodiazepine discontinuation in the short-term The most reliable predictor for successful taper outcome is a lower benzodiazepine dosage at the start of tapering-off [14,21,25] No differences have been reported between individual benzodiazepines during gradual discontinuation,[29] although after *abrupt* cessation a shorter elimination half-life resulted in a lower abstinence rate [21,26] There is no consistent pattern for the influence of demographic variables For example, successful taper outcome has been linked to both male[30] and female sex[13,14], and to both younger[12,14] and older age groups [22,27] In contrast, it has been repeatedly demonstrated that a high level of psychopathological symptoms, especially anxiety and depressive symptoms, resulted in lower abstinence rates, as well as the personality traits neuroticism, dependence, and vulnerability [14,15,21,22,24,25,27,29,31,32] In addition, these personality traits also led to the experience of a more severe benzodiazepine withdrawal syndrome following discontinuation [22,29] Whether benzodiazepine withdrawal symptoms during discontinuation independently affect taper outcome remains inconclusive [25,33] Moreover, neither the severity of benzodiazepine dependence, nor the diagnosis of benzodiazepine dependence, have been examined in relation to taper outcome [34]

The few follow-up studies of benzodiazepine discontinuation programmes carried out have used different selections of potential predictors [12,16] In addition, the predictors found did not show a consistent pattern due to small sample sizes and the lack of multivariate analyses The two follow-up studies that did carry out a multivariate analysis, however, reported that successful short-term taper predicted a benzodiazepine-free outcome at follow-up [14,35]

In this paper, we performed a multivariate prediction analysis of long-term taper outcome in 180 patients included in a benzodiazepine discontinuation trial in general practice As potential predictors, we evaluated benzodiazepine (usage) characteristics, personality traits, psychopathological symptoms, characteristics of benzodiazepine dependence, including the severity of dependence, and the use of psychoactive agents and drugs Our purpose was to identify independent predictors of taper outcome and, if possible, to identify which patients do or do not benefit from tapering-off with respect to benzodiazepine use during follow-up

Methods

Study design

The study is part of a two-step treatment study aimed at the reduction of chronic benzodiazepine use (> 3 months) in 30 general practices in the Netherlands. The clinical outcome of both interventions has been described elsewhere.[17,36]

A total of 180 chronic benzodiazepine users who were not able to stop their benzodiazepine use after the first step, i.e., a letter from their general practitioner (GP) containing advice to stop, gave informed consent for the second step, which consisted of a randomised controlled trial on the differential efficacy of tapering-off with group therapy (n=73), tapering-off alone (n=73), and a non-intervention control group (n=34). Patients assigned to one of the two active treatment groups in the second step visited their GP 6 times to taper their benzodiazepine dosage in steps of 25% per week, after being transferred to an equivalent dose of diazepam for two weeks. Patients assigned to the first group additionally received five weekly sessions of group psychotherapy starting halfway through the tapering-off. Patients in the control group were treated as usual and did not receive any help on the reduction of benzodiazepine use. The study received ethical approval from the University Medical Centre Nijmegen and was carried out between 1998 and 2001.

The mean (±sd) age of the 180 patients was 63 (±12), and 70% were female. Patients used benzodiazepines for a mean (±sd) duration of 13.5 (±9.6) years. The mean daily dosage significantly decreased from 8.4 mg diazepam equivalent (P_{25} = 4.1 mg; P_{50} = 6.3 mg; P_{75} = 9.9 mg) before the first (minimal) intervention (i.e., the letter containing advice to stop their use) to 5.9 mg (P_{25} = 1.7 mg; P_{50} = 3.8 mg; P_{75} = 6.6 mg) thereafter. At 18-month follow-up, the continued abstinence rate for tapering-off alone was significantly superior to the non-intervention control group (36% versus 15%, p=0.03). In contrast, outcome for tapering-off with brief psychotherapy was not significantly better than the control group (29% versus 15%, p=0.12).[17]

Measurements

Benzodiazepine use was monitored prospectively in the GP medical records for 18 months. Success was defined as receiving no prescriptions for a benzodiazepine from the GP during the whole 18-month follow-up period. Drug prescription data were extracted at patient level from the GP information system (= computerised medical records). Extracted were date of issue, Anatomical Therapeutic Chemical classification code (ATC-code)[37] and name of the drug, number of tablets and dose, and prescription rules. Gender, date of birth, and the administration number of individual patients were extracted to link prescription data with the additional assessments (see below). For patients who left the practice before the end of the follow-up, the date and reason for leaving the practice were recorded.

In addition, patients were assessed at baseline, at outcome three months after the start of the second intervention and at 18-month follow-up These assessments took place at the participants' homes by trained research assistants The following variables were measured exclusively hypnotic use of the benzodiazepine (yes/no), use and amount of caffeine, nicotine and alcohol (including the number of problem drinkers according to the 18-item list of Cornel)[38], psychological well-being (GHQ 12-item version)[39], mood (the scales depression, anger, fatigue, vigour and tension of the 32-item shortened profile of mood states, POMS)[40], the number and severity of benzodiazepine withdrawal symptoms (benzodiazepine withdrawal symptom questionnaire version 2, BWSQ-v2)[41], four dimensions of the severity of benzodiazepine dependence (problematic use, preoccupation, lack of compliance, and withdrawal, Bendep-SRQ)[34], and five personality traits (negativism, somatisation, shyness, psychopathology and extraversion, Dutch Shortened MMPI)[42] Although the Dutch shortened MMPI does not assess separately dependent or neurotic personality traits that have been related to taper outcome, psychometric studies showed no decrease in informational value compared to the original MMPI [43 44]

Statistical analysis

Predictors of continued abstinence were analysed by means of Cox-regression analysis using forward and backward elimination procedures[45] with time to the first prescription after the intervention period as the dependent variable, and the following independent variables more than 50% dose reduction after the minimal intervention (yes/no), benzodiazepine dosage at the start of tapering-off, half-life of benzodiazepine (dichotomised at 24 hours), use of a high potency benzodiazepine (yes/no, based on presence of a 4-aryl group), self-reported hypnotic or anxiolytic use, use of more than one benzodiazepine (yes/no), use of antidepressants (yes/no), use of pain medication (yes/no), and all clinical status variables measured at the baseline assessment Variables with risk ratios of $p<0.10$ after correction for the intervention received (i e , the crude risk ratios) were entered into the multivariate Cox-regression analyses to identify independent predictors of long-term successful taper outcome (i e , the adjusted risk ratios)

Results

The follow-up was completed for 170 of the 180 patients (94%) Patients lost to follow-up (moved home, n=9, unknown, n=1) were analysed until the moment of lost to follow-up (range 1 - 456 days) as censored observations

Table 1 presents all variables associated ($p<0.10$) with outcome during follow-up after correction for the intervention received We did not find significant differences in success rate

between individual benzodiazepines in patients who used exclusively one benzodiazepine (147/170, 86%). oxazepam, 21/53, temazepam 9/34, diazepam, 6/18, nitrazepam, 2/9, lorazepam, 1/6, lormetazepam, 2/5, benzodiazepines used by less than 5 patients put together, 3/22 Although the use of high potency benzodiazepines (n=27) was associated with a less successful outcome, this association was not detected for individual high potency benzodiazepines due to low patient numbers within these subcategories

Table 1

Predictors of long-term benzodiazepine abstinence (n=180)

Variables	Crude RR* [95% CI]	p-value	Adj. RR [95% CI]	p-value	% variance
Treatment group (vs no intervention)**					
Taper-off + group therapy	1 49 [0 94 2 36]	0 09	2 38 [1 46 - 3 85]	<0 001	18 9 %
Taper-off alone	1 92 [1 19 – 3 08]	0 007	2 92 [1 78 4 78]	<0 001	
Lower BZ dosage at the start of tapering-off *(per 10 mg diazepam eqv)*	1 68 [1 43 – 1 98]	<0 001	1 52 [1 22 - 1 89]	<0 001	13 7 %
Dose reduction by themselves *(0=less, 1=more than 50% dose reduction)*	2 25 [1 51 – 3 34]	<0 001	2 13 [1 40 - 3 25]	<0 001	12 5 %
Shorter duration of use *(per 10 years)*	1 24 [1 04 – 1 48]	0 02			
Potency of the benzodiazepine *(0 = high potency 1 = low potency)*	1 70 [1 06 – 2 73]	0 03			
Use of nicotine *(0=yes, 1=no)*	1 47 [1 03 – 2 10]	0 03			
Use of alcohol *(0=yes, 1=no)*	1 47 [1 02 – 2 10]	0 04	1 73 [1 19 2 52]	0 004	8 2 %
Withdrawal symptoms at baseline *(BWSQ-v2, range 0-42)*	1 04 [1 01 – 1 06]	0 007			
Preoccupation scale of Bendep-SRQ *(0=3 or higher 1=less than 3)*	1 85 [1 28 – 2 68]	0 001			
Lack of compliance of Bendep-SRQ *(0=3 or higher, 1=less than 3)*	4 52 [2 32 – 8 80]	<0 001	2 39 [1 10 - 5 19]	0 03	4 8 %
Negativism (Dutch shortened MMPI) *(range 0-44)*	1 03 [1 01 – 1 06]	0 01			
Tension (POMS) *(range 6-30)*	1 04 [1 00 – 1 07]	0 03			
			Model χ^2 = 74 1, df=6 p<0 001		58 %

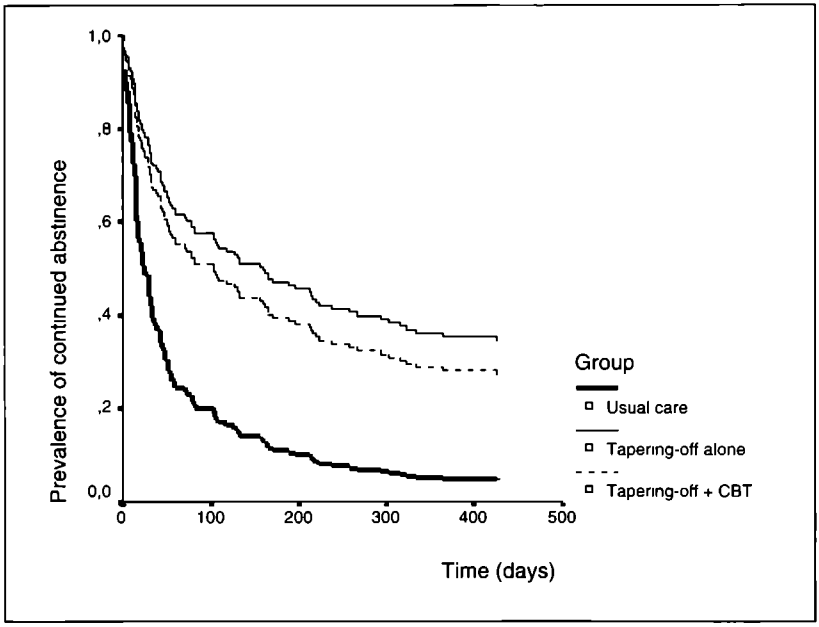
* Only corrected for treatment group

** Treatment group is a variable with three categories and therefore two risk ratios are calculated

Of the 12 variables, the multivariate Cox-regression analysis identified five independent predictors of continued abstinence using a stepwise forward procedure: (1) a low benzodiazepine dosage at the start of tapering-off, (2) active treatment instead of no intervention, (3) a dose reduction of more than 50% by themselves after the minimal intervention immediately before tapering-off, (4) no use of alcohol, and finally (5) a low score on the dimension 'lack of compliance with the therapeutic regime' of the Bendep-SRQ. These results were confirmed by a second multivariate Cox-regression analysis using a backward elimination (Wald) procedure. Figure 1 shows the survival curves of the three intervention groups corrected for the five independent predictors.

Figure 1

Survival time until first prescription after the intervention period



Visual inspection of the data of the independent predictors revealed some interesting findings. With respect to the benzodiazepine dose at the start of tapering-off, we found that of the 22 patients who used more than 10 mg diazepam equivalent a day (the recommended therapeutic dose), only two patients were able to achieve continued abstinence (9%). None of the nine patients who scored three or more on the dimension 'lack of compliance with the therapeutic regime' of the Bendep-SRQ achieved continued abstinence, and finally, none of the 14 patients who consumed over two units of alcohol per day were able to achieve an 18-month benzodiazepine-free state. With the aid of these three variables 38 patients in our sample could be identified, of which only 2 patients (5%) were able

to achieve long-term taper success. For the variables 'intervention' and 'dose reduction after the minimal intervention', we found no clear cut-off rates for achieving continued abstinence. No cut-off rates were identified that guaranteed successful long-term taper outcome for any of the independent predictors.

Negativism (personality trait) and tension (psychopathology) did not enter the multivariate analysis, which could be explained by their correlation with 'lack of compliance' (negativism: r=0.33, p<0.001; tension: r=0.28, p<0.001). Also the benzodiazepine dependence characteristic 'preoccupation with the availability of benzodiazepines' of the Bendep-SRQ did not enter the multivariate analysis. This variable was highly correlated with benzodiazepine dosage at the start of tapering-off, (r = 0.39, p< 0.001), dose reduction after the minimal intervention (r = 0.40, p< 0.001), and 'lack of compliance' (r = 0.33, p< 0.001) (see table 2).

Table 2

Correlation matrix of baseline values of the univariate predictors (n=180)

	Daily dosage	Dose reduction by themselves	Duration of use	High potency	Use of nicotine	Use of alcohol	Withdrawal symptoms	Preoccupation	Lack of Compliance	Negativism
Dose reduction by themselves *(%)*	-0 69 **									
Duration of use *(per 10 years)*	0.28 **	-0.16 *								
High potency *(yes/no)*	0 16 *	-0 05	0.16 *							
Use of nicotine *(yes/no)*	-0 09	0 03	0.07	0.18 *						
Use of alcohol *(yes/no)*	0 12	-0 09	0 08	0 14	0 13					
Withdrawal symptoms *(score BWSQ-v2)*	0 15 *	-0 13	0 11	0 05	-0 03	-0 04				
Preoccupation *(score Bendep-SRQ)*	0.39 **	-0 40 **	0 13	0.05	-0.15 *	-0 06	0 29 **			
Lack of Compliance *(score Bendep-SRQ)*	0.34 **	-0.22 *	0.24 **	0.08	-0.6	-0 03	0 20 *	0.33 **		
Negativism *(score NVM)*	0 14	-0 18 *	0 07	-0 03	-0 08	-0 14	0 41 **	0.32 **	0.33 **	
Tension *(score POMS)*	0 19 *	-0 13	0.10	-0 09	-0 10	-0 12	0.45 **	0.41 **	0.28 **	0.56 **

* Significant at p < 0.05

** Significant at p < 0.001

Discussion

In this study, five variables were independently related to long-term taper outcome of benzodiazepine discontinuation in general practice. These variables accounted for 58% of variance in outcome: 18.9% for active treatment (intervention type), 13.7% for dose reduction by patients themselves after the minimal intervention immediately before tapering-off, 12.5% for benzodiazepine dosage at the start of tapering-off, 8.2% for the use of alcohol, and finally 4.8% for lack of compliance. For the purpose of interpretation, Cohen[46] considers 1% variance as a small effect, 9% as a medium effect, and 25% as a large effect. These variables will be discussed systematically below.

Active treatment

Patients motivated to cut down their benzodiazepine use, but unable to do so by themselves by minimal intervention, were 2.4, respectively 2.9 times more likely to achieve long-term taper success when offered a taper-off programme compared with treatment as usual. Rickels *et al* (1991) and Couvée *et al* (2002) found successful cessation immediately after the taper-programme predictive for long-term taper success.[14 16] Their prediction models, however, could not analyse the impact of offering a taper-off programme to patients motivated for tapering-off as they did not randomise these patients between tapering-off and a non-intervention control group.

Benzodiazepine dosage

After treatment group, benzodiazepine dosage at the start of tapering-off was the next variable selected in the multivariate regression analysis. Benzodiazepine dose level at baseline is one of the most reported predictors of successful discontinuation in literature.[14 21-25] A dose reduction of more than 50% after the minimal intervention immediately before the tapering-off programme also independently contributed to a successful long-term outcome. Although dose reduction during the minimal intervention correlated positively with benzodiazepine dosage at the start of tapering-off, the results of the multivariate analysis showed no confounding between these two variables in relation to taper outcome.

Use of alcohol

We found that no use of alcohol independently predicted a successful long-term taper outcome in contrast to previous research.[1 22 25 26] Schweizer *et al* (1990) found, however, that mild-to-moderate alcohol use predicted a more severe benzodiazepine withdrawal syndrome upon discontinuation.[26] The effect of alcohol consumption on taper outcome might be explained by addictive behaviour in chronic benzodiazepine users, because in social drinkers the abuse liability of benzodiazepines has been related to the use of alcohol.[47,48] Moreover, high-dose benzodiazepine users are more often alcohol dependent, and use more caffeine and more nicotine compared to control subjects.[49] This association might have a

biological basis, as alcohol potentiates the effect of benzodiazepines on the $GABA_A$ receptor in the central nervous system

Benzodiazepine dependence

Although benzodiazepine dependence is frequently mentioned as an adverse effect of chronic benzodiazepine use, it has never been diagnosed according to ICD or DSM criteria in chronic benzodiazepine users taking part in a discontinuation programme In this study, we administered the Bendep-SRQ, a multidimensional self-report questionnaire that comprehensively establishes the severity of benzodiazepine dependence [34] A low score on the scale 'lack of compliance with the therapeutic regime' independently predicted good taper outcome Although the score for 'preoccupation with the availability of benzodiazepines' was univariately associated with taper outcome, it did not enter the multivariate analysis due to its high correlation with the amount of dosage reduction after the minimal intervention, making these two variables interchangeable in the multivariate model These findings suggest that diagnosing benzodiazepine dependence might be relevant in patients discontinuing chronic benzodiazepine use Most benzodiazepine discontinuation trials have only evaluated benzodiazepine withdrawal symptoms during the discontinuation process as proxy for benzodiazepine dependence [21 26 47] The association between the severity of these symptoms and taper outcome, however, remains inconsistent [51] The relationship between personality and taper outcome may partly explain this inconsistency [22 29] Schweizer *et al* (1998) found that patients who dropped out at an early stage of the benzodiazepine discontinuation process, when withdrawal symptoms were relatively mild, were the main cause of the association between personality traits and taper outcome [22] As we tried to identify predictors for taper success before the start of tapering-off, we did not assess benzodiazepine withdrawal symptoms during the discontinuation phase However, a further study exploring the role of withdrawal symptoms during tapering-off and pre-treatment dependence characteristics is in progress

Some negative findings

Although some personality traits, as well as the level of anxiety and depressive symptoms, have been reported to (independently) affect taper outcome[14 15 21 22 24 25 27 29 31 32], we only found significant univariate relationships for negativism and tension As the variables negativism and tension were both correlated to factors of benzodiazepine dependence (withdrawal, preoccupation, lack of compliance) it supported the claim that personality traits are important in influencing the dependence potential of the patient [15 29] The level of psychopathology also was of limited interest We did not find any relationship between depression or psychological distress and outcome, despite the many assertions that depressed chronic benzodiazepine users have more difficulty in benzodiazepine discontinuation [16 52] The univariate association of tension with taper outcome was relatively weak In addition, whether the benzodiazepine was used as a hypnotic or anxiolytic drug was irrelevant

Although in the population chronic benzodiazepine use is associated with female sex and a high age [53], these factors did not influence benzodiazepine discontinuation outcome, which was in line with previous research. In our study, shorter duration of benzodiazepine use was only univariately associated with better outcome. The follow-up studies of Rickels *et al* (1991) and Couvée *et al* (2002) found a relationship between a shorter benzodiazepine usage and successful taper outcome, whereas Holton *et al* (1992) found the opposite to be the case.[14 16]

We did not observe significant differences between individual benzodiazepines, which might have been because some benzodiazepines were only used by a few patients. In line with previous research of *gradual* benzodiazepine discontinuation, the elimination half-life of the drug did not influence taper outcome. The use of high potency benzodiazepines was univariately associated with a less successful outcome, although this finding did not reach statistical significance in the multivariate analyses. As only 27 patients in our population used a high potency benzodiazepine, we would suggest a more detailed study of this aspect in future research.

Final conclusions

We can conclude that active treatment increases the likelihood of long-term abstinence in a general practice population of chronic benzodiazepine users motivated to cut down their benzodiazepine consumption. In addition, the outcome of tapering-off depends on the dosage used by these patients and the ability of patients to lower their dosage first by themselves. Moreover, our data suggest that dependence characteristics are more important for taper outcome than the level of psychopathology, personality traits or benzodiazepine type, since all independent predictors can be considered as indicators of non-specific addictive behaviour.[45 54] A subgroup of patients could be identified that failed to achieve continued abstinence. It included patients using more than two units of alcohol per day, patients scoring three or more on the dimension 'lack of compliance with the therapeutic regime' of the Bendep-SRQ, and patients using more than 10 mg diazepam at the start of tapering-off *after* the minimal intervention. As more intensive treatment is probably necessary, these patients should be considered for referral to second-line treatment.

References

1 Ashton H. Guidelines for the rational use of benzodiazepines When and what to use. *Drugs* 1994, 48 25-40.

2. Committee on the Review of Medicines Systematic review of the benzodiazepines. *British Medical Journal* 1980, 1· 910-912.

3 Kan CC, Breteler MH, and Zitman FG. High prevalence of benzodiazepine dependence in out-patient users, based on the DSM-III-R and ICD-10 criteria *Acta Psychiatrica Scandinavica* 1997, 96 85-93

4. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis I. Psychotropic drugs. *Journal of the American Geriatric Society* 1999, 47. 30-9.

5. Hemmelgarn B, Suissa S, Huang A, *et al* Benzodiazepine use and the risk of motor vehicle crash in the elderly *Journal of the American Medical Association* 1997, 278. 27-31.

6 Rummans TA, Davis LJ, Jr., Morse RM, *et al* Learning and memory impairment in older, detoxified, benzodiazepine-dependent patients. *Mayo Clinics Proceedings.* 1993; 68: 731-7.

7 Tata PR, Rollings J, Collins M, *et al* Lack of cognitive recovery following withdrawal from long-term benzodiazepine use *Psychological Medicine* 1994, 24 203-13.

8. Paterniti S, Dufouil C, and Alpérovitch A Long-term benzodiazepine use and cognitive decline in the elderly The epidemiology of vascular aging study *Journal of Clinical Psychopharmacology* 2002, 22(3) 285-293

9. Rickels K, Lucki I, Schweizer E, Garcia-Espana F, Case WG. Psychomotor performance of long-term benzodiazepine users before, during, and after benzodiazepine discontinuation. *Journal of Clinical Psychopharmacology* 1999, 19 107-13.

10. College voor zorgverzekeringen Gebruik van benzodiazepinen 1993 - 1998 Edited by Piepenbrink JF *Geneesmiddelen Informatie Project (GIP-signaal)* 2000

11. Couvée, J.E., Oude Voshaar, R C , Van Balkom, A J L M , *et al* Strategies to discontinue long-term benzodiazepine use. A systematic review *Submitted for publication*

12. Ashton H. Benzodiazepine withdrawal outcome in 50 patients. *British Journal of Addiction* 1987, 82(6) 665-671

13. Golombok S, Higgitt A, Fonagy P, *et al.* A follow-up study of patients treated for benzodiazepine dependence *British Journal of Medical Psychology* 1987, 60 (Pt 2) 141-149

14 Rickels K, Case WG, Schweizer E, *et al.* Long-term benzodiazepine users 3 years after participation in a discontinuation program *American Journal of Psychiatry* 1991; 148(6)· 757-761

15 Holton A, Riley P, and Tyrer P. Factors predicting long-term outcome after chronic benzodiazepine therapy *Journal of Affective Disorders* 1992, 24(4) 245-252.

16. Zitman FG, and Couvee JE Chronic benzodiazepine use in general practice patients with depression: an evaluation of controlled treatment and taper-off Report on behalf of the Dutch Chronic Benzodiazepine Working Group *British Journal of Psychiatry* 2001, 178, 317-324.

17. Oude Voshaar RC, Gorgels WJMJ, Mol AJJ, *et al* Long-term outcome of a thre-condition, usual care controlled, benzodiazepine discontinuation trial *submitted for publication*

18. Vissers FHJA. Gebruik van slaap- en kalmeringsmiddelen in het dagelijks leven Determinanten, gevolgen en de rol van de huisarts [dissertation] Maastricht Universiteit Maastricht; 1998

19. Van der Waals FW, Mohrs J, Foets M Sex differences among recipients of benzodiazepines in Dutch general practice *British Medical Journal* 1993, 307(6900) 363-366

20 Oude Voshaar RC, Gorgels WJMJ, Mol AJJ, *et al.* Tapering off long-term benzodiazepine use with or without simultaneous group cognitive-behavioural therapy· three-condition randomised controlled trial, *British Journal of Psychiatry* 2003, 182 498-504.

21 Rickels K, Schweizer E, Case G, *et al.* Long-term therapeutic of benzodiazepines. I. Effects of abrupt discontinuation *Archives of General Psychiatry* 1990, (47) 899-907

22. Schweizer E, Rickels R, De Martinis N, *et al* The effect of personality on withdrawal severity and taper outcome in benzodiazepine dependent patients. *Psychological Medicine* 1998; (28). 713-720.

23 Udelman HD, Udelman DL Concurrent use of buspirone in anxious patients during withdrawal from alprazolam therapy. *Journal of Clinical Psychiatry* 1990; 51 Suppl· 46-50

24. Schweizer E, Case WG, Garcia-Espana F, *et al* Progesterone co-administration in patients discontinuing long-term benzodiazepine therapy effects on withdrawal severity and taper outcome *Psychopharmacology (Berl)* 1995, 117 424-429

25. Rickels K, DeMartinis N, Garcia-Espana F, *et al* Imipramine and buspirone in treatment of patients with generalized anxiety disorder who are discontinuing long-term benzodiazepine therapy *American Journal of Psychiatry* 2000, 157 1973-1979

26 Schweizer E, Rickels K, Case G, *et al* Long-term therapeutic of benzodiazepines I Effects of gradual taper *Archives of General Psychiatry* 1990, (47). 908-915

27. Cantopher T, Olivier S, Cleave N, Edwards JG Chronic benzodiazepine dependence. A comparative study of abrupt withdrawal under propranolol cover versus gradual withdrawal *British Journal of Psychiatry* 1990, 156 406-411

28 Tyrer P, Owen R, and Dawling S Gradual withdrawal of diazepam after long-term therapy *Lancet* 1983, I 1402- 1406

29 Murphy SM and Tyrer P A double-blind comparison of the effects of gradual withdrawal of lorazepam, diazepam and bromazepam in benzodiazepine dependence *British Journal of Psychiatry* 1991; 158 511-516.

30. Lader M, Farr I, and Morton S A comparison of alpidem and placebo in relieving benzodiazepine withdrawal symptoms. *International Clinical Psychopharmacology* 1993; 8 31-36

31 Rickels K, Case WG, Schweizer EE, *et al.* Low-dose dependence in chronic benzodiazepine users· a preliminary report on 119 patients. *Psychopharmacology Bulletin* 1986, 22 407-415

32. Ashton CH, Rawlins MD, and Tyrer SP. A double-blind placebo-controlled study of buspirone in diazepam withdrawal in chronic benzodiazepine users *British Journal of Psychiatry* 1990; 157: 232-238

33 Couvée JE, and Zitman FG The benzodiazepine withdrawal symptom questionnaire psychometric evaluation during a discontinuation programme in depressed chronic benzodiazepine users in general practice *Addiction* 2002, 91(3) 337-345.

34. OudeVoshaar RC, Mol AJJ, Gorgels *et al* Cross-validation, time course and predictive validity of the Benzodiazepine Dependence Self-Report Questionnaire in a benzodiazepine discontinuation trial *Comprehensive Psychiatry*, 2003, 44(3) 247-255

35 Couvée JE, Timmermans MA, Zitman FG The long-term outcome of a benzodiazepine discontinuation programme in depressed outpatients *Journal of Affective Disorders* 2002; 70(2). 133-141

36 Gorgels WJMJ, Oude Voshaar RC, Mol AJJ, *et al* Discontinuation of long-term benzodiazepine use in general practice by sending a letter to users *Submitted for publication*

37 WHO Collaborating Centre for Drugs Statistics Methodology Guidelines ATC classification and DDD assignment 1st edition 1996. Oslo, WHO/NCM.

38 Cornel M, Knibbe RA, Van Zutphen, W M., *et al*, Problem drinking in a general practice population the construction of an interval scale for severity of problem drinking *Journal on the Studies of Alcohol* 1994, 55 466-470.

39 Goldberg DP, Blackwell B Psychiatric illness in general practice. A detailed study using a new method of case identification *British Medical Journal* 1970; 1 439-443

40. Wald FDM, Mellenbergh GJ. De verkorte versie van de Nederlandse vertaling van de Profile of Mood States (POMS). *Nederlands Tijdschrift voor de Psychologie* 1990, 45 86-90.

41. Tyrer P, Murphy S, and Riley P The Benzodiazepine Withdrawal Symptom Questionnaire *Journal of Affective Disorders* 1990, (19) 53-61.

42. Luteijn F, Kok AR. NVM· Nederlands Verkorte MMPI (NVM· Dutch Shortened MMPI) Edited by Luteijn F, Kok AR *Swets & Zeitlinger* 1985

43. Luteijn F and Kingma L Een nieuwe verkorte MMPI *Nederlands Tijdschrift voor de Psychologie* 1979, 34 459-471

44. Swanenberg AJM. Testvergelijking MMPI and NVM. Den Haag, Publicatie Koninklijke Landmacht, 1982.

45 Kalbfleisch JD and Prentice RL The statistical analysis of failure time data. John Wiley & Sons Inc., New York, 1980

46 Cohen J. Statistical power analysis for the behavioral sciences, 2nd. ed Hillsdale, NJ Lawrence Erlbaum Associates; 1988.

47 Johanson CE, Uhlenhuth EH. Drug preference and mood in humans· diazepam. *Psychopharmacology* 1980, 71 269-273

48 De Wit, Pierri, Johanson, 1989

49 Lekka NP, Paschalis C, and Beratis S Nicotine, caffeine and alcohol use in high- and low-dose benzodiazepine users *Drug and Alcohol Dependence* 1997, (45). 207-212.

50. Tyrer P, Rutherford D and Huggett T Benzodiazepine withdrawal symptoms and propranolol *Lancet* 1981, 1. 520-522

51 Sanchez-Craig M, Cappell H, Busto U, *et al* Cognitive behavioural treatment for benzodiazepine dependence a comparison of gradual versus abrupt cessation of drug intake *British Journal of Addiction* 1987, 82 1317-1327

52 Lader M Anxiety or depression during withdrawal of hypnotic treatments *Journal of Psychosomatic Research* 1994, (38) 113-123

53 Isacson D Long-term benzodiazepine use factors of importance and the development of individual use patterns over time - A 13-year follow-up in a Swedish community *Social Science and Medicine* 1997, 44(12) 1871 1880

54 Perera KMH and Jenner FA Some characteristics distinguishing high and low dose users of benzodiazepines *British Journal of Addiction* 1987, (82) 1329 1334

Chapter 10

Economic evaluation of tapering off benzodiazepine usage in long-term users

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Abstract

Background - Benzodiazepine (BZ) discontinuation has never been evaluated in economic terms

Aim - To compare the relative costs and outcomes of tapering-off long-term BZ use combined with group cognitive-behavioural therapy (TO+CBT) and tapering-off alone (TOA) with usual care (UC)

Design of the study - A randomised controlled trial incorporating a cost-effectiveness analysis from a societal as well as a pharmaceutical perspective in general practice

Method - The cost of treatment, prescribed drugs, healthcare services, productivity loss, and patients' costs were measured using drug prescription data and cost-diaries The principal outcome was the proportion of patients able to discontinue BZ during the 18-month follow-up Secondary outcome measures were the quality of life (SF-36 and HUI3)

Results - One hundred and eighty patients were randomised over TO+CBT (n=73), TOA (n=73), and UC (n=34) Treatment costs were €172 99 for TO+CBT and €69 50 for TOA Both conditions significantly reduced BZ costs during follow-up compared to UC The incremental cost-effectiveness ratios (cost per percent abstinence) showed that, depending on the study perspective, TO+CBT cost €10 70 to €56 82 and TOA €0 77 to €41 24 for an incremental one percent successful benzodiazepine discontinuation compared to UC

Conclusions - TO+CBT and TOA both led to a significant reduction in BZ costs However, it remains uncertain which healthcare utilisation has a causal relationship with long-term BZ consumption or its treatment Although the incremental cost-effectiveness ratios were better for TOA than for TO+CBT, the differences were relatively small Extrapolation of our data showed that the investment in TOA was paid back after 20 months when corrected for treatment gain in the UC condition

Introduction

The prevalence of long-term users of benzodiazepines in the population has been estimated at 3% [1 3] This finding contrasts sharply with current guidelines, which advise prescription of these drugs for short-term periods only [4 8] In the Netherlands, the pharmaceutical cost of benzodiazepine usage is estimated at €100 million per year [9] In addition, the treatment of associated adverse effects generates costs related to benzodiazepine usage For example, the cost of hip fractures related to benzodiazepine usage has been estimated at €16 4 million per year [10] Therefore, conformity with the guidelines for primary care would not only imply better care for patients, but might also result in a more efficient mental healthcare

It has been reported that tapering-off long-term benzodiazepine use might lead to an increase in medical consumption and consequently a higher workload for physicians [11] Empirical studies, however, suggest the opposite effect Despite a temporary increase in psychiatric contacts in the year of withdrawal, Holton *et al* (1992) found a significant reduction in the mean number of both GP and psychiatric contacts in the five years after withdrawal [12] Furthermore, detoxification of high-dose benzodiazepine users significantly reduced GP contacts from 17 5 to 3 3 per year, and visits to mental health specialists from 7 6 to 2 1 per year [13] Finally, Bashir *et al* (1994) did not find an increase in GP contacts after a minimal intervention to reduce benzodiazepine use in primary care [14]

This paper presents an economic evaluation based on a randomised controlled design comparing two benzodiazepine tapering-off strategies with a usual care control group in primary care The main purpose of the study was to reduce unwarranted long-term benzodiazepine use, and consequently a reduction of associated side-effects (dependence, falls, traffic accidents, and cognitive impairment) Additionally, we measured the quality of life at baseline and follow-up No deterioration or even an increase in quality of life after benzodiazepine discontinuation was considered a prerequisite for tapering-off The cost-effectiveness analysis was performed from a societal perspective (including all costs possibly associated with benzodiazepine usage) as well as from a pharmaceutical perspective

Methods

Study design

A randomised controlled trial in primary care that compared tapering off long-term benzodiazepine use combined with group cognitive-behavioural therapy (TO+CBT) and tapering off alone (TOA) with a usual care control group (UC) was performed Patients were randomised in a ratio of 2 2 1 respectively to achieve maximum discriminative power between the two active treatment groups, and were followed up for 18 months after the start of the trial Patients assigned to TO+CBT or TOA were tapered-off in 6 visits to their general practitioner (GP) by dosage reduction in steps of 25% a week, after being transferred to an equivalent dose of diazepam Patients assigned to TO+CBT attended in

addition five weekly two-hour sessions of group CBT starting halfway through the taper programme The study received ethical approval from the University Medical Centre Nijmegen and was carried out between 1998 and 2001

Patients and recruitment

We identified all long-term benzodiazepine users (i e , use for over three months) by means of a computerised search for benzodiazepine prescriptions at 30 general practices in rural and urban areas of the Netherlands, in which 58 GPs delivered primary care to about 118,000 patients In order to include patients unable to stop, all long-term users were sent a letter by their GP advising discontinuation of benzodiazepine use [15] The exclusion criteria were current psychiatric treatment, current treatment for drug or alcohol dependence, medical history of psychosis, epilepsy, insufficient mastery of the Dutch language, or terminal illnesses Furthermore, people were excluded specifically at the GP's request because of severe co-morbidity or psychosocial reasons Three months after the letter was sent, patients were invited to visit the GP in order to evaluate the effect of the letter Patients still using benzodiazepines were asked to participate in the present study A total of 180 patients gave written informed consent

Benzodiazepine usage

The main outcome parameter measure was the percentage continued abstinence during the follow-up period, i e , 3 to 18 months after the start of the intervention according to the prescription data of the GP The mean daily benzodiazepine dosage prescribed after sending the letter advising discontinuation and before the start of the trial was considered the baseline benzodiazepine consumption

The clinical outcome of this study has been described elsewhere [16 17] Briefly, the 180 patients, of which 70% were female, had a mean (±sd) age of 63 (±12) Patients used benzodiazepines for a mean (±sd) duration of 13 5 (±9 6) years The mean daily dosage was 8 4 mg diazepam equivalent (P_{25} = 4 1 mg, P_{50} = 6 3 mg, P_{75} = 9 9 mg) before receiving the letter advising discontinuation , and 5 9 mg (P_{25} = 1 7 mg, P_{50} = 3 8 mg, P_{75} = 6 6 mg) at the start of the trial No differences were observed at baseline between the three conditions with respect to socio-demographical variables, benzodiazepine usage, or psychological functioning At the end of the 15-month follow-up period, TOA (n=69) resulted in a significantly higher abstinence rate compared to UC (n=33) (36% vs 15%, p=0 03), in contrast to TO+CBT (n=68) (29% vs 15%, p=0 12)

Quality of life

Patients were assessed on three occasions before treatment (baseline), after treatment completion (three months after the start of the trial), and at 18 months (outcome) Structured interviews were conducted at the patients' homes by research assistants The questionnaires included the Medical Outcome Study Short-Form 36 (SF-36) and the Health Utility Index-Mark-III (HUI-3) [18 19]

The SF-36 is a generic descriptive instrument measuring a spectrum of function, disability, and distress It consists of eight domains (physical functioning, social functioning, role limitation due to physical problems, role limitation due to emotional problems, mental health, vitality, pain, and general health perception) The Dutch version of the SF-36 was previously tested and validated [20] The HUI-3 is a multi-attribute health-state classification system frequently applied for the economic evaluation of healthcare programmes It is a self-administered questionnaire for determining 8 functional aspects (i e , attributes) of quality of life (vision, hearing, speech, emotion, pain, ambulation, dexterity, and cognition) These attributes are summarised into a utility score ranging from 0 (death) to 1 (perfect health)

Costs

Costs were elicited from a societal perspective in which all costs generated within the healthcare sector, patient and family costs, as well as costs generated in other sectors (productivity losses), were evaluated over the 15-month follow-up period Because underlying diseases and reasons for taking benzodiazepines may be heterogeneous and largely unknown, costs were measured broadly regardless of whether they could be related to the use of benzodiazepines Since the causal relationship between most costs and the status of benzodiazepine use remained unclear, the cost-effectiveness analysis was performed from a societal as well as a pharmaceutical perspective

The intervention costs (GP contacts and psychotherapy sessions) were obtained from the case record forms Pharmaceutical costs were calculated based on the drug prescription database (including ATC-code[21], number and dose of tablets and prescription rules) of the GP, which was monitored longitudinally Other costs were obtained by four 3-week cost-diaries completed at 3, 6, 12, and 18 months after the start of the trial, and were extrapolated for the 15-month follow up period assuming linearity Diaries comprised regular and non-regular healthcare utilization, over-the-counter (OTC) drugs, productivity loss at work as well as housekeeping activities, and costs related to the status of benzodiazepine use Healthcare utilisation comprised a number of visits to the GP, first aid medical ward, medical specialists and paramedical specialists (physiotherapists, psychologists, and social workers), non-regular medical care, and days of hospital admissions The first week of each diary was filled in retrospectively with help from a research assistant The next two weeks had to be filled in by the patients themselves The completed diaries had to be returned by post A research assistant phoned patients in the event diaries were incomplete or not returned on time

To determine cost prices, several assumptions were made Cost prices for visits to GPs, medical specialists, medical first aid ward, psychologists and social workers were derived from the guidelines for pharmaco-economic research in the Netherlands [22] Costs for alternative medicine, over-the-counter medication, and costs of patients related to the status of benzodiazepine use ('extra costs') were priced according to the costs reported by patients in the cost-diaries The prices for prescribed drugs were sourced from the Dutch Health Care Insurance Council, plus a standardised compensation per

prescription for pharmacists in the Netherlands [23] The costs of benzodiazepines were calculated according to the price for the generic agents in the Netherlands for individual benzodiazepines, i e , the lowest price for an individual benzodiazepine [23] Prescriptions for drugs other than benzodiazepines were priced exactly if issued more than 100 times during baseline and follow-up, while other prescriptions were priced at €40 per 90-day treatment period [23] All prices are in euros and indexed at 2001 prices [24]

Analysis

The primary outcome parameter was the percentage continued benzodiazepine abstinence during follow-up in the three groups according to the prescription data of the GP To analyse the difference in costs between the three groups, the total costs during follow-up were calculated and expressed as mean amount per patient per condition As the distribution of costs was skewed, non-parametric tests were performed

The differential quality of life across the three conditions at follow-up was tested for each subscale of the SF-36, and for the utility score of the HUI-3 separately, with a repeated measure ANOVA with time (baseline vs follow-up assessment) as a two-level within subject factor, and treatment condition (TO+CBT, TOA, UC) as a three-level between subject factor

Results

Study participation and compliance

Table 1

Study adherence during follow-up for the different measurements in absolute number of patients per condition

		Cost-diaries					Interview assessment		Prescription data
Intervention (no)		*Baseline*	*3 month*	*6 month*	*12-month*	*18 month*	*Baseline*	*18-month*	*0 18 months*
TO+CBT	**(n=73)**	69	58	52	49	52	73	58	68
TOA	**(n=73)**	69	60	52	52	54	73	59	69
UC	**(n=34)**	33	24	26	24	24	34	26	33

180 patients were included and randomised over TO+CBT (n=73), TOA (n=73) and UC (n=34) The sample size differs for the different outcome measures (table 1) Prescription data were available for 170 of the 180 patients (94%) for the whole follow-up period The baseline assessment was available for all 180 patients, while 143 (79%) patients completed the 18-month follow-up assessment The number of dropouts for the 18-month assessment did not differ significantly across the three groups (χ^2 = 1 85, df=2, p=0 40) and was not related to benzodiazepine use during follow-up

(p=0.52). Finally, the cost-diaries were completed by 171 patients at baseline and during follow-up by 142 patients at 3 months, 130 patients at 6 months, 125 patients at 12 months, and 143 patients at 18 months.

Table 2

Utility score (HUI-3) at baseline and at 18-month follow-up per condition (n=180)

	Health Utility Index – 3		
Intervention:		*Baseline* *	*18-month* **
TO + CBT	Mean ±sd (n)	61 ± 25 (63)	66 ± 22 (42)
TOA	Mean ±sd (n)	64 ± 28 (63)	58 ± 30 (49)
UC	Mean ±sd (n)	61 ± 27 (32)	69 ± 26 (17)

* No utility score could be derived for 22 (12%) of the 180 patients assessed at baseline based on the algorithm for the HUI-3

** No utility score could be derived for 22 (15%) of the 143 patients assessed at outcome based on the algorithm for the HUI-3

Quality of life

No differences were observed between the three groups at baseline with respect to quality of life (tables 2 & 3). The scores on the SF-36 were low compared to the norm scores for the general Dutch population.[20] The repeated measures ANOVA comparing baseline and outcome scores over the three groups did not result in significant condition x time (=baseline vs. outcome) interactions for any of the measures. A comparison between abstinent and non-abstinent patients did not show significant differences at follow-up.

Table 3

Quality of life (SF-36) at baseline and at 18-month follow-up per condition (n=180) mean ±s.d.

	Short-Form 36							
Intervention	physical functioning	social functioning	role limitation (physical)	role limitation (emotional)	mental health	vitality	pain	general health perception
Norm scores[20]	82	87	79	84	77	67	80	73
TO+CBT:								
Baseline (n=73)	67 ±26	61 ±21	51 ±40	63 ±39	64 ±18	55 ±23	62 ±27	58 ±23
End of follow-up (n=58)	68 ±26	68 ±22	57 ±44	67 ±41	71 ±17	63 ±20	67 ±26	62 ±19
TOA:								
Baseline (n=73)	66 ±25	64 ±24	54 ±42	69 ±39	66 ±20	57 ±23	60 ±24	52 ±20
End of follow-up (n=59)	65 ±26	64 ±26	54 ±42	76 ±39	76 ±39	61 ±20	61 ±27	57 ±20
UC:								
Baseline (n=34)	68 ±25	66 ±19	69 ±35	70 ±42	64 ±23	56 ±24	66 ±26	58 ±22
End of follow-up (n=26)	72 ±26	69 ±19	76 ±36	81 ±29	81 ±29	63 ±24	69 ±22	55 ±22

Cost of the interventions

The actual number of tapering-off visits to the GP contrasted with the standardised 6 consultations as patients assigned to TO+CBT and TOA visited their GP 4.2 (sd 2.7) and 3.9 (sd 2.6) times respectively. Patients assigned to TO+CBT attended on average 2.3 (sd 2.2) therapy sessions.[16] This resulted in an actual cost for the interventions of €172.99 for TO+CBT, €69.50 for TOA, and nihil for UC.

Cost of prescribed drugs

The pharmaceutical costs for benzodiazepines at baseline were identical over the three conditions (χ^2=0.5; df=2; p=0.80). The costs for benzodiazepines differed significantly during follow-up (TO+CBT, €68.73; TOA, €51.93; and UC, €94.04; χ^2=9.8; df=2; p=0.01). Post hoc analyses showed that the cost of benzodiazepine usage in the UC group was significantly higher compared with the TO+CBT (p=0.05) and the TOA groups (p=0.002). TO+CBT and TOA did not differ significantly (p=0.17) from each other. The cost of prescribed drugs other than benzodiazepines did not differ over the three groups at baseline (χ^2=2.8; df=2; p=0.24) nor during follow-up (χ^2=3.4; df=2; p=0.18).

Table 4

Generated costs based on the 3-week cost-diaries per group during follow-up in euros indexed at 2001

	Time				
	Baseline	*3 months*	*6 months*	*12 months*	*18 months*
TO+CBT (n=73):					
General practitioner	6 20	13 09 **	8 39	7 36	8 91
Medical specialist / first aid medical ward	10 81	10 75	14 63	14 31	6 02
Psychologist / social worker	1 90	3 56	1 71	18 04	3 43
Physiotherapist	17 98 *	23.34	23 94	24 86 **	14 91
Non-regular medicine	1 69	1 85	1 22	0	0 84
Over-The-Counter drugs	2 06	3 46	4 37	3.47	6 09
Productivity loss	16 81	16 63	35 20	23 27	35 20
Costs related to status of BZ use	1.71	1 78	1 73	2 22	0 90
TOA (n=73):					
General practitioner	8.26	8 26	9 52 **	13 90	6 18
Medical specialist / first aid medical ward	10 18	15 13	20 19 **	21 50	23 19 **
Psychologist / social worker	3 16	4 52	16 59	6 24	1.68
Physiotherapist	8 71	10 36	12 79	11 47	7.90
Non-regular medicine	0 64	0	0	0 30	0 69
Over-The-Counter drugs	3 11	0 92 **	1 46	1 16	1.59
Productivity loss	12 81	37 74 **	26 24	13 67	22 31
Costs related to status of BZ use	1 44	2 54	3 40 **	3 57 **	1 29
UC (n=34):					
General practitioner	10 80	17 05	7 54	8 91	11 14
Medical specialist / first aid medical ward	22 61	40.07	27 00	7 98	20 12
Psychologist / social worker	0	0	3 36	1 99	0
Physiotherapist	3 52	10 11	0	7 05	10 50
Non-regular medicine	3 62	1 03	0	0	0 99
Over-The-Counter drugs	2 25	2 27	2 15	2 54	1 90
Productivity loss	30 55	34 83	22 31	10 04	16 69
Costs related to status of BZ use	4 28	3 25	1 62	0 75 **	1 27

* p<0 05 compared to physiotherapist visit at baseline for patients assigned to TOA and UC

** Significant difference (p<0 05) compared to baseline (Wilcoxon test) in the treatment condition

Cost-diaries

Other costs were based on the cost-diaries (see table 4). The three groups differed at baseline as patients assigned to TO+CBT visited physiotherapists significantly more (χ^2=7.0; df=2; p=0.03) compared to patients assigned to TOA or UC.

During follow-up, the costs varied widely both within and between the groups at the different follow-up assessments. The three groups differed at 3 months with respect to the costs of OTC drugs (p=0.04), and at 6 months with respect to the number of GP (p=0.02) and physiotherapist contacts (p=0.01), and the additional costs ('extra costs') of patients related to the status of benzodiazepine use (p=0.04). During follow-up, none of the patients were admitted to hospital due to falls or traffic accidents.

Each follow-up assessment was pairwise tested (Wilcoxon test) with the baseline assessment to evaluate trends within each condition for the parameters examined. Ten of the 96 tests yielded significant p-values (p<0.05). Compared to baseline, patients in the TO+CBT group had significantly more visits to the GP at 6 months, and to the physiotherapist at 12 months, while patients in the TOA group had significantly more visits to the GP at 6 months, to the medical specialist at 6 and 18 months, spent less money on OTC drugs at 3 months, had more productivity loss at 3 months, and had increased 'extra costs' at 6 and 12 months. Patients in the UC group had significantly decreased 'extra costs' at 12 months compared to baseline.

Table 5

Mean cumulative costs in euros at baseline and follow-up per condition

Costs		Baseline*	Follow-up**	Δ
Intervention (treatment):				
TO+CBT	(n=73)	0	172 99	172 99
TOA	(n=73)	0	69 5	69 5
UC	(n=34)	0	0	0
Cost-diaries:				
TO+CBT	(n=73)	961.20	1817 25	856 05
TOA	(n=73)	785 25	1664 37	879 12
UC	(n=34)	1261 66	1486 62	224 96
Drug use other than BZ:				
TO+CBT	(n=73)	932 33	1096 36	164 03
TOA	(n=73)	1258 30	1626 12	367 82
UC	(n=34)	1115 25	1280 59	165 34
Benzodiazepine use:				
TO+CBT	(n=73)	135 85	68 73	-67 12
TOA	(n=73)	148 33	51 92	-96 41
UC	(n=34)	136 14	94 04	-42 10

* Baseline diary linearly extrapolated for a period of 15 months

** Linear extrapolation of the four 3-week diaries during follow-up over the 15-month follow-up period

Cost-effectiveness analyses

To assess the cost-effectiveness from a societal perspective, the costs assessed in the cost-diaries were extrapolated linearly over the follow-up period. The cost of prescribed drugs other than benzodiazepines, and the costs of the separate categories in the diaries, were 5 to 15 times higher than the costs for treatment or benzodiazepine use. Table 5 shows the mean cumulative costs at baseline (extrapolated to a 15-month period) and during the 15-month follow-up period. Table 6 presents the (incremental) cost-effectiveness ratios from different perspectives compared with the UC group based on the mean change between baseline and follow-up. UC resulted in the lowest cost per unit success (proportion of patients able to discontinue) independent of the study perspective, while the differences in costs per unit success were small between the two taper strategies. The incremental cost-effectiveness ratios show that for every percent abstinence above that achieved by usual care, TOA is cheaper than TO+CBT.

Table 6

Costs (C), effectiveness (E), cost-effectiveness ratio (C/E), incremental cost (ΔC), incremental effectiveness (ΔE), and incremental cost-effectiveness ratio (ΔC/ΔE) per patient based on the mean change score reported in table 5 for TO+CBT and TOA compared to UC during 18-month follow-up

Perspective:		**C** (euro)	**E** (%)	**CE** (euro / %)	**ΔC**	**ΔE**	**ΔC/E**
Societal:							
TO+CBT	(n=73)	1073 23	29%	37 01	795 5	14%	56 82
TOA	(n=73)	1143 87	36%	31 77	866 14	21%	41 24
UC	(n=34)	277 73	15%	18 52			
Pharmaceutical (comprehensive):							
TO+CBT	(n=73)	269 90	29%	9 31	146 66	14%	10 48
TOA	(n=73)	340 91	36%	9 47	217 67	21%	10 37
UC	(n=34)	123 24	15%	8 22			
Pharmaceutical (limited):							
TO+CBT	(n=73)	106 63	29%	3 68	149 74	14%	10 70
TOA	(n=73)	-27 09	36%	-0 75	16 11	21%	0 77
UC	(n=34)	-43 11	15%	-2 87			

The data for the pharmaceutical perspective showed that when corrected for UC, TO+CBT saves €25.02 during follow-up and TOA €54.31 due to the reduction in benzodiazepine usage. However, these savings were less than the cost of the treatment (investment). The savings in the last 6 months of follow-up were €8.40 for TO+CBT, and €17.20 for TOA when corrected for treatment gain by UC. Carrying the results of the last 6 months of follow-up linearly forward showed that the treatment costs break even after 20 months follow-up for TOA and after 141 months for TO+CBT.

Discussion

Up until now, benzodiazepine taper-off studies have not included an economic evaluation This study estimated the hypothesised 'added value' of both tapering-off with group CBT (TO+CBT) and tapering-off alone (TOA) compared to usual care (UC) during an 18-month follow-up in relation to the associated costs As most benzodiazepine users receive prescriptions from their GP, the study was carried out in primary care Since GPs treated their patients themselves, our results are representative for daily practice, and do not have to be corrected when implemented

The costs of benzodiazepine usage during follow-up were significantly lower among patients assigned to TO+CBT or TOA compared with patients receiving UC The incremental cost-effectiveness ratios showed that TOA was associated with the lowest incremental costs per percent patients able to discontinue over the success rate of UC, independent of the applied study perspective An increase of one percent successful discontinuation cost €41 24 from a societal perspective, €10 37 from a comprehensive pharmaceutical perspective, and €0 77 from a limited pharmaceutical perspective when treating patients by tapering-off alone instead of usual care The question is whether policy makers at different levels are prepared to pay an extra €0 77 to €41 24 for a one percent successful discontinuation of benzodiazepine usage The addition of group CBT does not increase the success rate and the treatment costs are higher When corrected for usual care, TO+CBT resulted in comparable or inferior incremental cost-effectiveness ratios than TOA (depending on the study perspective)

Compared to the general population, our population had a low quality of life, which corresponded with surveys of long-term benzodiazepine users in the population [25 27] However, the quality of life did not change significantly as a result of our interventions, nor as a result of treatment outcome Consequently the prerequisite for conducting a cost-effectiveness analysis was met, since patients did not deteriorate after benzodiazepine discontinuation

A limitation typical of many economic analyses in mental healthcare[28], is the lack of pilot study service data for this patient group, together with the skewed distribution of observed economic data in this trial Our decision to measure healthcare utilisation with four 3-week cost-diaries during an 18-month follow-up was based on numerous assumptions Nonetheless, despite these shortcomings, our study is one of the largest benzodiazepine discontinuation trials published[29 32] and included far more patients than previous evaluations of taper programmes with additional psychotherapy, which had a maximum of 20 patients per group [33 37] However, our sample size was still relatively small considering the high prevalence of benzodiazepine use, and was also too small to evaluate the incidence of hospital admissions resulting from falls and traffic accidents since no such incidents were observed in our study

In contrast to the cost-diary data, the drug prescription data were longitudinally monitored and were available for 94% of the patients However, the causal relationship between prescribed drugs

other than benzodiazepines and benzodiazepine use and discontinuation remained unclear A previous report of this study showed that the use of psychotropic drugs did not significantly change as a result of benzodiazepine discontinuation[17], which has also been reported by others [18] For these reasons, additional cost-effectiveness analyses were performed from two pharmaceutical perspectives a comprehensive one including all prescribed drugs, and a limited one exclusively looking at the cost of treatment and benzodiazepine usage

Application of the limited pharmaceutical perspective, and extrapolation of the results for the last 6 months of follow-up, showed that treatments costs were paid back after 141 months for TO+CBT, and 20 months for TOA when corrected for treatment gain by UC Since most relapses occurred within the first 6 to 9 months of follow-up, extrapolating our follow-up over 20 months seemed reasonable, while extrapolation over 141 months might be questionable [17 38]

We recommend motivating patients to taper-off long-term benzodiazepine use in general practice, as these programmes result in significantly higher abstinence rates compared with usual care, and no loss in quality of life The additional cost of tapering-off alone per percent success is low and varies between €0 77 and €41 24 depending on the economic perspective applied We preferred application of the limited pharmaceutical perspective, resulting in an incremental cost-effectiveness ratio of 0 77 €/%, because we did not find a clear association between the measured healthcare utilisation characteristics and benzodiazepine usage, while these costs exceeded those for treatment and benzodiazepine usage Furthermore, tapering off benzodiazepine use might lead to a reduction in the cost for mental healthcare since treatment costs would be paid back after 20 months of follow-up The addition of group CBT to tapering-off had no clinical or economical advantages

References

1 Taylor S, McCracken CFM, Wilson, KCM Extent and appropriateness of benzodiazepine use *British Journal of Psychiatry* 1998,173 433 438

2 Tu K, Mamdani MM, Hux JE, *et al* Progressive trends in the prevalence of benzodiazepine prescribing in older people in Ontario, Canada *Journal of the American Geriatric Society* 2001,49 1341-1345

3 Zandstra SM, Führer JW, Van de Lisdonk EH, *et al* Different study criteria affect the prevalence of benzodiazepine use *Social Psychiatry andPsychiatric Epidemiology* 2002, 37(3) 139 144

4 Food and Drug Administration Prescribing of minor tranquillizers *FDA Drug Bulletin* 1980,10 2-3

5 Committee on the Review of Medicines Systematic review of the benzodiazepines *British Medical Journal* 1980, **1:** 910-912

6 Knuistingh-Neven A, Graaff WJ de, Lucassen PLBJ, *et al* NHG-standaard Slapeloosheid en

7 slaapmiddelen *Huisarts en Wetenschap* 1992,35 212-219

8 Neomagus GJH, Terluin B, Aulbers LPJ, *et al* NHG-standaard Angststoornissen *Huisarts en Wetenschap* 1997,40 167-175

9 Van Balkom AJLM, Van Dyck R, Van Megen HJGM, *et al* Richtlijn farmacotherapie angststoornissen Nederlandse Vereniging voor Psychiatrie1998

10 College voor zorgverzekeringen Gebruik van benzodiazepinen 1993 - 1998 [Use of benzodiazepines 1993 1998] Edited by Piepenbrink JF *Geneesmiddelen Informatie Project (GIP-signaal)* 2000

11 Herings RMC Geneesmiddelen als determinant van ongevallen [Drugs as determinants of accidents] Utrecht Faculteit Pharmacie, 1994

12 Cormack MA, Howells E Factors linked to the prescribing of benzodiazepines by general practice principals and trainees *Family Practice* 1992, 9(4) 466-471

13 Holton A, Riley P, Tyrer P Factors predicting long-term outcome after chronic benzodiazepine therapy *Journal of Affective Disorders* 1992, 24(4) 245-252

14 Burke KCh, Meek WJ, Krych R, *et al* Medical services use by patients before and after detoxification from benzodiazepine dependence *Psychiatric Services* 1995, 46(2) 157 160

15 Bashir, K , King, M , and Ashworth, M Controlled Evaluation of Brief Intervention by General Practitioners to Reduce Chronic Use of Benzodiazepines *British Journal of General Practice* 1994,44(386) 408 12

16 Oude Voshaar RC, Gorgels WMJM, Mol AJJ, *et al* Reduction of benzodiazepine use by letter in primary care first results of the Benzoredux study stage I *The Jouranl of the European College of Neuropsychopharmacology* 1999, 9 (suppl 5) S341

17 Oude Voshaar RC, Gorgels WJMJ, Mol AJJ, *et al* Long term outcome of a three condition, usual care controlled, benzodiazepine discontinuation trial *Submitted for publication*

18 Ware JE, Sherbourne CD The MOS 36-item Short-Form Health Survey (SF 36), I conceptual framework and item selection *Medical Care* 1992, 30 473-483

19 Furlong WJ, Feeny DH, Torrance GW, *et al* Multiplicative multi-attribute utility function for the health utility index mark 3 (HUI3) system a technical report Working paper 98-11 Torronto McMaster University Centre for Health Economics and Policy Analysis 1998

20 Van der Zee KI, Snaderman R Het meten van de algemene gezondheidstoestand met de RAND 36 Een Handleiding [Measuring general health status with the RAND 36 Users Manual] Groningen Nothern Center of Health Care Research, 1993

21 WHO Collaborating Centre for Drugs Statistics Methodology Guidelines ATC classification and DDD assignment 1st edition 1996 Oslo, WHO/NCM

22 Oostenbrink JB, Koopmanschap MA, Rutten FFH Handleiding voor kostenonderzoek, methoden en richtlijnprijzen voor economische evaluaties in de gezondheidszorg Amstelveen College voor zorgverzekeringen, 2000

23 Commissie Farmaceutische Hulp van het College voor zorgverzekekeringen (CVZ) *Farmacotherapeutische kompas* Amstelveen CVZ, 2002 p 53-66, p 69-81

24 CBS statistieken, bron statline [www cbs nl] 2002

25 Oude Voshaar RC, Gorgels WJMJ, Mol AJJ, *et al* Tapering-off long-term benzodiazepine use with or without simultaneous group cognitive behavioural therapy a three-condition randomised controlled trial *British Journal of Psychiatry* 2003, 182 498-504

26 Rodrigo EK, King MB, Williams P Health of long term benzodiazepine users *British Medical Journal* 1988, 296 603606

27 Simpson RJ, Power KG, Wallace LA Controlled comparison of the characteristics of long-term benzodiazepine users in general practice *British Journal of General Practice* 1990, 40 22 26

28 Van hulten R, Teeuw KB, Bakker A, *et al* Health related quality of life in current benzodiazepine users and general population controls In Blue Boy Why not? Studies on benzodiazepine use in a Dutch community [Dissertation, p73-88], 1998

29 Gray A, Marshall M, Lockwood A, *et al* Poblems in conducting economic evaluations alonside clinical trials *British Journal of Psychiatry* 1997, 170 47-52

30 Zitman, F G & Couvee, J E (2001) Chronic benzodiazepine use in general practice patients with depression an evaluation of controlled treatment and taper-off Report on behalf of the Dutch Chronic Benzodiazepine Working Group *British Journal of Psychiatry*, 178, 317-324

31 Schweizer E, Rickels K, Case WG, *et al* Long term therapeutic use of benzodiazepines II Effects of gradual taper *Archives of General Psychiatry* 1990, 47 908-915

32 Schweizer E, Rickels K, De Martinis N, *et al* The effect of personality on withdrawal severity and taper outcome in benzodiazepine dependent patients *Psychological Medicine* 1998, 28 713 720

33 Rickels K, DeMartinis N, Garcia Espana F, *et al* Imipramine and buspirone in treatment of patients with generalized anxiety disorder who are discontinuing long term benzodiazepine therapy *American Journal of Psychiatry* 2000, 157 1973-1979

34 Higgitt A, Golombok S, Fonagy P, *et al* Group treatment of benzodiazepine dependence *British Journal of Addiction* 1987, 82 517 532

35 Sanchez-Craig M, Cappell H, Busto U, *et al* Cognitive behavioural treatment for benzodiazepine dependence a comparison of gradual versus abrupt cessation of drug intake *British Journal of Addiction* 1987, 82 1317 1327

36 Otto MW, Pollack MH, Sachs GS, *et al* Discontinuation of benzodiazepine treatment efficacy of cognitive-behavioral therapy for patients with panic disorder *American Journal of Psychiatry* 1993, 150 1485 1490

37 Elsesser K, Sartory G, Maurer J The efficacy of complaints management training in facilitating benzodiazepine withdrawal *Behavioural Research and Therapies* 1996, 34 149-156

38 Charney DA, Paraherakis AM, Gill KJ The treatment of sedative hypnotic dependence evaluating clinical predictors of outcome *Journal of Clinical Psychiatry* 2000, 61 190-195

39 Couvée JE, Timmermans EAY, Zitman FG The long term outcome of a benzodiazepine discontinuation programme in depressed outpatients *Journal of Affective Disorders* 2002,70(2) 133-141

Chapter 11

Summary and general discussion

Introduction

The focus of this thesis is an evaluation of the outcome of different strategies to discontinue long-term benzodiazepine use in general practice The study started with a systematic review and meta-analysis of the literature in order to summarise the available knowledge on benzodiazepine discontinuation strategies systematically (Part I) Thereafter, three strategies were evaluated using data obtained from a larger research project the Benzoredux project (Parts II, III, and IV)

In this chapter, the findings will be summarised for all of the four Parts of the thesis Subsequently, some methodological issues of the Benzoredux project will be discussed in order to establish the strengths and limitations of the results Finally, the key conclusions will be summarised, as will the implications for clinical practice and a suggested approach for future research

Summary

Part I: Literature review

In chapter 3 a systematic review and meta-analysis is carried out of the literature on discontinuation strategies of long-term benzodiazepine use Sixty original papers were identified by a systematic literature search, which yielded four types of discontinuation strategies a minimal intervention, a systematic discontinuation programme without additional treatment, a systematic discontinuation programme in combination with psychotherapy, and a systematic discontinuation programme in combination with pharmacotherapy Success rates were calculated at a patient level for each intervention type per coded variable The effects of the coded variables were analysed by means of Pearson's chi-square tests and controlled for possible two-way interaction effects using additional Pearson chi-square tests over the confounding variables Review papers, double publications, animal research, clinical trials evaluating the efficacy of benzodiazepine treatment for a fixed period, and case reports less than five cases were excluded

Minimal interventions were defined as simple interventions applied for large groups of patients advising them to stop benzodiazepine use by themselves The effect of these interventions was examined in five studies, three using a randomised controlled design by including a non-intervention control group receiving usual care The mean success rate of 22% at 6 to 9 months follow-up was significantly superior to the 9% success rate in the control group All minimal interventions were carried out in general practice

Systematic discontinuation strategies were defined as treatment programmes guided by a physician Two-thirds of patients managed to discontinue long-term benzodiazepine use directly after systematic discontinuation The success rate could be increased by tapering off after transfer to a long-acting benzodiazepine if patients were treated as outpatients or if they used more than 15 mg diazepam equivalent per day The theoretical advantage of transfer to a long-acting agent before tapering-off is

the occurrence of less severe withdrawal symptoms caused by a more gradual blood level decrease. Inpatient treatment resulted in a higher success rate than outpatient treatment The success rate for the inpatient group was independent of dose level, while in the outpatient group a high dose level (more than 30 mg diazepam equivalent) was associated with lower success rates Although symptom-guided taper methods indicated to result in the highest success rate and fixed taper-off schemes seemed superior to abrupt discontinuation, firm conclusions could not be made due to lack of head-to-head comparisons of these methods In addition, the impact of the underlying disease could not be evaluated properly, although multiple drugs users and insomniacs seemed to have inferior success rates We failed to detect any influences on the success rate of publication year, duration of benzodiazepine use, and setting

The addition of psychotherapy to facilitate discontinuation did not result in higher success rates However, low patient numbers (i e , less than 20 patients per group), as well as the lack of randomised controlled comparisons, made any firm conclusion difficult Two well-designed randomised controlled trials, however, suggested different efficacy in different diagnostic patient groups The addition of CBT proved to be efficacious in patients diagnosed with panic disorder, but not in substance abusers The addition of the psychoactive drugs carbamazepine and imipramine resulted in significantly higher success rates than systematic discontinuation alone

The lack of long-term data (longer than one year) was a major limitation in the evaluation of minimal intervention strategies Only five studies reported long-term follow-up results of systematic discontinuation programmes Aggregation of these data was difficult because the success rates varied widely (from 16 - 82%) due to the different outcome criteria for benzodiazepine use Finally, a two-step approach used in the Benzoredux project had never been applied before

Part II: Minimal intervention

The Benzoredux project was carried out in 30 general practices in the Netherlands, where 58 general practitioners (GPs) delivered primary healthcare to 118082 patients A computerised search identified all the patients who had received at least one benzodiazepine prescription during the previous year Of these, 2964 were identified as long-term benzodiazepine users (more than three months), and 2004 fulfilled the inclusion criteria for the Benzoredux project These patients received the first intervention of the project, namely a letter from their GP advising discontinuation of benzodiazepine use

In chapter 4, the effect of this minimal intervention is evaluated over a 21-month follow-up period Three practices were excluded from the analyses because prescription data could not be extracted from them In addition, some patients were lost to follow-up due to moving homes, dead or technical problems with extraction of follow-up data The sample therefore comprised 2248 long-term benzodiazepine users (in stead of the 2964 identified at study start), for which complete follow-up was available Of this group, 1601 patients met the inclusion criteria and actually received the minimal intervention The short-term evaluation, 3 to 6 months after the initial letter was sent, showed that 28%

(446/1601) of patients did not receive benzodiazepine prescriptions anymore This success rate was superior to the mean success rate of the minimal interventions described in chapter 3 During the 21-month follow-up period, the success rate for continued abstinence dropped to 16% (251/1601)

In order to avoid Hawthorne effects, we recruited retrospectively a blinded control group of 2061 long-term benzodiazepine users in 16 additional practices, of which 1585 patients were available for analysis The in- and exclusion criteria for receiving the minimal intervention were not applied for these patients in order to prevent recall bias A comparison between the 1585 control subjects with the 2248 long-term users in the experimental practices revealed significantly higher dosage reductions in the experimental practices (24% versus 5%, p<0 01) Moreover, 24% of the patients in the experimental group did not receive any benzodiazepine prescription 4 to 6 months after receiving the discontinuation letter (quitters), versus 12% of the patients in the control group (p<0 01) Quitters used significantly lower dosages before receiving the discontinuation letter compared to non-quitters Of the quitters, 42% in the control group and 56% in the experimental group remained benzodiazepine prescription abstinent till the end of follow-up (p<0 01) The patients who relapsed used significantly lower benzodiazepine dosages at 21 months compared with their baseline level

In chapter 5, a more extensive follow-up is presented of users who stopped in the short term and who gave informed consent for a more intensive follow-up Of the 2004 long-term benzodiazepine users who originally received the minimal intervention, 1321 patients responded to a second letter asking them to visit their GP Of the 1321 visitors, 285 said they had stopped their benzodiazepine use, and 109 (38%) gave informed consent for the follow-up study After a mean follow-up period of more than two years, 49% were still completely abstinent from benzodiazepines Furthermore, 60% of those patients who relapsed showed better usage patterns during follow-up, i e , using benzodiazepines intermittently for periods of less than 90 days Benzodiazepine consumption during follow-up was not related to psychological functioning Patients did not change their benzodiazepine use for other psychotropic drugs Two independent predictors of relapse were indentified use of more than 10 mg diazepam equivalent a day before receiving the initial letter and a poor general health perception

Part III: Short-term results of taper-off strategies

Of the 1321 patients that visited the GP three months after the minimal intervention, 1036 patients said they were still using benzodiazepines, of which 180 agreed to participate in the second stage, a randomised controlled trial (RCT) The patients were randomised over tapering-off combined with simultaneous group cognitive behavioural therapy (CBT) (n=73), tapering-off alone (n=73), and a no-intervention control group (n=34) The short-term results presented in Part III are based on self-report outcome measures

In chapter 6, we describe the short-term effect of the RCT based on intent-to-treat analysis, on self-report abstinence rates, and psychological functioning at the end of treatment (available for 141 patients, 78%) Both taper programmes yielded significantly higher abstinence rates compared with

the no-intervention control group tapering off combined with group CBT, 58%, tapering off alone, 66%, and non-intervention, 21% Contrary to our hypothesis, the addition of group CBT did not increase the success rate of the tapering-off programme

Some interesting findings were noted (a) patients did not suffer adverse effects from (trying to) taper-off since neither intervention type nor treatment outcome critically affected any of the secondary outcome parameters (severity of withdrawal symptoms, psychological distress, mood swings, or the use of psychoactive agents), (b) the participation rate was poor 17% (180/1036) of the eligible patients gave informed consent to participate in the trial, (c) although these patients did not respond to the minimal intervention, 23 of the 146 patients (20%) assigned to one of the taper-off strategies stopped their benzodiazepine use after giving informed consent while waiting to join the programme, (d) attendance at group CBT was poor 65% attended three or more sessions, (e) the programmes showed good feasibility in general practice, and (f) the majority of patients were satisfied with the treatment received

In chapter 7, the Benzodiazepine Dependence Self-Report Questionnaire (Bendep-SRQ) was cross-validated to establish its usefulness in daily practice The Bendep-SRQ is a self-report questionnaire that measures the severity of benzodiazepine dependence on four domains 'awareness of problematic use', 'preoccupation with the availability of benzodiazepines', 'lack of compliance with the therapeutic regime', and 'withdrawal' Three out of the four domains had good scalability Some concerns arose about the scalability of the preoccupation scale, which emphasized the need for cross-validation in clinically relevant populations All scales showed excellent reliability (subject discriminability, item discriminability), while construct and discriminant validity were adequate All four scales contributed significantly to the prediction of complete abstinence after the tapering-off programme This prediction was independent of the other prognostic variables (baseline benzodiazepine dosage and smoking status), except for those in the domain 'problematic use' The scales 'problematic use' and 'preoccupation' showed good sensitivity to change during follow-up

Part IV: Long-term results of taper-off strategies

The 18-month prospective follow-up study consisted of (a) a computerised extract of all drug prescription data from the GP information system, (b) a self-report follow-up assessment at 18 months identical to the baseline and short-term outcome assessment, and (c) five three-week cost-diaries at baseline and at 3, 6, 12 and 18-month follow-up

In chapter 8, the clinical outcome study is presented longitudinally investigating the 18-month outcome of benzodiazepine discontinuation with respect to benzodiazepine use, psychotropic drug use, and psychological functioning The drug prescription data were available for 170 of the 180 patients included in the trial (94%) Fifty patients (29%) did not receive benzodiazepine prescriptions during follow-up Tapering-off alone resulted in a significantly higher continued abstinence rate compared to the control group (36% versus 15%, p=0 03), while simultaneous group CBT had no added value for

tapering-off alone In addition, actively treated patients who failed to discontinue benzodiazepine use lowered their dosage significantly more than the patients receiving usual care Moreover, 47% of patients receiving tapering-off combined with group CBT, and 54% of those receiving tapering-off alone used benzodiazepines intermittently for periods of less than 60 days Patients did not switch from benzodiazepines to other psychotropic drugs, nicotine, or alcohol Although patients were suffering from mild anxiety and depressive symptoms, neither intervention type nor outcome adversely affected psychological functioning

Chapter 9 presents a Cox-regression analysis used to identify independent predictors of long-term taper success Potential predictors included benzodiazepine (usage) characteristics, psychopathological symptoms, personality traits, and characteristics of (benzodiazepine) dependence Independent predictors of success included offering a taper-off programme with or without group CBT, a lower daily dosage at the start of tapering-off, a substantial dose reduction after a minimal intervention immediately before tapering-off, a low score on the 'lack of compliance' scale of the Bendep-SRQ and no use of alcohol Patients who used over 10 mg of diazepam equivalent, who had a score of three or more on the 'lack of compliance' scale of the Bendep-SRQ, or who drank more than two units of alcohol per day failed to achieve long-term abstinence

Chapter 10 presents the economic evaluation of the follow-up study This study examined the incremental cost-effectiveness ratios (= costs per unit extra effect) of tapering-off benzodiazepine usage with and without group CBT compared to usual care We planned *a priori* a cost-effectiveness analysis from a societal perspective for the condition that the quality of life increased or remained stable This prerequisite was confirmed as neither intervention type, nor outcome, affected the quality of life

The medical consumption, as measured with five 3-week cost-diaries, did not significantly change during follow-up, and was independent of intervention type or treatment outcome However, fluctuations within, and between, groups questioned the reliability of these measures Moreover, these costs and the costs for prescribed drugs other than benzodiazepines exceeded the intervention costs and the pharmaceutical costs for benzodiazepines, while the causal relationship with benzodiazepine usage remained uncertain Therefore, the cost-effectiveness ratios were also calculated from two other perspectives a pharmaceutical perspective limited to intervention costs and benzodiazepine usage, and a comprehensive pharmaceutical perspective also including the costs of prescribed drugs other than benzodiazepines Both tapering-off strategies led to a significant reduction in benzodiazepine costs Although the incremental cost-effectiveness ratios were better for tapering-off alone than for tapering-off with group CBT, when compared with usual care, the differences were small Extrapolation of our data showed that the costs for tapering-off alone were paid back after 20 month follow-up when corrected for treatment gain in the usual care group

Methodological issues of the Benzoredux project

The results - summarised above - have already been discussed in the various chapters In this general discussion, the methodological strengths and limitations of the Benzoredux project are discussed together with the implications for interpretation of the results The following aspects will be discussed setting, subjects, attrition rate and effect size of the minimal intervention, attrition rate and randomisation procedure of the RCT, interventions of the RCT (taper protocol and group CBT), the primary outcome parameter, benzodiazepine dosage levels, and finally the measurements

Setting

The Benzoredux project was carried out in general practice as most long-term users (89%) receive benzodiazepine prescriptions from their GP [1] The high prevalence of benzodiazepine use and the daily practice of a GP gave the opportunity to evaluate a two-stage treatment approach starting with a minimal intervention Moreover, in general practice, long-term benzodiazepine use is often taken for granted and hardly evaluated anymore [2] Furthermore, most long-term users do not receive additional treatment for anxiety or insomnia anymore that would be interrupted by the minimal intervention [3]

Previous minimal interventions were also conducted in general practice, while the more intensive tapering-off strategies were mainly conducted in psychiatric inpatient or outpatients clinics, which limits generalisability to general practice [4 11] These discontinuation studies contrast with the pragmatic nature of the Benzoredux project that concentrates on the effectiveness of tapering off in daily practice Moreover, 76% of the patients in our study preferred treatment by their GP, while only 7% preferred referral to other specialists (see chapter 6), which is in line with survey data of benzodiazepine users [12] A large benzodiazepine discontinuation study in general practice found comparable short-term success rates (66%) and a somewhat lower long-term success rate This study was restricted to depressive long-term benzodiazepine users, while no pre-selection was carried out through a minimal intervention [13]

Subjects

The main purpose was to reduce long-term benzodiazepine consumption in general practice by recruiting as much as possible long-term benzodiazepine users We therefore identified *a priori* all long-term benzodiazepine users to provide detailed information on the effect of our approach in an 'average Dutch general practice' However, two factors might limit the generalisability of our results to the 'average long-term benzodiazepine user in the population' First, 12% of the long-term benzodiazepine users (297/2425) had to be excluded in order to prevent interference with the treatment they were receiving in psychiatric or addiction outpatient clinics Secondly, the inclusion and exclusion criteria had to be checked by the general practitioner themselves, which was justified by the pragmatic nature of the Benzoredux project If a GP wanted to exclude a patient for a reason not

covered by our exclusion criteria, he/she had to motivate that decision and subsequently discuss it with one of the researchers Nevertheless, 10% of the patients (251/2425) were excluded specifically on instigation of the GP An interesting finding was that a substantial number of GPs excluded the oldest patients at the first check By discussing the checklist, most GPs were persuaded to include the elderly As the outcome of both treatment stages (minimal intervention / tapering-off) was independent of the patient's age, this finding stresses the influence of prejudice on the patient's chances of discontinuing benzodiazepine use Moreover, these results indicate that especially the elderly should be included in the programme, since adverse effects increase with old age [14 16]

In previous studies on minimal intervention strategies, the GP had not only to check the inclusion and exclusion criteria, but also to identify the long-term users in his/her practice[17 19], while two studies did not provide information how long-term users were identified [20 21]

Attrition rate of the minimal intervention

Our study is the first study that identified all long-term benzodiazepine users before starting recruitment, and it therefore provides detailed information on the recruitment process To validly evaluate the effect of a letter containing advice to stop benzodiazepine use, gaining informed consent *a priori* was impossible Asking informed consent afterwards was not necessary, since the effect of the letter was evaluated using anonymous prescription data that could only be linked to individual patients by the GP Therefore, the results of the minimal intervention were not hampered by non-respondent bias in contrast to the studies of Bashir *et al* (1994), Jones (1991) and O'Leary (1989) [17 18 21] The study of Cormack *et al* (1994) on the efficacy of a discontinuation letter was also performed without informed consent of the patients [19] This study was carried out in three general practices with ten GPs and 209 long-term benzodiazepine users Therefore, the influence of individual GPs could not be ruled out and subgroup analyses could not be performed [19]

Thirty five percent of the patients who received the discontinuation letter did not respond to the invitation of the GP three months later to discuss the effect On the one hand, it might reasonably for GPs not to want to see everyone personally as participation in the study would than increase their workload substantially by 40 consultations over 4 to 10 weeks However, a busy surgery does not fully explain why 35% of the patients refused to visit the GP Drug-seeking behaviour or avoidance of patients combined with a non-restrictive policy or attitude of the GP might have played a role, which is also suggested by the personal reasons patients gave for not visiting the GP (see chapter 4) [12 22]

Effect size of the minimal intervention

The effect of the minimal intervention was compared to a matched control group that was recruited retrospectively Of the seven previous studies evaluating a minimal intervention strategy, three studies did not include a control group[17 23 24], while the others recruited controls from the same general practices [18 21] As participation in a benzodiazepine reduction trial is likely to influence the prescription

behaviour of the GP (Hawthorne-effect), the allocation of controls from non-intervention practices in a blinded fashion was preferable [25 26] The proportion of patients who discontinued benzodiazepine use was 14 1% among users excluded for the minimal intervention in the experimental practices (thought to have more difficulty in benzodiazepine discontinuation), while 11 7% discontinued in the matched control practices Although this finding could reflect a Hawthorne-effect, it might also be caused by GP participation bias

GPs in the control practices were not asked to apply the exclusion criteria on the list of long-term benzodiazepine users for two reasons First, the control practices were recruited retrospectively, which might lead to recall bias in applying the inclusion and exclusion criteria Second, the knowledge of *really* sending the letter (experimental practices) or the knowledge of *not* sending the letter (control practices) might influence the exclusion of patients specifically on instigation of the GP The long-term effectiveness of this intervention was therefore evaluated by comparing all long-term users in the experimental practices (whether or not they were excluded from the intervention) with all long-term benzodiazepine users in the control practices As no matched control group was available for the patients who actually received the letter, the exact effect size of the intervention remains unknown

Attrition rate of the RCT

The participation rate in the second stage was 17% Therefore, the results of the two tapering-off strategies can not be generalised to all long-term benzodiazepine users in general practice Patient and GP related factors can be put forward to explain this finding GP-related factors are likely to have been influential since the number of patients included in the RCT ranges from 0 patients in 6 practices (group as well as solopractices) to 15 patients in a solo practice and 22 in a group practice This might reflect different attitudes among GPs regarding long-term benzodiazepine use On the other hand, GPs might have participated primarily in relation to the first stage, not being fully aware of the second stage or discouraged by the increased workload of evaluation visits after the minimal intervention Patient-related factors should also be considered As 40% of all benzodiazepine users in general practice are dependent according to the DSM-III-R criteria, dependence on benzodiazepines might have played a role [28] In addition, Linden *et al* (1998) found that two-thirds of long-term low-dose benzodiazepine users rejected a drug holiday in general practice [29] According to Russell and Lader (1992), benzodiazepine withdrawal involves a preliminary period of negotiation between patient and doctor, during which underlying fears and attitudes should be explored [30] The period of negotiation in our trial was limited to one or, on instigation of the patient, two consultations and some information sheets Furthermore, patients might have had a general resistance to taking part in an RCT, a specific reluctance to one of the treatment arms (for example the no-intervention control group or the group CBT), or a reluctance to be visited at home If this were the case, the participation rate would probably be higher in clinical practice However, we hypothesise that the participation rate in our study reflects

the daily practice in which GPs have to agree on a treatment with patients, and the participation would only increase substantially by exerting more pressure on patients

Although the relative participation rate was rather low, our study is one of the largest benzodiazepine discontinuation trials ever published Because we identified all the long-term users before we recruited them, our attrition rate cannot be compared with that of other studies which recruited referred patients in specialised settings or through advertisements [4-11] A study conducted in general practice reported a recruitment rate of 47%, which was estimated retrospectively [13] Moreover, this study was restricted to depressed long-term benzodiazepine users that were put on paroxetine or placebo, and were only tapered-off if their depression responded to that treatment

Randomisation

The benzodiazepine discontinuation study in the second stage of the Benzoredux project is the first study in which patients are randomised between tapering-off and a no-intervention control group It is therefore the first study providing evidence for the efficacy of tapering-off long-term benzodiazepine use Moreover, this design enabled a controlled evaluation of psychological functioning and psychotropic drug use during long-term follow-up

An advantage of randomisation at a GP level might be a shorter waiting time for group CBT, since most patients of a particular practice were recruited within limited timelines We randomised at patient level and not at GP level to avoid bias due to different attitudes of the GPs and different taper-off results in the different practices [13] The effect of the GP on outcome and recruitment was also found in our study and confirmed our choice (see chapter 4) In addition, GPs were not forced to apply different protocols to their patients as the protocol for both taper programmes (with and without group CBT) were identical for the GP The fact that GPs were not blinded whether patients received additional group CBT could be seen as a limitation, but reflects daily/clinical practice as GPs have to refer patients for additional treatment The knowledge of the GP concerning the possibilities and effects of the taper scheme might have enlarged the success rate in the control group, which made our results rather conservative

Taper protocol

The taper protocol was based on that of Schweizer *et al* (1990), namely a fixed taper scheme, 25% of the baseline dosage per week, in six consultations with the GP [4] In contrast with clinical studies using strict protocols, patients in our study were treated within the daily practice of their GP Although the mean number of consultations was 5 8, the number varied widely (range 1-10) which showed the pragmatic nature of the trial As presented in chapter 6, our tapering-off programme had good feasibility in general practice and patients were satisfied with the treatment received

As reported in chapter 3, the different taper rates did not influence outcome Other published tapering-off studies used fixed taper schemes, although one study that used patient-tailored taper

schemes reported very high long-term success rates [31] Due to the pragmatic nature of the Benzoredux project, our treatment can be considered to lie somewhere between a fixed and a patient-tailored taper scheme Patient-tailored taper schemes with taper periods of up to 15 months and combined with additional pharmacological and psychological treatment, as performed by Ashton (1987), are, however, difficult to carry out in general practice [31]

Group cognitive-behavioural therapy

The extent to which the therapists abided by the protocols ('adherence') was investigated by overhearing the audiotapes of a selection of treatment sessions by an independent assessor [32] Adequate adherence, however, does not mean that the treatment was received satisfactorily Of the 73 patients assigned to additional group CBT, only 34 patients attended three or more sessions, which at least partly explains why this therapy did not have any effect It might reflect an overall resistance to group psychotherapy among long-term benzodiazepine users This would be in line with findings in other studies and with our interpretation of the personal reasons why patients refused to attend group therapy sessions [20] To get enough patients to make the therapy programme feasible for first-line treatment, we could not select on psychiatric diagnoses or age group The heterogeneous nature of the group might therefore have affected the group process

The content of the therapy also has to be considered For cognitive-behavioural therapy, five sessions is not very many Treatment comprised group support, psycho-education, relaxation exercises and cognitive restructuring of the dysfunctional interpretation of withdrawal symptoms As many patients, especially low-dose users, may experience limited withdrawal symptoms, the usefulness of the cognitive part could be questioned [33] In addition, the tape recordings showed that this part of the programme was the most difficult, especially for elderly patients Since the therapy was given simultaneous with the tapering-off visits to the GP, it might have been too much for some patients Therefore, tapering-off within therapy sessions without consultations with the GP or psychotherapy afterwards to prevent relapse might improve the results The latter option, however, was not supported by preliminary analyses of our data

Primary outcome parameter

The primary outcome parameter was the use of benzodiazepines When discussing our data, we have to bear in mind that prescription data should be interpreted with caution First, not all patients fill their prescription, secondly, there is no guarantee that the patient actually takes the filled prescription, thirdly, a doctor could fail to record a written prescription in the medical record, and fourthly, there is a possibility that patients may obtain benzodiazepines from other sources The bias caused by prescriptions of other medical specialists is limited as 89% of all benzodiazepine prescriptions are issued by general practitioners and only 9% by medical specialists, half of those being psychiatrists [1] In our study, psychiatric treatment was an exclusion criterion In addition to prescription data, we also measured the

self-reported benzodiazepine usage. In the light of the dependence liability of benzodiazepines, the validity of the self-report assessment might be questionable. Geiselmann & Linden (1991), however, found an average compliance-coefficient of 0.8, which was similar to non-compliance with other forms of medication.[34]

Available long-term studies have assessed benzodiazepine use exclusively by self-report measurements or prescription data, while we assessed both. One may argue whether it would be worthwhile to obtain also benzodiazepine plasma levels or urine collections as in some short-term discontinuation trials. Orchs *et al.* (1987) did not detect the reported drug in the plasma of 25 of the 77 benzodiazepine users.[35] Conversely, in 10 of the 225 patients, benzodiazepines which were not reported were detected (diazepam, flurazepam). The discrepancies can partly be explained by intermittent use rather than regular use. In our study, a substantial number of patients used benzodiazepines intermittently during follow-up, which would threaten the validity of benzodiazepine plasma levels and urine collection. Moreover, the pragmatic nature of the study, the general practice setting, and the interview assessments at the patients' homes limited the possibilities for such analysis. If the patients had to give blood or urine samples, as well visit the hospital for checks, it would decrease the participation rate of the trial or lead to bias due to selectively missing data. The kappa for the agreement of reported and recorded benzodiazepine consumption at the end of follow-up was 0.73 ($p<0.001$) in our study. Although adequate, the kappa is supposed to be conservative due to different time windows for reported and recorded benzodiazepine consumption. Inspection of our data also showed that most discrepancies were found in patients using benzodiazepines intermittently during follow-up.

Benzodiazepine dosage levels

Although high-dose benzodiazepine users were not excluded at forehand in the Benzoredux project, the average benzodiazepine dose levels in our study were rather low and within the therapeutic range. The average dosages used by our patients, however, were comparable to the average dose levels of long-term benzodiazepine users in a Dutch general practice. Before sending the letter containing stop advice, patients used on average 7.9 mg diazepam equivalent a day, while the sub group of patients who participated in the second stage of the project used on average 8.4 mg diazepam equivalent at this stage of the study. The latter patients used 5.9 mg diazepam equivalent a day between sending the letter and the start of tapering-off. The 103 patients who actually underwent tapering-off (see figure 1, chapter 6) were transferred to an equivalent dose of 7.8 mg diazepam equivalent at the start of tapering-off programme. Although these dosages seem rather low, these patients were not able to discontinue by themselves and thus really needed more help.

As dose level before the intervention was an important predictor of outcome in our study, our results do not apply to high dose users. Stratified analyses of the minimal intervention showed a sharp decrease in effect for patients using more than 10 mg diazepam equivalent. Moreover, patients using

more than 10 mg diazepam equivalent had a significantly higher risk of relapse in the long term The tapering-off programme showed almost comparable results with patients using more than 10 mg diazepam equivalent having a 1 5 lower chance to discontinue in the long-term An interesting finding with respect to the dose level at the start of tapering-off was that this result was not confounded by the dosage reduction of patients by the minimal intervention Therefore our results suggest that a minimal intervention immediately before tapering-off add to the effects of tapering-off

Secondary assessments

Psychiatric diagnosis - It has been suggested that patients with a depressive disorder or a panic disorder have less success in benzodiazepine discontinuation [9 16] These reports suggest that diagnosing patients would contribute to more sophisticated conclusions and the identification of important predictors However, the categorical nature of such data would lead to a relatively small sample size per diagnosis, limiting the statistical power to find a significant interaction effect between outcome and diagnosis Therefore, we decided to only measure the severity of some psychopathological symptoms In addition, the GHQ-12 scores suggested that approximately one third of the patients fulfilled the criteria for a psychiatric disorder according to DSM-criteria As presented in chapter 9, no influence of depressive symptoms was found on taper outcome, while tension was only univariately related to outcome

Sleep parameters - Although 58% of our patients reported use of benzodiazepines exclusively as hypnotics, we did not assess sleep parameters How important is it to establish sleep parameters? According to guidelines for hypnotic treatment, patients may only be treated with benzodiazepines if day-time functioning is hindered Day-time functioning was measured with the POMS, GHQ-12, and the SF-36 at baseline as well as at follow-up As shown in chapters 6 and 8, these parameters were not affected by tapering-off Secondly, the reliability and validity of the available sleep questionnaires was doubtful[37] and sleep EEG or sleep/wake diaries would burden patients too much

Cost-diaries - The medical consumption during follow-up was measured with four 3-week diaries and linearly extrapolated over the whole follow-up period The reliability of these measurements is questionable as only 12 of the 65 weeks were measured and the dropout was about 30% at each measurement The high variation within, and between groups, reflects low reliability Moreover, the relationship between healthcare utilisation and the use or non-use of benzodiazepines was uncertain, while these costs exceeded the costs of the interventions combined with the pharmaceutical costs of benzodiazepines Therefore, the cost-effectiveness analysis from a societal perspective must be interpreted with caution Due to these limitations, the cost-effectiveness was also analysed from a pharmaceutical perspective

Conclusions

Sending a letter to long-term benzodiazepine users advising them to discontinue their use is an effective strategy for reducing benzodiazepine usage in general practice in the long term About 28% of the patients discontinued benzodiazepine usage over the short term, while 16% remained benzodiazepine-free during the 21-month follow-up Both success rates, as well as the amount of reduction among patients continuing use, were significantly superior to long-term benzodiazepine users in the control practices The biggest impact was on patients using 10 mg diazepam equivalent or less The main predictor of relapse was a benzodiazepine dosage of more than 10 mg diazepam equivalent before receiving the letter Pharmacological and patient factors had no or limited impact on relapse

Patients who continued benzodiazepine usage after receiving the letter could be helped to stop using through a systematic taper strategy However, only one out of six patients were prepared to participate in such a programme In the short-term, 62% of the patients receiving tapering-off alone, and 58% receiving tapering-off combined with group CBT, discontinued benzodiazepine use The Bendep-SRQ was found to be a valid and reliable questionnaire to estbablish the severity of benzodiazepine dependence in this population Moreover, low scores on three of the four subscales were independently related to successful discontinuation

The short-term success rates dropped to 36% and 29% when longitudinally monitored for 18 months, but remained significantly superior to the non-intervention control group Because other benzodiazepine discontinuation studies lack such a control group, this is the first study that provides evidence for both the short-term and long-term effectiveness of tapering-off In addition, patients who continued using used significantly lower dosages compared with patients in the control group Neither intervention type nor outcome affected psychological functioning or the use of psychoactive agents or drugs Offering a tapering-off programme to patients, a low dosage before tapering-off, a marked reduction of the benzodiazepine dosage after receiving the discontinuation letter, no use of alcohol, and a low score on the Bendep-SRQ Lack of compliance scale, all independently contributed to a more favourable outcome of tapering-off during follow-up

In general, patients were satisfied with the treatment received, while GPs thought the tapering-off programme feasible in general practice The economic evaluation did not show an increase in workload for the GP or an increase in medical consumption after the discontinuation programme Extrapolating the financial consequences showed that a reduction in benzodiazepine usage saved the intervention costs for tapering-off alone, corrected for regular healthcare, within 20 months of follow-up

Implications for clinical practice

This study clearly showed the effectiveness of a two-step treatment approach as a strategy to discontinue long-term benzodiazepine use in general practice. The effectiveness was shown by the proportion of patients able to stop completely as well as by the significant dosage reduction among patients who continued using. GPs judged both interventions feasible in general practice.

The long-term effectiveness of the first stage, the minimal intervention, justifies its use as a pre-selection for the tapering-off strategy. Moreover, a dosage reduction after a minimal intervention independently contributed to a more successful outcome of the tapering-off programme. Therefore, the first step in clinical practice should be to identify all long-term benzodiazepine users, and to advise them to reduce their usage. This advise should be as personal as possible, but it should also be as simple as possible. We would recommend the use of our discontinuation letter at this stage. Patients using more than 10 mg diazepam equivalent, who stop using after receiving the letter, need to be monitored as there is a significant risk of relapse.

Patients not able to stop by themselves (and perhaps patients who relapse after the minimal intervention as well) should be motivated to participate in a tapering-off programme to support them in this process. Especially, since we found that patients do not deteriorate after tapering-off or switch from benzodiazepine use to alcohol, nicotine or other psychotropic drugs. Moreover, we estimated that the costs of this treatment will be saved within 20 months of follow-up when provided in general practice. Other reasons for tapering-off in general practice are: (a) discontinuation success rates are similar in the different settings, (b) patients prefer to be treated by their GP instead of being referred, and (c) both GPs and patients were satisfied with the tapering-off programme.

Additional psychological interventions should not be applied simultaneously with the tapering-off programme, because the meta-analysis and the results of the Benzoredux-project did not show any additional effect. Patients who do not manage to stop in the short-term can be supported in a second attempt with the addition of carbamazepine or imipramine (see chapter 3). Patients who use more than 10 mg diazepam equivalent, who drank more than two units of alcohol a day or who score three or more on the Lack of compliance scale of the Bendep-SRQ have a significantly higher risk of failing in the long term. Perhaps these patients should receive second-line treatment straightaway. There is no obvious appropriate treatment (after the adding carbamazepine or imipramine) for patients in general practice who cannot stop in the short term or who relapse in the long term. In these cases, the GP and the patient should analyse together the pros and cons of long-term benzodiazepine usage. Psychiatric screening would probably help identify the appropriate solution.

Recommendations for future studies

The major difficulty when dealing with the problem of long-term benzodiazepine use in general practice is motivating patients to stop using and preventing relapse in the long term. Our findings therefore not only suggest the need to optimise discontinuation strategies, they also stress the importance of preventing long-term use.

Future discontinuation studies should focus on how to motivate patients (and GPs) to discontinue benzodiazepine use. For example, researching the effect of introducing the stages of change like those used to motivate patients with alcohol or drug dependency. Since almost 50% of patients relapse after successful discontinuation, relapse prevention strategies should be developed, for example, reminders or supporting consultations with a GP or psychologist. In addition, the effect of treating underlying psychiatric disorders after tapering-off benzodiazepines should be evaluated to see if this helps prevent relapse. Finally, stepped care approaches should be evaluated to examine the effect of other additional therapies on tapering-off, especially in treatment-refractory patients, such as pharmacological treatment or individual psychotherapy. These programmes should not be limited to general practice, but should also include referrals for second-line treatment of patients who fail to stop benzodiazepine usage in general practice.

References

1 College voor zorgverzekeringen. Gebruik van benzodiazepinen 1993 - 1998 Edited by Piepenbrink JF *Geneesmiddelen Informatie Project (GIP-signaal)* 2000

2. Van der Waals FW, Mohrs J, Foets M Sex differences among recipients of benzodiazepines in Dutch general practice *British Medical Journal* 1993,307:363-366.

3. Lagro-Jansen ALM, Liberton IJW. Profielen van regelmatige gebruikers van benzodiazepinen in een huisartspraktijk *Nederlands Tijdschrift voor Geneeskunde* 1993, 137(39) 1969-1973

4. Schweizer E, Rickels K, Case WG, *et al.* Long-term therapeutic use of benzodiazepines II Effects of gradual taper *Archives of General Psychiatry* 1990; 47:908-915

5. Schweizer E, Rickels K, De Martinis N, *et al* The effect of personality on withdrawal severity and taper outcome in benzodiazepine dependent patients. *Psychoogical Medicine* 1998; 28 713-720.

6. Rickels K, DeMartinis N, Garcia-Espana F, *et al* Imipramine and buspirone in treatment of patients with generalized anxiety disorder who are discontinuing long-term benzodiazepine therapy. *American Journal of Psychiatry* 2000, 157.1973-1979.

7 Higgitt A, Golombok S, Fonagy P, *et al* Group treatment of benzodiazepine dependence *British Journal of Addiction* 1987; 82 517-532

8 Sanchez-Craig M, Cappell H, Busto U, *et al* Cognitive-behavioural treatment for benzodiazepine dependence· a comparison of gradual versus abrupt cessation of drug intake *British Journal of Addiction* 1987, 82 1317-1327.

9 Otto MW, Pollack MH, Sachs GS, *et al* Discontinuation of benzodiazepine treatment. efficacy of cognitive-behavioral therapy for patients with panic disorder. *American Journal of Psychiatry* 1993; 150:1485-1490

10 Elsesser K, Sartory G, Maurer J. The efficacy of complaints management training in facilitating benzodiazepine withdrawal. *Behavioural Research and Therapies* 1996, 34 149-156

11 Charney DA, Paraherakis AM, Gill KJ. The treatment of sedative-hypnotic dependence: evaluating clinical predictors of outcome. *Journal of Clinical Psychiatry* 2000, 61·190-195

12 Vissers FHJA Gebruik van slaap- en kalmeringsmiddelen in het dagelijks leven Determinanten, gevolgen en de rol van de huisarts Dissertatie Universiteit van Maastricht, 1998

13. Zitman FG, Couvée JE Chronic benzodiazepine use in general practice patients with depression an evaluation of controlled treatment and taper-off Report on behalf of the Dutch Chronic Benzodiazepine Working Group. *British Journal of Psychiatry* 2001, 178(4) 317-324

14. Greenblatt DJ, Shader RI, Harmatz JS. Implications of altered drug disposition in the elderly· Studies of benzodiazepines *Journal of Clinical Pharmacology* 1989; 29 866-872

15 Pomara N, Stanley B, Block R, *et al* Increased sensitivity of the elderly to the central depressant effects of diazepam *Journal of Clinical Psychiatry* 1985: 46 185-187

16. Lord SR, Anstey KJ, Williams P, *et al* Psychoactive medication use, sensori-motor function and falls in older women *British Journal of Clinical Pharmacology* 1995;(39) 227-234

17 O'Leary M: A novel approach to tackling the "benzodiazepine problem" in general practice. *Psychiatric Bulletin* 1989, 13 180-181

18 Bashir K, King M, Ashworth M Controlled evaluation of brief intervention by general practitioners to reduce chronic use of benzodiazepines *British Journal of General Practice* 1994, 44 408-412

19 Cormack MA, Sweeney KG, Hughes-Jones H, Foot GA Evaluation of an easy, cost-effective strategy for cutting benzodiazepine use in general practice. *British Journal of General Practice* 1994, 44.5-8

20 Cormack MA, Owens RG, Dewey ME The effect of minimal interventions by general practitioners on long- term benzodiazepine use *Journal of the Royal College of Geneneral Practitioners* 1989, 39:408-411

21. Jones D Weaning elderly patients off psychotropic drugs in general practice· a randomised controlled trial *Health Trends* 1990; 22:164-166

22. De Berk HAA. Over gebruik van benzodiazepinepreparaten in de huisartsenpraktijk Dissertatie 1988. Nijmegen ISBN 90-9002477-8

23. Vissers FHJA, Jongbloet AJ, Knottnerus JA, *et al.* Benzodiazepinen de gebruiker en zijn huisarts. Bijwerkingen, satisfactie, afhankelijkheid en stoppen gezien door de bril van gebruiker en huisarts *Huisarts en Wetenschap* 1988, 41(7).329-334.

24. Tattersall ML, Hallstrom C Self-help and benzodiazepine withdrawal *Journal of Affective Disorders* 1992, 24·193-198

25 Morgan J D , Wright D J & Chrystyn H Pharmacoeconomic evaluation of a patient education letter aimed at reducing long term prescribing of benzodiazepines *Pharmacy World and Science* 2002, 24 231 236

26 De Brugh S, Mant A, Mattick RP, *et al* A controlled trial of educational visiting to improve benzodiazepine prescribing in general practice *Australian Journal of Public Health* 1995, 19 142-148

27 Holm M Intervention against long-term use of hypnotics/sedatives in general practice *Scandinavian Journal of Primary Health Care* 1990, 8 113-117

28 Kan CC, Breteler MH, Zitman FG High prevalence of benzodiazepine dependence in out-patient users, based on the DSM III-R and ICD 10 criteria *Acta Psychiatrica Scandinavica* 1997,**96** 85-93

29 Linden M, Bar T, Geiselmann B Patient treatment insistence and medication craving in long-term low- dosage benzodiazepine prescriptions *Psychological Medicine* 1998,**28** 721-9

30 Russel J, Lader MH Guidelines for the prevention and treatment of benzodiazepine dependence on behalf of the Substance Abuse Committee of the Mental Health Foundation Edited by Russel J, Lader MH The Mental Health Foundation, 1992

31 Ashton H Benzodiazepine withdrawal outcome in 50 patients *British Journal of Addiction* 1987, 82 665-671

32 Waltz J, Addis ME, Koerner K, et al Testing the integrity of a psychotherapy protocol Assessment of adherence and competence *Journal of Consultative Clinical Psychology* 1993, 61 620-630

33 Busto U, Sellers EM, Naranjo CA, et al Withdrawal reaction after long term therapeutic use of benzodiazepines N Engl J Med 1986, 315 854 859

34 Geiselmann B, Linden M Prescription and intake patterns in long-term and ultra-long term benzodiazepine treatment in primay care practice *Pharmacopsychiatrica* 1991, 24 55-61

35 Orchs HR, Miller LG, Greenblatt DJ, *et al* Actual versus reported benzodiazepine usage by medical outpatients *Euopean Journal of Clinical Pharmacology* 1987, (32) 383 388

36 Lader M Anxiety or depression during withdrawal of hypnotic treatments *Journal of Psychosomatic Research* 1994, (38) 113-123

37 Van Diest R, Milius H, Markusse R, *et al* De Slaap-Waak Ervaring Lijst *Tijdschrift voor Sociale Gezondheidszorg* 1989, 67 343-347

Nederlandse samenvatting (Summary in Dutch)

Inleiding

In deze Nederlandstalige samenvatting wordt kort ingegaan op de achtergronden van het onderzoek en het onderzoeksdesign van het Benzoredux project waarop dit proefschrift grotendeels gebaseerd is Vervolgens worden de belangrijkste onderzoeksbevindingen van de 4 delen van het proefschrift samengevat Voor gedetailleerde bespreking van deze resultaten wordt verwezen naar de discussies van de afzonderlijke hoofstukken De samenvatting eindigt met enkele implicaties voor de klinische praktijk en suggesties voor verder onderzoek

Achtergronden van (langdurig) benzodiazepinegebruik

Benzodiazepinen is de verzamelnaam van een groep geneesmiddelen voor de behandeling van slaapstoornissen en angststoornissen Deze stoffen behoren tot de meest voorgeschreven geneesmiddelen in de Westerse samenleving Ten tijde van de start van dit onderzoek in 1998 kregen 1 9 miljoen Nederlanders in totaal 11 6 miljoen recepten voor een benzodiazepine Negenentachtig procent van deze voorschriften werd afgegeven door de huisarts Een prevalentieschatting uitgaande van onze definitie van langdurig gebruik (gebruik meer dan 3 maanden) komt uit op ca 3%, overeenkomend met 72 patienten in een gemiddelde huisartspraktijk

Benzodiazepinen zijn uiterst effectieve geneesmiddelen voor een kortdurende behandeling van slaap- en angststoornissen Gerandomiseerd en gecontroleerd onderzoek naar de effectiviteit op lange termijn is echter nauwelijks voorhanden Enkele uitzonderingen daargelaten, geven zowel nationale als internationale richtlijnen betreffende het gebruik van benzodiazepinen dan ook aan dat deze middelen slechts kortdurend moeten worden voorgeschreven Daarentegen zijn de bijwerkingen van langdurig gebruik de afgelopen decennia steeds meer naar voren gekomen Zo blijkt dat 40%, respectievelijk 52% van de gebruikers in de Nederlandse huisartspraktijk afhankelijk is van deze middelen volgens de criteria van de DSM-III-R, respectievelijk ICD-10 Het gebruik van benzodiazepinen leidt tot een afname van de geheugenfunctie en mogelijk predisponeert het tot een versnelde cognitieve achteruitgang Bovendien hebben gebruikers een toegenomen kans op een verkeersongeluk en een verhoogd risico op vallen met als gevolg een heupfractuur Hoewel benzodiazepinen relatief veilig zijn bij overdosering, worden zij bij bijna de helft van alle suicidepogingen gebruikt Uit Engels onderzoek blijkt dat per miljoen prescripties voor benzodiazepinen 5 9 mensen overlijden als gevolg van het gebruik Ondanks de relatieve lage prijs voor een benzodiazepine, lopen de farmaceutische kosten in Nederland door het frequente en langdurig gebruik van deze middelen op tot meer dan 95 miljoen euro per jaar De behandeling van heupfracturen als gevolg van het gebruik van benzodiazepinen wordt geschat op meer dan 16 miljoen euro per jaar

De discrepantie tussen de relatief hoge prevalentie van langdurig benzodiazepinegebruik en de richtlijnen voor het gebruik van deze middelen wordt multifactorieel veroorzaakt Zowel eigenschappen van het geneesmiddel zelf, als karakteristieken van de patient, arts en praktijkvoering lijken een rol te spelen Deze discrepantie heeft geleidt tot de ontwikkeling van diverse behandelstrategieen om langdurig benzodiazepinegebruikers te helpen hun gebruik te staken Deze behandelstrategieen kunnen worden onderverdeeld in minimale interventies en gereguleerde dosisreductie programma's Met behulp van minimale interventies worden patienten uitgenodigd op eigen kracht te stoppen door hen bewust te maken van de bezwaren van langdurig gebruik (bijvoorbeeld een brief met stopadvies of een voorlichtingsbijeenkomst) Hiermee lukt het 1 op de 5 patienten het gebruik te beeindigen Lange termijn effecten van minimale interventies zijn echter nooit onderzocht Gereguleerde dosisreductie is een intensievere behandelingsvorm, waarbij de dosering geleidelijk wordt verlaagd onder begeleiding van een arts Een dergelijk aanpak leidt bij 2 van de 3 patienten tot succes Omdat alleen gemotiveerde gebruikers deelnemen aan gereguleerde dosisreductie en deze interventie nooit binnen een gerandomiseerde opzet is vergeleken met het natuurlijk beloop van benzodiazepinegebruik onder langdurig gebruikers, is de werkelijke effectiviteit van deze behandeling feitelijk onbekend Bovendien is follow-up onderzoek schaars en spreken beschikbare resultaten elkaar tegen De economische consequenties van deze behandeling zijn zelfs nog nooit geevalueerd Verder is het opvallend dat de meeste studies zijn uitgevoerd in de tweede lijn, terwijl de meerderheid van de langdurig benzodiazepinegebruikers hun recepten via de huisarts verkrijgt Diverse psychotherapeutische of farmacologische behandelingen zijn voorgesteld om het effect van gereguleerde dosisreductie te vergroten Desondanks is de toegevoegde waarde van adjuvante psychotherapie nooit in een gerandomiseerd, gecontroleerd onderzoek geevalueerd Tenslotte wordt in de praktijk herhaaldelijk aanbevolen te starten met een minimale interventie om vervolgens alleen patienten die niet op eigen kracht kunnen stoppen gereguleerde dosisreductie aan te bieden Een dergelijke trapsgewijze aanpak is eveneens nog nooit onderzocht

Vraagstellingen en onderzoeksopzet

De hoofdvraagstelling van dit proefschrift richt zich op het evalueren van verschillende behandelmethoden om langdurig benzodiazepinegebruik te staken Specifieke vraag- en doelstellingen waren

- Het op systematische wijze samenvatten van de huidige kennis om patienten te helpen hun benzodiazepinegebruik te staken
- Het evalueren van de lange termijn effecten op het voorschrijven van benzodiazepinen na een minimale interventie strategie in de huisartspraktijk

- Het evalueren van zowel de korte als lange termijn resultaten van gereguleerde dosisreductie met en zonder aanvullende psychotherapeutische ondersteuning onder patiënten die hun benzodiazepinegebruik niet konden stoppen met behulp van een minimale interventie.
- Het verkrijgen van inzicht in enkele factoren die het effect van gereguleerde dosisreductie beïnvloeden, waarbij de mate waarin mensen verslaafd zijn aan deze middelen in het bijzonder wordt onderzocht.
- Het evalueren van de kosteneffectiviteit van de twee gereguleerde dosisreductie programma's ten opzichte van een reguliere behandeling, dat willen zeggen geen interventie gericht op het staken van benzodiazepinegebruik.

De studie startte met een meta-analyse van eerder onderzoek met betrekking tot het staken van langdurig benzodiazepinegebruik (deel I). Daarna werden opeenvolgende behandelstrategieën in de huisartspraktijk geëvalueerd (deel II, III en IV). Deze gegevens werden verkregen binnen een groter onderzoeksproject: het Benzoredux project.

Het Benzoredux project

Het Benzoredux project werd uitgevoerd onder 58 huisartsen in Nederland, werkzaam in 30 praktijken met in totaal 118082 patiënten. In deze praktijken werden alle patienten geselecteerd die het jaar voorafgaande aan het project een recept hadden ontvangen voor een benzodiazepine. Uit deze lijst werden 2964 langdurig benzodiazepinegebruikers (langer dan drie maanden) geïdentificeerd, waarvan uiteindelijk 2004 patiënten voldeden aan de criteria voor het Benzoredux project. Deze 2004 patienten werden geïncludeerd in de eerste fase van het onderzoek en kregen allen een minimale interventie, te weten een persoonlijke brief van hun huisarts waarin zij gewezen werden op de bezwaren van langdurig gebruik en geadviseerd werden hun gebruik geleidelijk te staken (stopbrief). Het medicatiegebruik van deze patiënten werd geevalueerd met behulp van het elektronisch medisch dossier van de huisarts en vergeleken met het 'natuurlijk beloop' van het benzodiazepinegebruik van langdurig gebruikers in 16 retrospectief geworven controlepraktijken (zie hoofdstuk 4).

Alle stopbrief ontvangers werden 3 maanden later uitgenodigd op het spreekuur van hun huisarts. Van de 1321 patiënten die hun huisarts daadwerkelijk bezochten, zeiden 285 patiënten gestopt te zijn en 1036 de benzodiazepinen nog te gebruiken. Aan de stoppers werd toestemming gevraagd voor een intensievere follow-up studie bestaande uit een 'baseline' en een follow-up meting met behulp van zelfbeoordelingsvragenlijsten (zie hoofdstuk 5). Aan de niet-stoppers werd deelname gevraagd aan de tweede interventie van het Benzoredux project; een gerandomiseerde, gecontroleerde trial (RCT). In totaal werden 180 van 1036 patiënten (17%) gerandomiseerd over gereguleerde dosisreductie gecombineerd met gelijktijdige groeps cognitieve-gedragstherapie (CGT; n=73), gereguleerde dosisreductie alleen (n=73) en een controle groep waarin patiënten geen hulp kregen bij

het staken van hun benzodiazepinegebruik (n=34) Het medicatiegebruik van deze patienten werd eveneens geevalueerd met behulp van het elektronisch medisch dossier Ter aanvulling kreeg deze groep drie interviewmetingen bestaande uit zelfbeoordelingsvragenlijsten welke werden afgenomen op baseline en 3, respectievelijk 18 maanden follow-up en hielden zij vijf keer een 'kostendagboekje' bij ter evaluatie van de medische consumptie gedurende 3 opeenvolgende weken (zie figuur 1, hoofdstuk 2)

Samenvatting en conclusies

Deel I: Literatuuroverzicht

Voor het bestuderen van de effecten van behandelingen gericht op het staken van langdurig benzodiazepinegebruik (langer dan 3 maanden) werd een meta-analyse verricht Met behulp van een systematische zoekstrategie werden 60 originele publicaties geidentificeerd, betreffende vier typen interventies, te weten minimale interventies, gereguleerde dosisreductie zonder aanvullende behandeling of gecombineerd met psychotherapie en/of farmacotherapie Overzichtsartikelen, dierexperimenteel onderzoek, effect onderzoek naar benzodiazepinen met een afbouwtraject nadien en casusbeschrijvingen met minder dan vijf patienten werden geexcludeerd Na het poolen van data werd per behandelvorm de succeskans geschat en het effect van diverse variabelen en hun onderlinge interactie berekend met behulp van Pearson Chi-kwadraat toetsen

Het effect van minimale interventies werd in 5 studies onderzocht, waarvan 3 studies het effect binnen een gerandomiseerd design vergeleken met een controlegroep bestaande uit reguliere medische zorg Zes tot negen maanden na de interventie had 22% van de gebruikers hun benzodiazepinegebruik volledig gestaakt, tegenover 9% in de controle groepen Minimale interventies waren alleen in de huisartspraktijk uitgevoerd

Met behulp van gereguleerde dosisreductie kon tweederde van de patienten hun benzodiazepine-gebruik staken Dit effect werd verbeterd door patienten alvorens af te bouwen om te zetten op een langwerkend benzodiazepine indien zij poliklinisch werden begeleid of wanneer zij meer dan 15 mg diazepam equivalent per dag gebruikten Het theoretische voordeel van het omzetten van het gebruikte benzodiazepine naar een langwerkend middel is een stabielere bloedspiegel en een geleidelijker daling hiervan tijdens de behandeling Klinische behandeling leidde eveneens tot een hogere succeskans vergeleken met een ambulante behandeling Tijdens klinische behandeling bleek de hoogte van de dosering niet gerelateerd aan het behandelresultaat, terwijl ambulante behandeling tot een slechter resultaat leidde bij patienten die hogere doseringen gebruikten Hoewel dosisvermindering op geleide van de symptomen van de individuele patient de beste resultaten gaf en gereguleerde dosisreductie weer superieur leek ten opzicht van abrupt staken, moet worden vermeld dat deze behandelingen nooit binnen één studie met elkaar vergeleken zijn Hoewel de data te beperkt waren

om de succeskans voor de verschillende psychiatrische stoornissen apart te evalueren, werden aanwijzingen gevonden dat multipele drugsgebruikers en patiënten met een slaapstoornis moeilijker te behandelen waren. Wij vonden geen invloed van het jaar van publicatie van de studie, de duur van het benzodiazepinegebruik, en de setting.

Studies waarin psychotherapeutische ondersteuning naast een dosisreductie programma werd onderzocht toonden geen additioneel effect hiervan voor de 'gemiddelde' benzodiazepinegebruiker. Definitieve conclusies werden beperkt doordat de behandelgroepen klein waren. Ze bestonden uit maximaal 20 patienten per behandelingsgroep. Slechts 2 studies hadden een gerandomiseerde, gecontroleerde opzet. De resultaten van deze twee studies suggereren dat het effect van adjuvante psychotherapie afhankelijk is van de onderliggende aandoening. Zo blijkt het de kans op een succesvolle afbouw voor patienten met een paniekstoornis te verbeteren en voor patiënten met een afhankelijkheid van multipele middelen te verslechteren. Tenslotte resulteerde het toevoegen van de psychofarmaca carbamazepine en imipramine tot een hogere succeskans van gereguleerde dosisreductie.

Een van de belangrijkste beperkingen met betrekking tot de huidige stand van zaken is het gebrek aan follow-up resultaten. De lange termijn effecten van minimale interventies zijn nooit onderzocht. Slechts vijf studies evalueerden follow-up resultaten (langer dan 1 jaar) van gereguleerde dosisreductie. Aggregatie van deze data was echter niet mogelijk omdat succes percentages fors verschilden tussen de studies afhankelijk van de gehanteerde definitie van benzodiazepine abstinentie (range 16 - 82%). Tenslotte bleken trapsgewijze behandelingsprogramma's, zoals onderzocht in het Benzoredux project, nimmer te zijn geëvalueerd.

Deel II: Minimale interventie

In hoofdstuk 4 zijn de lange termijn effecten van de eerste interventie van het Benzoredux-project, te weten de stopbrief, geëvalueerd gedurende een 21 maanden durende follow-up periode. In verband met computerproblemen in een drietal huisartspraktijken en uitval van een aantal patiënten door verhuizingen, overlijden en technische problemen bij de extractie van follow-up gegevens, omvatte de uiteindelijke onderzoekspopulatie 2248 langdurig benzodiazepinegebruikers (i.p.v. de aanvankelijk geïdentificeerde 2964). Van deze groep ontvingen 1601 patienten daadwerkelijk de stopbrief (zie figuur 1, hoofdstuk 4). Drie tot zes maanden na verzending van de stopbrief kregen 28% (446/1601) van de stopbrief ontvangers geen recepten meer voor benzodiazepinen, hetgeen iets hoger was dan het gemiddelde succespercentage van een minimale interventie zoals gevonden in hoofdstuk 3. Na 21 maanden bleek 16% van alle stopbriefontvangers (251/1601) volledig abstinent te zijn gebleven.

Ter voorkoming van het Hawthorne-effect werd retrospectief een geblindeerde controlegroep gerekruteerd in 16 huisartspraktijken met 2061 langdurig benzodiazepinegebruikers, waarvan uiteindelijk voor 1585 benzodiazepinegebruikers alle gegevens beschikbaar waren voor analyse. De in- en exclusie criteria, zoals gehanteerd voor het verzenden van de stopbrief, werden niet toegepast op

deze patienten ter voorkoming van recall bias Vergelijking van de 1585 patienten uit de controlepraktijken met de 2248 patienten uit de experimentele huisartspraktijken, toonde een significant hogere mate van reductie van het totale benzodiazepinegebruik in de experimentele praktijken (24% versus 5%, p<0 01) Op korte termijn (4-6 maanden na verzending stopbrief) bleek de kans om te stoppen twee keer zo groot in de experimentele praktijken vergeleken met de controlepraktijken (24% versus 12%, p<0 01) Vergeleken met niet-stoppers gebruikten stoppers significant lagere doseringen op baseline Bovendien bleef van de stoppers uit de experimentele praktijken (24%, n=536) 56% volledig gestopt tijdens follow-up, tegenover 42% van de stoppers uit de controlegroep (12%, n=183) (p<0 01) De gemiddelde dosering van stoppers die terugvielen was aan het eind van de follow-up significant lager dan de dosering op baseline

In hoofdstuk 5 wordt de follow-up studie gepresenteerd van de stoppers die toestemming gaven voor de aanvullende, prospectieve follow-up metingen Het doel van dit hoofdstuk was het beschrijven van prescriptiepatronen tijdens terugval, het evalueren van het gebruik van overige psychofarmaca, het identificeren van voorspellers van terugval, en tenslotte een evaluatie van het psychisch functioneren

Van de 285 patienten die drie maanden na ontvangst van de stopbrief aangaven gestopt te zijn gaven 109 (38%) toestemming voor deelname aan deze follow-up studie Na een gemiddelde follow-up duur van meer dan 2 jaar bleef 49% volledig abstinent Drie van de vijf patienten die terugvielen hadden tijdens follow-up betere gebruikspatronen dan voor ontvangst van de stopbrief, hetgeen wil zeggen dat zij nu intermitterend benzodiazepinen gebruikten in perioden van minder dan 90 dagen Het al dan niet gebruik van benzodiazepinen tijdens follow-up was niet gerelateerd aan het psychisch functioneren Bovendien trad geen verandering op in het voorschrijven van andere psychofarmaca Twee onafhankelijke predictoren voor terugval werden geidentificeerd gebruik van meer dan 10 mg diazepam equivalenten per dag voor ontvangst van de stopbrief en een slechtere algemene gezondheidsbeleving door de patient

Deel III: Korte termijn effecten van gereguleerde dosisreductie

Deel III bespreekt het korte termijn effect van de tweede stap in het Benzoredux project, te weten de uitkomst van de gerandomiseerde, gecontroleerde vergelijking van gereguleerde dosisreductie met en zonder cognitieve-gedragstherapie (CGT) met een controlegroep waarin geen behandeling wordt gegeven gericht op het gebruik van benzodiazepinen De resultaten in deel III zijn gebaseerd op zelfgerapporteerde uitkomstmaten zoals verkregen uit de interviewmetingen bij patienten thuis

In hoofdstuk 6 worden de korte termijn effecten op zelfgerapporteerde benzodiazepinegebruik en psychologisch functioneren geanalyseerd op basis van een intention-to-treat principe (gegevens beschikbaar voor 141 patienten, 78%) Beide experimentele behandelingen gaven significant hogere succes percentages te zien dan de controlegroep 58% voor gereguleerde dosisreductie met CGT, 66% voor gereguleerde dosisreductie alleen, en 21% voor de controlegroep In tegenstelling tot onze hypothese, bleek toevoeging van CGT het succes percentage niet te verhogen

Daarnaast werden enkele interessante secundaire bevindingen gedaan Het psychisch functioneren van patienten bleef onveranderd, ongeacht het al dan niet gebruiken van benzodiazepinen en ongeacht het al dan niet ontvangen van behandeling Bovendien bleek dat 23 van de 146 (16%) patienten toebedeeld aan één van de experimentele behandelingen hun gebruik alsnog op eigen kracht staakten tijdens de wachttijd voor de behandeling De bereidheid tot deelname aan gereguleerde dosisreductie was laag slechts 17% (180/1036) van de beschikbare patienten participeerde uiteindelijk Tevens was de opkomst tijdens de psychotherapie sessies laag 65% van de patienten toebedeeld aan gereguleerde dosisreductie met CGT bezocht drie of meer sessies Desondanks was de overgrote meerderheid van de deelnemende patienten tevreden met de verkregen behandeling en bleek gereguleerde dosisreductie goed uitvoerbaar in de huisartspraktijk

In hoofdstuk 7 wordt een cross-validatie verricht van de Benzodiazepine Dependence Self-Report Questionnaire (Bendep-SRQ) om de bruikbaarheid hiervan in de klinische praktijk te testen De Bendep-SRQ is een zelfbeoordelingsvragenlijst die de ernst van de afhankelijkheid van benzodiazepinen meet op vier domeinen, te weten 'bewustzijn van problematisch gebruik', 'preoccupatie met betrekking tot de beschikbaarheid van benzodiazepinen', 'gebrekkige trouw aan het therapeutisch regime', en 'onttrekking' Hoewel de psychometrische eigenschappen van deze vragenlijst in cross-sectioneel onderzoek veelbelovend zijn gebleken, is de predictieve validiteit en de sensitiviteit voor verandering tijdens benzodiazepine detoxificatie nooit onderzocht

Rasch-analyse op de baselinegegevens van de Bendep-SRQ toonde voor drie van de vier subschalen een goede schaalbaarheid De schaalbaarheid van de preoccupatieschaal kon echter niet worden bevestigd, hetgeen het belang van cross-validatie in verschillende, klinisch relevante populaties onderstreept Alle subschalen hadden een zeer goede betrouwbaarheid (subject discriminabiliteit, item discriminabiliteit) en een adequate construct en discriminante validiteit

Alle subschalen droegen significant bij aan het voorspellen of een patient al dan niet in staat was zijn gebruik te staken met behulp van gereguleerde dosisreductie Met uitzondering van de schaal 'problematisch gebruik' was de voorspellende waarde onafhankelijk van andere prognostische variabelen (dosering benzodiazepine en roken) De schalen 'problematisch gebruik' en 'preoccupatie' waren sensitief voor veranderingen tijdens follow-up Deze resultaten pleiten voor afname van de Bendep-SRQ voor en na benzodiazepine detoxificatie, zowel in onderzoek als in de klinische praktijk

Deel IV: Lange termijn resultaten van gereguleerde dosisreductie

De 18-maanden follow-up studie bestond uit (a) een geautomatiseerde extractie van alle prescriptie data uit het elektronisch medisch dossier van de huisarts, (b) een follow-up meting na 18 maanden met behulp van zelfbeoordelingsvragenlijsten, identiek aan de meting op baseline, en (c) vijf kostendagboekjes die een periode van 3 weken bestreken en ingevuld werden op baseline en na 3, 6, 12 en 18 maanden follow-up

In hoofdstuk 8 wordt het longitudinale beloop van het benzodiazepinegebruik, het gebruik van overige psychofarmaca, en het psychologisch functioneren na 18 maanden geevalueerd. De prescriptie data waren volledig beschikbaar voor 170 van 180 (94%) patiënten in de trial. Vijftig patiënten (29%) ontvingen geen enkele benzodiazepine prescriptie gedurende de follow-up. Na 18 maanden bleek gereguleerde dosisreductie zonder CGT een significant hoger succes percentage te hebben dan de controle groep (36% versus 15%, p=0.03). Evenals op de korte termijn had toevoeging van CGT aan gereguleerde dosisreductie geen meerwaarde. Patiënten die deelnamen aan één van de experimentele behandelingen maar die hun gebruik niet volledig staakten, gebruikten significant lagere doseringen tijdens follow-up in vergelijking met patiënten uit de controle groep. Bovendien kregen 48% van de patiënten toegewezen aan gereguleerde dosisreductie met CGT en 55% van de patiënten toegewezen aan gereguleerde dosisreductie zonder CGT benzodiazepinen nu intermitterend voorgeschreven in perioden van minder dan 90 dagen. Patiënten kregen niet vaker andere psychofarmaca voorgeschreven en gingen ook niet meer nicotine of alcohol consumeren. Hoewel patiënten milde angst- en depressieve symptomen rapporteerden, had noch het type interventie, noch de uitkomst hiervan invloed op het psychologisch functioneren.

Hoofdstuk 9 presenteert de uitkomsten van een Cox-regressie analyse ter identificatie van onafhankelijke voorspellers voor het kunnen staken van benzodiazepinen op lange termijn. Als potentiële voorspellers werden benzodiazepine (gebruiks)karakteristieken, psychopathologie, persoonlijkheidskenmerken en karakteristieken van (benzodiazepine) afhankelijkheid meegenomen. Onafhankelijke voorspellers van succes waren: (a) het aanbieden van een dosisreductie programma met en zonder CGT, (b) een lagere benzodiazepine dosering bij aanvang van de gereguleerde dosisreductie, (c) een substantiële dosisreductie op eigen kracht na een minimale interventie direct voor aanvang van de gereguleerde dosisreductie, (d) een lage score op schaal 'gebrek aan therapietrouw' van de Bendep-SRQ, en (e) geen gebruik van alcohol. Slechts 2 van 38 patienten die meer dan 10 mg diazepam equivalenten gebruikten, die drie of hoger scoorden op de schaal 'gebrek aan therapietrouw' van de Bendep-SRQ, of die meer dan 2 eenheden alcohol per dag consumeerden lukte het om langdurig abstinent te blijven.

Hoofdstuk 10 presenteert een economische evaluatie door de incrementele kosten-effectiviteits ratios (= kosten per eenheid extra effect) van gereguleerde dosisreductie met en zonder CGT te bepalen ten opzichte van reguliere huisartsenzorg, dat wil zeggen het verlenen van normale medische zorg zonder gerichte interventie op het staken van benzodiazepinegebruik. A priori werd een kosten-effectiviteits analyse vanuit maatschappelijk perspectief gepland, onder de voorwaarde dat de kwaliteit van leven zou verbeteren of constant zou blijven. Aan deze voorwaarde werd voldaan, aangezien noch het type interventie, noch de uitkomst enig effect had op de kwaliteit van leven zoals gemeten met twee zelfbeoordelingsvragenlijsten (Short-Form 36 en Health Utility Index 3).

Gezien de fluctuaties in de medische consumptie zoals gemeten met de vijf kostendagboekjes, zowel binnen als tussen de drie condities, werden vraagtekens geplaatst bij de betrouwbaarheid van

deze gegevens Bovendien overstegen de kosten voor de medische consumptie zoals vastgesteld in de kostendagboekjes, alsmede de kosten voor medicatiegebruik anders dan benzodiazepines, vele malen de gezamenlijke kosten voor de interventie en het benzodiazepinegebruik tijdens follow-up, terwijl geen relatie met het gebruik van benzodiazepinen tijdens follow-up werd gevonden, noch met de verkregen behandeling Om deze redenen werden tevens incrementele kosten-effectiviteit ratios berekend vanuit twee andere perspectieven een beperkt farmaceutisch perspectief beperkt tot de interventiekosten en de kosten voor benzodiazepinegebruik sec en een uitgebreid farmaceutisch perspectief waarin ook de kosten van alle overige prescripties werden meegenomen Zowel gereguleerde dosisreductie met als zonder CGT leidde tot een significante reductie in kosten voor benzodiazepinen Hoewel de incrementele kosten-effectiviteits ratios beter waren voor gereguleerde dosisreductie zonder CGT dan voor gereguleerde dosisreductie met CGT waren de verschillen klein Extrapolatie van onze data liet zien dat na correctie voor de effecten van reguliere zorg, de kosten van gereguleerde dosisreductie zonder CGT na 20 maanden waren terugverdiend door reductie in de kosten voor benzodiazepinegebruik

Consequenties voor de klinische praktijk

Deze studie bewijst dat een getrapte aanpak ter reductie van langdurig benzodiazepinegebruik in de huisartspraktijk zowel effectief als goed uitvoerbaar is Deze effectiviteit betreft zowel de proportie patienten die hun gebruik volledig stoppen alsmede een significante dosisreductie onder niet-stoppers

De effectiviteit van een minimale interventie (lees stopbrief) op lange termijn rechtvaardigt het gebruik als preselectie voor gereguleerde dosisreductie Bovendien blijkt dosisvermindering naar aanleiding van een stopbrief het succes van gereguleerde dosisreductie onafhankelijk van andere prognostische factoren positief te beinvloeden In de klinische praktijk moet daarom de eerste stap bestaan uit het identificeren van alle langdurig benzodiazepinegebruikers om hen vervolgens te adviseren dit gebruik op eigen kracht te staken Dit advies moet zo persoonlijk mogelijk zijn, alsmede zo eenvoudig mogelijk Voor dit stadium raden wij onze stopbrief aan Patienten die ondanks gebruik van meer dan 10 mg diazepam equivalenten per dag stoppen, moeten intensiever vervolgd worden in verband met een verhoogd risico op terugval

Patienten die niet in staat zijn op eigen kracht te stoppen (en eventueel patienten die terugvallen na een minimale interventie) moeten gemotiveerd worden voor gereguleerde dosisreductie, mede gezien het feit dat patienten niet verslechteren door het staken van benzodiazepinen en hun benzodiazepinegebruik niet verruilen voor alcohol, nicotine of andere psychofarmaca Bovendien wordt geschat dat de investeringskosten na ongeveer 20 maanden zullen zijn terugverdiend indien deze interventie plaatsvindt in de huisartspraktijk Andere redenen om gereguleerde dosisreductie in de huisartspraktijk uit te voeren zijn het feit dat (a) succespercentages in een andere settings

vergelijkbaar zijn (zie hoofdstuk 3), (b) patienten voorkeur hebben voor behandeling door hun eigen huisarts en (c) zowel deelnemende huisartsen als patienten tevreden zijn over deze behandeling Patienten die meer dan 10 mg diazepam equivalenten per dag gebruiken voor aanvang van gereguleerde dosisreductie, die meer dan 2 eenheden alcohol per dag nuttigen of een score van drie of hoger hebben op de schaal 'gebrek aan therapietouw' van de Bendep-SRQ, zouden reeds op voorhand verwezen kunnen worden naar een tweedelijns setting

Additionele psychotherapeutische interventies gelijktijdig met gereguleerde dosisreductie moeten worden vermeden, aangezien zowel uit onze meta-analyse, als binnen onze eigen studie, geen meerwaarde hiervan werd gevonden Indien een patient zijn gebruik niet kan stoppen met behulp van gereguleerde dosisreductie, kan een tweede poging worden ondernomen na toevoeging van carbamazepine of imipramine (zie hoofdstuk 3) Vooralsnog blijft echter onduidelijk wat de behandeling van eerste keus is voor patienten die hun gebruik niet kunnen staken (ook na toevoeging van de eerder genoemde psychofarmaca) of terugvallen In deze gevallen zullen huisarts en patient samen de voor- en nadelen van langdurig benzodiazepinegebruik moeten afwegen Psychiatrische screening en/of advies kan een waardevolle aanvulling zijn bij het maken van een juiste beslissing

Aanbevelingen voor verder onderzoek

Belangrijke aandachtsgebieden bij het terugdringen van langdurig benzodiazepinegebruik in de huisartspraktijk is het motiveren van patienten hun gebruik te staken en het voorkomen van terugval na succesvol staken Het lijkt dan ook niet zinvol alleen te zoeken naar optimalisatie van de huidige behandelingsvormen, maar ook aandacht te besteden aan preventie van langdurig gebruik

Toekomstig onderzoek moet zich richten op het motiveren van patienten (en huisartsen?) voor benzodiazepine reductie Zo kunnen bijvoorbeeld de 'stages of change', zoals gebruikt in de verslavingszorg worden gebruikt Aangezien ongeveer 50% van de succesvol afgebouwde patienten op termijn terugvalt, zullen terugvalpreventie programma's moeten worden ontwikkeld, bijvoorbeeld schriftelijke reminders of ondersteunende consulten door huisarts of psycholoog Daarnaast zal het effect van het behandelen van onderliggende psychiatrische aandoeningen na afbouw geevalueerd moeten worden, met name in het licht van terugvalpreventie Tenslotte zullen trapsgewijze studies moeten worden uitgevoerd om het effect te onderzoeken van adjuvante medicamenteuze of psychotherapeutische ondersteuning bij therapieresistente patienten Deze programma's dienen niet beperkt te blijven tot de huisartspraktijk, maar zullen ook verwijzingen naar de tweede lijn moeten evalueren wanneer benzodiazepineafbouw in de eerste lijn faalt

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Curriculum vitae and list of publications

Curriculum vitae

Richard Christiaan Oude Voshaar

Date of birth March 13, 1973

Place of birth Almelo, The Netherlands

Married to M A H W Peeters (January 18, 2002)

Education

Atheneum-B ('High school') (1991)

Pius-X-college, Almelo, The Netherlands

Dutch, English, Mathematics-B, Physics, Chemistry, Biology, Economics-I, Economics-II

Master of Science in Medicine (1995, Cum Laude)

University of Nijmegen, The Netherlands

Medical Doctor / Internships (1998, Cum Laude)

University Medical Center Nijmegen, The Netherlands

Master of Science in Epidemiology (2001)

University of Nijmegen, The Netherlands

Positions held

Resident in Adult Psychiatry (September 2002 – present)

Department of Psychiatry, University Medical Center Nijmegen, The Netherlands

Research Physician (January - September 2002, 0 2 fte)

Department of Psychiatry, VU Medical Center Amsterdam, The Netherlands

Medical Doctor (January-September 2002, 0 88 fte)

Nijmegen Mental Health Center (GGz Nijmegen), The Netherlands

- Acute ward and long-stay ward for chronic psychiatric patients

Research Physician (May 1998- December 2001)

Department of Psychiatry, University Medical Center Nijmegen, The Netherlands

- The Benzoredux-project, a two-stage intervention study of benzodiazepine discontinuation in general practice
- A double blind, balanced order cross-over randomised study evaluating effects of additional oxazepam dosages in long-term users of oxazepam using subjective (VAS, STAI-DY-2) and objective measures (acoustic startle response, saccadic eye movements, simple and complex reaction time task, 15-words test)
- A randomised controlled trial comparing temazepam and zolpidem with respect to rebound insomnia and withdrawal effects

Professional societies

Secretary (1996-1997) and President (1997-1998) of the Council for Internships of the University of Nijmegen (KO-raad), including membership of the following committees:

- Committee for Education in Medicine (Opleidingscommissie geneeskunde).
- Committee for Practical Medical Training (Alco-commissie).
- Committee for Education in General Practice and Social Medicine (Onderwijscommissie Huisarts-, Sociale - en Verpleeghuisgeneeskunde).
- Public Relations Committee (PR-commissie).
- Committee for Physician's Examinations (Examenregelingencommissie).

Coordinator (1996-1998) of the Workgroup for the Legal Status of Internships (Werkgroep Rechtspositie Co-assistenten, WRC).

Participant (1996-1998) of the National Committee for Internships (Landelijk Overleg Co-Assistenten, LOCA).

Professional publications

Oude Voshaar RC, Gorgels WJMJ, Mol AJJ, van Balkom AJLM, Breteler MHM, Van de Lisdonk EH, Mulder J, and Zitman FG. Predictors of relapse after discontinuation of long-term benzodiazepine use by minimal intervention: 2-year follow-up study. *Family Practice* 2003; 20(4): 370-372.

Oude Voshaar RC, Gorgels WJMJ, Mol AJJ, Van Balkom AJLM, Van de Lisdonk EH, Breteler MHM, Van den Hoogen HJ, and Zitman FG. Tapering off long-term benzodiazepine use with or without group cognitive-behavioural therapy: three condition, randomised controlled trial. *British Journal of Psychiatry* 2003; 182: 489-504.

Mol AJJ, Oude Voshaar RC, Gorgels WJMJ, Breteler MHM, Van Balkom AJLM, Van de Lisdonk EH, Van der Ven AHGS, and Zitman FG. Development and psychometric evaluation of the Benzodiazepine Craving Questionnaire. *Addiction* 2003; 98: 1143-1152.

Oude Voshaar RC, Gorgels WJMJ, Mol AJJ, Van Balkom AJLM, Breteler MHM, and Zitman FG. Cross-validation, prective validity and time course of the Bendep-SRQ in a benzodiazepine discontinuation trial. *Comprehensive Psychiatry* 2003; 44(3): 247-255.

Oude Voshaar RC and Mol AJJ. Afkicken van benzodiazepinen: waarom en hoe? *Modern Medicine* 2001; 10: 907-910.

Gorgels WJMJ, Oude Voshaar RC, Mol AJJ, Van de Lisdonk EH, Breteler MHM, and Zitman FG. Het langdurig gebruik van benzodiazepinen. *Nederlands Tijdschrift voor Geneeskunde* 2001; 145(28): 1342-1346.

Oude Voshaar RC, Gorgels WJMJ, Mol AJJ, Couvée JE, Van Balkom AJLM, and Zitman FG. Behandelmethoden om langdurig benzodiazepinegebruik te staken. *Nederlands Tijdschrift voor Geneeskunde* 2001; 145 (28): 1347-1350.

Kortmann FAM and Oude Voshaar RC Aspecten van pharmacotherapie bij etnische minderheden *Tijdschrift voor Psychiatrie* 1998 (3) 143-155

Papers presented at conferences

Oude Voshaar RC, *et al* Follow-up resultaten van een gerandomiseerde en gecontroleerde benzodiazepine dosisreductie studie Oral presentation at the Voorjaarcongres Nederlandse Vereniging voor Psychiatrie, April 3, 2003, Amsterdam, The Netherlands

Oude Voshaar RC, *et al* Benzoredux-study a two-phase appraoch to reduce chronic benzodiazepine use Oral presentation at the American Psychiatric Association, May 8, 2001, New Orleans, United States of America

Oude Voshaar RC, *et al* Een getrapte aanpak van chronisch benzodiazepine gebruik het Benzoredux-project Oral presentation at the Voorjaarscongres Nederlandse Vereniging voor Psychiatrie, March 30, 2000, Maastricht, The Netherlands

Oude Voshaar RC, *et al* Reduction of chronic benzodiazepine use by letter in primary care first results of the Benzoredux study Poster presentation, September, 1999, 12th European Congress of Neuro-Pharmacology, London, United Kingdom

Research submitted

Oude Voshaar RC, Van Balkom AJLM, and Zitman FG Zolpidem is not superior to temazepam with respect to rebound insomnia a randomised controlled study *European Neuropsychopharmacology*, accepted for revision

Oude Voshaar RC, Verkes RJ, Van Luijtelaar ELJM, Edelbroek PM, and Zitman FG Effects of additional oxazepam in long-term users of oxazepam

Oude Voshaar RC, Couvée JE, Van Balkom AJLM, and Zitman FG Strategies to discontinue long-term benzodiazepine use a systematic review and meta-analysis

Gorgels WJMJ, Oude Voshaar RC, Mol AJJ, Van de Lisdonk EH, Van Balkom AJLM, Van den Hoogen HJ, Mulder J, Breteler MHM, and Zitman FG Discontinuation of long-term benzodiazepine use by sending a letter to users in family practice

Oude Voshaar RC, Gorgels WJMJ, Mol AJJ, Van Balkom AJLM, Mulder J, Van de Lisdonk EH, Breteler MHM, and Zitman FG Long-term outcome of a three-condition, usual care controlled, benzodiazepine discontinuation study

Oude Voshaar RC, Gorgels WJMJ, Mol AJJ, Van Balkom AJLM, Mulder J, Van de Lisdonk EH, Breteler MHM, and Zitman FG Predictors of long-term taper success after a benzodiazepine withdrawal programme in general practice

Mol AJJ, Gorgels WJMJ, Oude Voshaar RC, Breteler MHM, Van Balkom AJLM, Van de Lisdonk EH, Kan CC, and Zitman FG Associations of benzodiazepine craving with other clinical variables in a population of general practice patients

Gorgels WJMJ, Oude Voshaar RC, Mol AJJ, Van de Lisdonk EH, van Balkom AJLM, Van den Hoogen HJ, Mulder J, Breteler MHM, and Zitman FG. Predictors of benzodiazepine prescription reduction after sending a discontinuation letter to long-term benzodiazepine users in general practice.

Oude Voshaar RC, Krabbe PFM, Adang EMM, Gorgels WJMJ, Van Balkom AJLM, and Zitman FG. Economic evaluation of tapering off benzodiazepine usage in long-term users.

Stellingen bij het proefschrift

Consecutive Treatment Strategies to discontinue Long-term Benzodiazepine Use

A systematic evaluation in general practice

Richard Oude Voshaar

18 november 2003

1 Het vragen van informed consent kan valide klinisch onderzoek onmogelijk maken
(dit proefschrift)

2 Het is problematisch dat veel artsen benzodiazepine-prescripties continueren zonder dat zij weet hebben van de redenen waarvoor het middel indertijd gestart is
(dit proefschrift)

3 Een hogere dosering benzodiazepinen is, ongeacht het type interventie, de belangrijkste voorspeller of iemand in staat is zijn gebruik te staken, alsmede voorgoed gestaakt te blijven
(dit proefschrift)

4 Voor een substantieel deel van de benzodiazepinegebruikers draagt het benzodiazepinegebruik niet in positieve zin bij aan hun psychisch welbevinden
(dit proefschrift)

5 Slechts 1 op de 6 langdurig benzodiazepinegebruikers is bereid onder begeleiding van zijn huisarts een poging te doen zijn gebruik te staken
(dit proefschrift)

6 Ziektekostenverzekeraars moeten benzodiazepinen voor maximaal 4 maanden per jaar vergoeden indien zij worden voorgeschreven in de eerste lijn

(dit proefschrift)

7 Vanwege de hoge prevalentie van psychiatrische co-morbiditeit zijn diagnose behandel combinaties, de zogenaamde DBC's, in de psychiatrie een ondoenlijke zaak

8 Beweringen dat patienten met een specifieke psychiatrische aandoening benzodiazepinegebruik moeilijker kunnen staken dan anderen kan niet wetenschappelijk worden onderbouwd

9 Gereguleerde dosisreductie is een effectieve wijze om langdurig benzodiazepinegebruik op langere termijn te reduceren

(dit proefschrift)

10. De verslavende eigenschappen van benzodiazepinen spelen een belangrijke rol bij het niet kunnen staken van deze middelen

(dit proefschrift)

11 De idee dat een proefschrift een reflectie is van iemands levenswerk staat in schril contrast met de gemiddelde leeftijd van promovendi

12 Geld maakt niet gelukkig, wel de relatieve hoeveelheid ten opzichte van je omgeving

13 De hoogte van de impactfactor van het tijdschrift waarin een manuscript geplaatst wordt, wordt naast de wetenschappelijke kwaliteit van het onderzoek bepaald door de mate waarin een onderwerp wetenschappelijk in de mode is

14 Het is eenvoudiger stelling te nemen dan een stelling te maken