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Craving for benzodiazepines : the development of the benzodiazepine craving questionnaire

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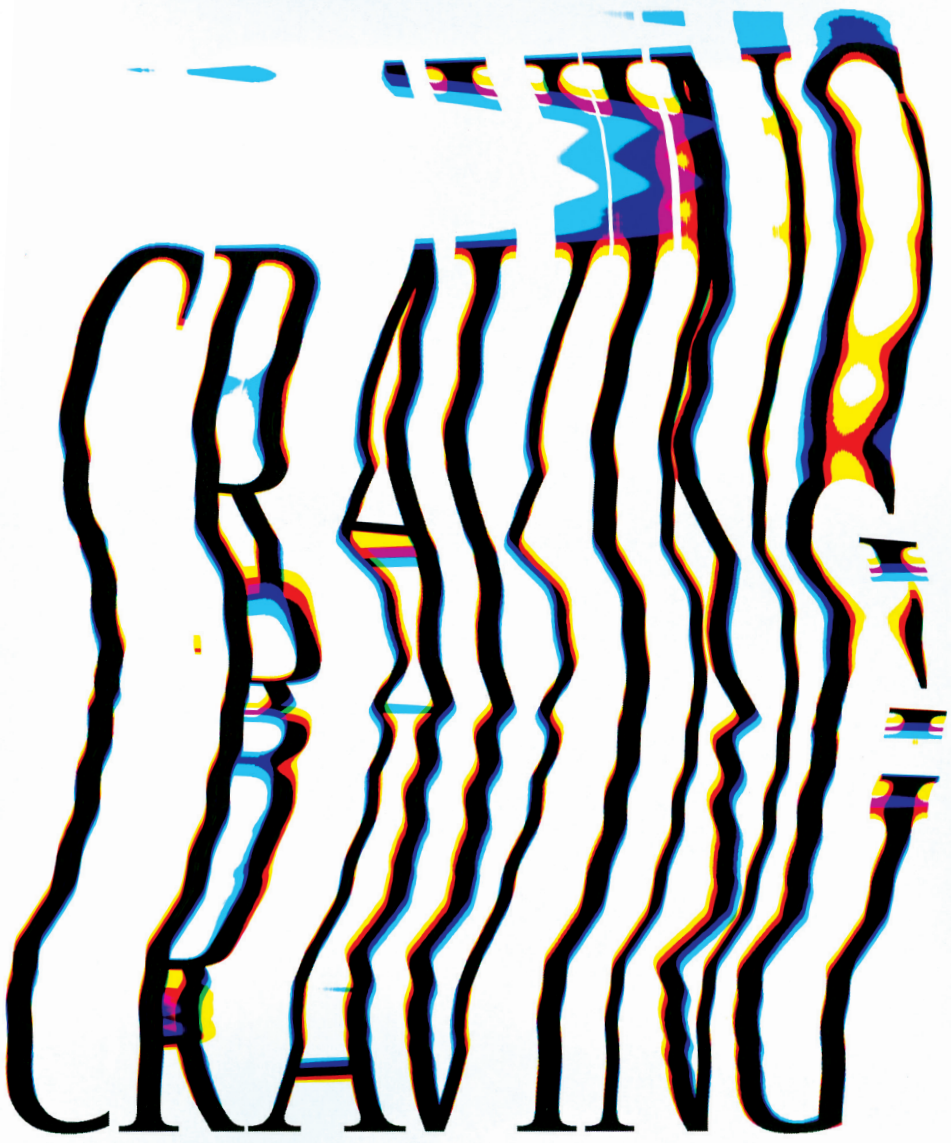
The development of the Benzodiazepine Craving Questionnaire

Audrey JJ Mol



Audrey Mol

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CRAVING FOR BENZODIAZEPINES
The development of the Benzodiazepine Craving Questionnaire

Proefschrift

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- Aún aprendo -

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Chapter 1

Introduction and thesis outline

INTRODUCTION

Benzodiazepines belong to the most prescribed drugs in Western countries.[1] In the Netherlands they are registered for the symptomatic treatment of pathological anxiety, tension and severe insomnia.[2] Their use is indicated, with some reserve, for short-term treatment (two weeks or four weeks of intermittent use) of severe insomnia with poor daytime functioning, and for the treatment of pathological anxiety and tension for a period no longer than two months. Nonetheless, in none of the Dutch guidelines for the treatment of mental disorders benzodiazepines are considered as a first treatment option for any disorder.[3-5]

In 2005 approximately 10.9 million prescriptions for benzodiazepines were issued in the Netherlands. In that year the number of benzodiazepine users was estimated at 1.9 million, which corresponds with a prevalence rate in one year of about 11.7% (of the total Dutch population of 16.3 million people).[6]

In spite of the above mentioned guidelines and the lack of evidence concerning the effectiveness of benzodiazepines with prolonged treatment,[7] in actual practice a considerable number of patients are using these drugs long-term. Reported prevalence rates of long-term use vary considerably as a consequence of differences in definition and observation period.[1] Nonetheless, in 1998 37% of all benzodiazepine users in the Netherlands could be considered long-term users, ranging from at least three months to many years of daily or intermittent use (prevalence rate 4.1% - 5.3% a year, based on a total population of 15.4 million people with health insurance).[8] This group received at least 13 prescriptions a year in an amount of 311 defined daily dosages (DDD*) according to therapeutic dosages of the World Health Organisation (WHO), which was actually lower than the current recommended dosage. In 39% of the long-term users, the benzodiazepines were indicated for anxiolytic use, in 32% for hypnotic use, and the remaining 29% received prescriptions for both purposes.[8] The demographic characteristics of these long-term benzodiazepine users show that half to two-thirds are female and half are aged 65 or over.[1,8-10] Most long-term users (89%) receive their benzodiazepine prescription from their general practitioner.[8]

In this thesis long-term use is defined as use for at least three months: 1) this time window corresponds well with the guidelines for the maximum treatment duration and 2) research has shown that there is a significant decrease in spontaneous discontinuation of benzodiazepine use after this period.[11,12]

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* Defined Daily Dosage [standaarddagdosering] (DDD) is an international unit of pharmaceutical utilisation. It is an approximation of the amount of active substance that an adult with a bodyweight of 70 kg receives per day. For example, the DDD for diazepam is 10 mg. DDDs are established by the Nordic Council on Medicines and the World Health Organization Drug Utilisation Research Group.[48]

Long-term use of benzodiazepines is not free of risks, particularly not in the elderly: benzodiazepines can cause cognitive disturbance (effects on memory), have a negative influence on driving behaviour and increase the risk of falling and consequently of hip fractures (for an overview, see e.g.[6]).

Another important issue in the long-term use of benzodiazepines is their potential for causing dependence. Not long after their discovery in the 1960's, there were reports of benzodiazepines causing physical dependence after long-term high dose treatment.[13] Not long thereafter physical dependence in normal-dose benzodiazepine usage was reported.[14,15] Research has shown that benzodiazepines have all the characteristics of drugs of dependence,[16] including tolerance, escalation of dosage, continued use despite efforts to stop and knowledge of adverse effects, several behavioural features, and a withdrawal syndrome (table 1). A substantial number of general practice patients using normal dosages of benzodiazepines are dependent on these drugs, i.e. 40% according to DSM-III-R-criteria, and 52% when applying ICD-10 criteria.[19] Long-term users make up the largest group of benzodiazepine-dependent patients.[16]

Table 1 Criteria for benzodiazepine dependence according to DSM-IV[17] and ICD-10[18] criteria

Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)	International Classification of Diseases, 10th edition (ICD-10)
Three (or more) of the following, occurring any time in the same 12-month period:	Three or more of the following have been present together at some time during the previous year:
• Tolerance	• Tolerance
• Withdrawal	• Physiological withdrawal state when substance use has ceased or been reduced
• The substance is often taken in larger amounts or over a longer period than intended	• -
• There is a persistent desire or unsuccessful efforts to cut down or control substance use	• Difficulties in controlling substance-taking behaviour in terms of its onset, termination, or levels of use
• A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects	• Progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain or take the substance or to recover from its effects
• Important social, occupational, or recreational activities are given up or reduced because of substance use	• -
• The substance use is continued despite knowledge of having a persistent physical or psychological problem that is likely to have been caused or exacerbated by the substance	• Persisting with substance use despite clear evidence of overtly harmful consequences
• -	• Craving: a strong desire or sense of compulsion to take the substance

In addiction literature craving is regarded as an important aspect of dependence. The International Classification of Diseases, 10th edition (ICD-10) has listed craving, simply defined as a 'strong desire or compulsion' to use a drug, as one of the dependence criteria.[18] Although craving is likely to be experienced by most (if not all) individuals with substance

dependence,[17] there is still little consensus about its definition and theory, its causes and consequences, and its measurement.[20-22]

Current psychological craving models (phenomenological, conditioning and cognitive) are mainly based on models of addiction. Neither provides a sufficient explanation for the nature of craving and the conditions under which it might occur. Moreover, some have not been empirically tested yet. Psychobiological models of craving assume a neurobiological basis for conditioning processes. Involvement of neurotransmitter systems, such as the dopaminergic system, has been reported in drug craving.[23] These models are predominantly based on animal studies and have often not been tested in humans. For an overview of contemporary craving models, see e.g[24-28].

Nevertheless, from a psychological perspective, there is general agreement that craving is a subjective state in humans associated with drug dependence and that it has multiple determinants.[21] Craving has been proposed as a factor in maintaining continued use or relapse in substance-dependent subjects, although, some studies have shown that craving not always precedes drug use and does not always result in drug use (e.g.[29-32]). Dependent subjects may even continue to experience craving years after their last drug use (e.g.[33-35]) and regular substance users describe experiencing craving even when they are not attempting to abstain from drug use (e.g.[36,37]).

As mentioned above there is no standardised methodology for measuring craving, nor is there a general agreement about how to develop psychometrically sound indices. Physiological measures, e.g. heart rate, skin temperature and skin conductance, have also been used as an indicator of craving. However, the relationship between these measures and self-reported craving is ambiguous.[24] In the past few years, craving researchers have also used neuroimaging methods (e.g. positron emission tomography (PET) and functional magnetic resonance imaging (fMRI)) to analyse the involvement of certain brain structures (e.g. certain frontal cortical areas and limbic structures) in the behavioural, cognitive and emotional processes that are assumed to be at the core of addiction. Several studies have found a consistent relationship between activation of certain brain areas and self-reported craving (for a review see e.g.[23,38,39]). These methods, however, are beyond the scope of this thesis.

As craving is generally regarded as a subjective phenomenon, its assessment is often based on self-reports. Most craving measures today use gradual or continuous scales, varying from visual analogue scales (e.g.[40]), single-item Likert-type scales (e.g.[41]) to multi-item multidimensional questionnaires (e.g.[36,37,42]). There are only few instruments of which the psychometric properties have been addressed and have proven to be promising.

The Questionnaire on Smoking Urges (QSU)[36] and the Cocaine Craving Questionnaire (CCQ),[37] are self-report instruments directed at four, respectively, five distinct conceptual areas relevant to craving, in order to cover current craving theories as widely as possible: desire to use, anticipation of positive outcome, relief of withdrawal or (withdrawal-associated) negative affect, intention to use, and lack of control. The data obtained with the QSU and CCQ have shown multidimensional features of craving. These questionnaires

have provided a model for the development of many other questionnaires, among which the Benzodiazepine Craving Questionnaire (BCQ), described in this thesis.

Benzodiazepine craving research is scarce. In the late 1980's, Van and Zitman[43] called for attention to the concept of craving (defined as 'the urge for renewed use') as part of benzodiazepine dependence. In an explorative study among 17 female benzodiazepine users taking part in a so-called self-help group, they found that 12 females met their criteria for craving (their questionnaire was not tested on psychometric properties, however) and 13 females made verbatim reports of yearning for their benzodiazepine. Since then there have been few studies addressing the concept of craving in the context of benzodiazepine use and dependence, and they yielded contradicting results. In a study by Lucki, Volpicelli and Schweizer,[44] patients who had discontinued their benzodiazepine use, including the long-term users, expressed little or no craving for the drug. Patients completed a craving questionnaire that asked about the intensity and frequency of their desire or urge for benzodiazepines during the previous week. Contrasting findings were reported by Linden, Bar and Geiselmann,[45] who argued that the refusal of about two thirds of their general practice patients, with long-term low-dose benzodiazepine dependence, to accept a short drug-free intermission, provided evidence for drug-seeking or craving behaviour. Apparently, these authors regarded craving to be the equivalent of drug insistence. Kan and colleagues[19] suggested that about 84% of their general practice patients using benzodiazepines experienced craving, as operationalised by four items of the SCAN (Schedules for Clinical Assessment in Neuropsychiatry). The SCAN items were adapted for benzodiazepines, but the validity of this approach to measure craving has not been tested.

THESIS OUTLINE

The main purpose of this study is to initiate benzodiazepine craving research in order to fill the gap in the craving research area and to advance our knowledge about benzodiazepine craving.

Chapter 2 describes the development and psychometrical evaluation of the Benzodiazepine Craving Questionnaire (BCQ) in a sample of 193 long-term general practice benzodiazepine users, participating in the Benzoredux project. The construction of the BCQ is described and Rasch analysis is carried out to assess its scalability. Subsequently, the reliability of the BCQ is evaluated in terms of subject and item discriminability. In order to determine the validity of the BCQ, construct and discriminative validity are assessed. In light of the results, the utility of the BCQ is discussed.

Chapter 3 characterises long-term general practice benzodiazepine users (n = 113) and former long-term benzodiazepine users (n = 80) reporting craving for benzodiazepines. Furthermore, it describes which subject-related variables, based on associations frequently

found with craving in other substances, are associated with benzodiazepine craving. The length to which these results support and challenge existing craving theories and other empirical findings is discussed.

Chapter 4 addresses the course of benzodiazepine craving, over a 21-month follow-up period by means of four repeated measurements of benzodiazepine craving, in a sample of 117 patients. We assess whether the self-reported craving severity, as measured with the BCQ, differs among several assessments in time and whether the overall experienced craving differs between patients who have quit their benzodiazepine use, patients who continue using benzodiazepines, and patients with intermittent use patterns. In addition, we examine whether the way in which patients have attempted to discontinue their benzodiazepine use (of their own accord or with additional tapering off guided by their general practitioner, with or without group cognitive-behavioural therapy) influences their self-reported craving over time.

Chapter 5 addresses the issue of craving conceptualisation. A broad conceptualisation of benzodiazepine craving, as represented by the BCQ, is compared to a narrow conceptualisation, as represented by the Benzodiazepine Desire Scale (BDS). The BDS is composed of three single-item Likert-type scales assessing frequency, global and peak intensity of the desire for benzodiazepines. Together with other (benzodiazepine dependence related) variables, they are analysed by means of factor analysis. Implications of our findings are discussed.

Chapter 6 examines the predictive value of craving on benzodiazepine relapse after discontinuation of long-term benzodiazepine use. Predictors of benzodiazepine relapse found in other studies, benzodiazepine use characteristics, and the variables measured at the baseline assessment, are analysed in long-term benzodiazepine users who have successfully quit their usage by themselves after a minimal intervention (n = 79), respectively, after a supervised benzodiazepine tapering off programme in general practice (n = 45).

Chapter 7 presents a general discussion, in which the major conclusions are summed up, limitations of the study are discussed, and adaptations and ideas for further research are suggested in order to further substantiate the psychometric properties of the BCQ. The thesis is concluded by a summary.

All data were collected within the Benzoredux project. The general structure of this project is briefly presented below in box 1.

Box 1 Design of the Benzoredux project

The Benzoredux project was carried out with ethical approval of the Radboud University Nijmegen Medical Centre between 1998 and 2001. It was funded by the Dutch Health Care Insurance Council (College voor Zorgverzekeringen, project OG97-015).

The Benzoredux project was designed to evaluate a stepped care approach to reduce long-term benzodiazepine use in general practice. Long-term benzodiazepine use was defined as use for at least three months with a prescribed amount sufficient for at least 60 days of consumption in accordance with the recommended dosage. In the first phase of the study, a so-called 'minimal' intervention strategy was evaluated. Patients received a letter from their general practitioner with the advice to gradually cut down their use of benzodiazepines by themselves and, if possible, to stop using them altogether. Patients who did not discontinue their use of benzodiazepines after this intervention were encouraged to participate in a more intensive consecutive phase of the study: a randomised controlled trial consisting of a tapering off programme with or without simultaneous group cognitive-behavioural therapy.

At the evaluation consultation three months after the minimal intervention, patients were asked to give their informed consent for the study, after which the baseline assessment was carried out. The baseline assessment took place approximately three months after the start of the minimal intervention. Three months after the start of the second intervention, patients received a short-term outcome assessment, followed by three follow-up assessments, 6, 12 and 18 months, respectively, after the start of the discontinuation trial. All five assessments consisted of structured interviews carried out at the patients' homes by trained interviewers, during which patients filled in various questionnaires, including the BCQ. For a more elaborate outline of the Benzoredux project and its study results, we refer to Gorgels et al.[46] and to Oude Voshaar et al.[47].

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Chapter 2

Development and psychometric evaluation of the Benzodiazepine Craving Questionnaire

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EH van de Lisdonk, AHGS van der Ven & FG Zitman
(Addiction 2003;98:1143-1152)

ABSTRACT

Aim – To assess the scalability, reliability and validity of a newly constructed self-report questionnaire on craving for benzodiazepines (BZs), the Benzodiazepine Craving Questionnaire (BCQ).
Setting and participants – The BCQ was administered once to a sample of 113 long-term and 80 former long-term general practice BZ users participating in a large BZ reduction trial in general practice.
Measurements – (1) Unidimensionality of the BCQ was tested by means of the Rasch model. (2) The Rasch-homogeneous BCQ items were assessed for subject and item discriminability. (3) Discriminative and construct validity were assessed.
Findings – The BCQ met the requirements for Rasch homogeneity, i.e. BZ craving as assessed by the scale can be regarded as a unidimensional construct. Subject and item discriminability were good. Construct validity was modest. Highest significant associations were found with POMS depression (Kendall's tau-c = 0.15) and Dutch Shortened MMPI negativism (Kendall's tau-c = 0.14). Discriminative validity was satisfactory. Highest discriminative power was found for a subset of eight items (Mann–Whitney U z = -3.6, p = 0.000). The first signs of craving are represented by the acknowledgement of expectations of positive outcome, whereas high craving is characterized by direct intention to use.
Conclusions – The BCQ proved to be a reliable and psychometrically sound self-report instrument to assess BZ craving in a general practice sample of long-term BZ users.

INTRODUCTION

Benzodiazepines (BZs) are among the most widely prescribed drugs in the western world[1] and there have been many reports on their liability to cause dependence (e.g. among Dutch general practitioner (GP) patients[2,3]). Craving is regarded as an important aspect of dependence. It is posited frequently as having an influence on relapse and ongoing substance abuse.[4,5] Although it is still an ill-defined concept with little consensus about its definition and theory, its causes and consequences and its measurement,[6-8] craving is likely to be experienced by most (if not all) individuals with substance dependence.[9] Nevertheless, BZ craving research is scarce.

In a study by Lucki, Volpicelli & Schweizer patients who had discontinued their BZ use, including the long-term users, expressed little or no craving for the drug.[10] Contrasting findings were reported by Linden, Bar & Geiselmann who argued that the refusal of about two-thirds of their general practice patients with long-term low-dose BZ dependence to accept a short drug-free intermission, provided evidence for drug seeking or craving behaviour.[11] Apparently, these authors regarded craving to be the equivalent of drug insistence. Kan et al. suggested that about 84% of their general practice patients using BZs experienced craving, as operationalised by four items of the SCAN (Schedules for Clinical Assessment in Neuropsychiatry).[2] Although the SCAN items were adapted for BZs, the validity of this approach has never been tested.

As craving is generally regarded as a subjective phenomenon, its assessment in other substances of abuse is mainly based on self-reports. Most instruments to assess self-reported craving are limited to questionnaires of unknown validity and reliability. Some use only one or two items to evaluate craving and approach craving as a unidimensional construct.[12] Tiffany & Drobes took a different approach when they developed the Questionnaire on Smoking Urges (QSU).[13] This is a self-report instrument directed at four different conceptual areas relevant to (cigarette) craving, in order to cover current craving theories as widely as possible: desire to use, anticipation of positive outcome, relief of withdrawal or (withdrawal-associated) negative affect and intention to use. The data obtained with the QSU showed multi-dimensional features of craving among smokers. A two-factor solution apparently best described the item structure. However, the two factor scales were fairly highly correlated, with high reliability coefficients for both factors.[13,14]

Studies illustrate that craving above all is a socially defined construct. In the absence of a unique objective referent for craving in the real world, the development of craving instruments should in our opinion focus on its usefulness as the second best option. Until now BZ withdrawal studies have not shown any consistent predictors for achieving and maintaining complete abstinence.[15,16] As the role of craving in BZ withdrawal has never been evaluated, a reliable and valid instrument to measure BZ craving is needed to gain more insight into its role. It is not clear whether a multi-dimensional measure will have better predictive validity than a unidimensional scale. Nor is it clear which measure would be able to differentiate better between patients in terms of tailoring of treatment.

The present study describes the development of the multi-item Benzodiazepine Craving Questionnaire (BCQ) to assess the extent of BZ craving, based on assumptions pertaining to the QSU developed by Tiffany & Drobes, including multi-dimensionality.[13] The research questions of this study were: (1) can BZ craving be usefully construed as a multi-dimensional concept? (2) Is the BCQ a reliable and psychometrically sound instrument to assess craving for BZs? Furthermore, initial indications of validity were explored.

METHODS

Setting

Patients from a large study on the efficacy of a two-part treatment intervention that aimed to reduce long-term BZ use in general practice in the Netherlands received a number of questionnaires, including the BCQ.[17] The study started in 1998. Patients' responses to the BCQ formed the basis of present study.

Subjects and procedure

We identified long-term BZ users by means of a computerised search for BZ prescriptions at 30 general practices with 55 GPs. Long-term users were selected on the basis of the following two criteria: (1) having received BZ prescriptions for at least 3 months, and (2) having received prescriptions in an amount sufficient for at least 60 days in the 3 months prior to this study.

Exclusion criteria were: current psychiatric treatment, current treatment for drug or alcohol dependence, psychosis in medical history, epilepsy, insufficient mastery of the Dutch language, or suffering from a terminal illness. Patients could also be excluded specifically on the GP's request because of severe comorbidity or for psychosocial reasons.

When patients met the definition of long-term use, their GP sent them a letter with the advice to quit their BZ use gradually.[17,18] Three months later they were invited to consult their GP to evaluate their current use status and the preceding period. The GP asked respondents to participate in the study. After full explanation of the study procedures, written informed consent was obtained from all participants.

A total of 317 patients enrolled in the study, of whom 28 dropped-out before the first assessment. The remaining 289 patients participated in the baseline interview; about 42% had quit their use since receiving the letter from their GP. Due to a delay in the development of the questionnaire, not all the patients could be given the BCQ at baseline. However, analysis showed that there were no significant differences between the patients who received the BCQ at baseline (BCQ group, n = 193) and the patients who had not received the BCQ at baseline (n = 82), or had received the BCQ, but had missing BCQ values (n = 14).

Measures

During the baseline interview data were gathered on BZ use and socio-demographic characteristics. In addition to the BCQ, the following questionnaires were administered: an 18-item self-report questionnaire to measure the extent of problem drinking (alcohol users only);[19] the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ2), a 20-item self-report questionnaire to assess BZ withdrawal symptoms during discontinuation;[20,21] the Benzodiazepine Dependence Self-Report Questionnaire (Bendep-SRQ), a 20-item self-report questionnaire, consisting of four Rasch homogeneous scales, to measure the severity of BZ dependence;[22] the Dutch Shortened MMPI (NVM) to assess personality traits;[23] the Profile of Mood States Dutch shortened version (POMS), a 32-item self-report questionnaire to measure five short-term changeable mood states;[24] and the General Health Questionnaire 12-item version (GHQ-12) to assess psychological well-being (sum score according to Goldberg).[25] All questionnaires show good reliability and validity. The BCQ was developed by our research group. Interviews were conducted by specially trained interviewers at the patients' homes.

BCQ

Item formulation

Items for the BCQ were generated to represent four distinct conceptualizations of drug urges, in line with Tiffany & Drobes[13]: (1) desire to use; (2) anticipation of positive outcome from BZ use; (3) anticipation of relief from withdrawal or withdrawal-associated negative affect; and (4) intention to use. A fifth category, 'lack of control over use', was derived from the Cocaine Craving Questionnaire (CCQ).[26] The QSU and CCQ are assumed to have satisfactory psychometric properties.[26]

The 50 items (32 from the QSU and 18 from the CCQ) were translated into Dutch and back into English to ensure correct translation. To obtain a good face validity, the items were judged by eight experts in the field of BZ research. Some adaptations were made to achieve clearer comprehension in Dutch and better application to BZ use. In the next phase, eight BZ users were asked to fill in the resulting questionnaire and comment on comprehensibility, ambiguity and recognition. Some items were altered subsequently or removed. The remaining 48 items constituted the initial BCQ. The order of statements in the BCQ was determined at random.

Format

At the top of the BCQ the interviewer noted the current date, current time and time and date of the patient's last BZ consumption. In the second section, patients completed the BCQ according to their current feeling, by indicating the extent to which they agreed or disagreed with each item on a seven-point Likert-type scale. The end points of the scale were labelled 'strongly disagree' (1) and 'strongly agree' (7).

Data analyses

All data analyses were conducted using SPSS 10.0.5 with the exception of the Rasch analyses, which were conducted using the Rasch Scaling Program (RSP).[27] Initial factor analyses were used to explore dimensionality. These were followed by Rasch analyses to test more strict assumptions.

Factor analysis

We performed exploratory factor analysis on our data using principle axis extraction for factor determination with the promax rotation method (power = 3), in line with Tiffany & Drobes.[13] To test the goodness-of-fit of the factor structure, we also performed a maximum likelihood factor analysis. We did not expect the five conceptualizations of craving to emerge as distinct factors in the factor analysis, because they have not done so in previous research.[13,26,28,29]

Rasch analysis

One important reason for using the Rasch model is that it is the only one in which a subject's sum score is a 'sufficient statistic' for the underlying unidimensional latent trait,[30] i.e. the sum score reflects all information that is contained in the item scores. Although in factor analysis sum scores are also used, different information is contained in the item scores, thereby obscuring the associations under investigation (e.g. population characteristics are well-known confounders of factor structures).

Furthermore, in questionnaire research continuous single peaked item characteristic curves (ICCs) may occur occasionally, which do not justify the use of sum scores.[31] Rasch homogeneity requires continuous strictly monotone increasing ICCs, a requirement which is accounted for in Rasch analysis.

A third assumption tested in Rasch analysis is local stochastic independence. The two questions 'Do you crave?' and 'Does it feel bad?', for example, are not local stochastic-independent, the latter depending on the former. In Rasch analysis, people who admit to an item indicating serious craving problems will also admit to the preceding 'less serious' items, so subjects can be ranked according to craving severity. This is another advantage over factor analysis.

Glas developed two statistical tests for the dichotomous Rasch model, known as R1 and R2.[32] The statistics R1 and R2 are especially sensitive to the property of equi-discriminability (R1) and to uni-dimensionality and local stochastic independence (R2). If R1 is not significant ($p > 0.01$), the null hypothesis that all the items have equal discriminative power cannot be rejected and equi-discriminability can be assumed. The same applies to R2. Rasch homogeneity is accepted if both R1 and R2 hold true. The respective values of R1 and R2 are dependent on the method that is used to estimate the subject and item parameters. In this paper the method of Conditional Maximum Likelihood (CML) was used.

Scale discriminability/reliability

In order to estimate the reliability of the BCQ, subject discriminability and item discriminability were assessed. To test subject discriminability (internal consistency) the Kuder–Richardson-20 coefficient (KR-20) was computed. The KR-20 is the equivalent of Cronbach's alpha for dichotomous items. The size of the KR-20 reflects the reliability of the scale.

Item discriminability was tested by Cochran's *Q*-test. The item discriminability coefficient (IDC, described first by Kan et al.[22]) was computed to show the extent to which the differences between items are systematic.

Validity

In order to determine the validity of the BCQ, construct and discriminative validity were assessed. To establish construct validity sum scores of the BCQ were associated with BWSQ2, Dutch Shortened MMPI, Bendep-SRQ, GHQ-12, POMS and nicotine, alcohol and coffee consumption.

The discriminative validity was investigated by assessing associations of the BCQ with current use of or abstinence from BZs.

RESULTS

Socio-demographic features and pattern of BZ use

Table 1 shows the socio-demographic characteristics and mean values for BZ dose and duration of use in the total BCQ sample.

The majority of patients were elderly, female, married, had a secondary education level and were living on a pension. Compared to the men in our population, the women were significantly more often (χ^2, $p < 0.05$) divorced or widowed, living alone, living on their partner's income or on a pension and more often had a primary education level. Men used alcohol more often (χ^2, $p = 0.02$), on average consumed more units per day (Mann–Whitney *U*, $p = 0.003$) and were more often classified as problem drinkers (χ^2, $p = 0.004$).

On average, BZ dosage did not exceed the therapeutic dosage recommended by the World Health Organization (WHO). Patients had been using BZs from a duration of 4 months up to a maximum of 33 years and 99.5% of the patients for a duration of 6 months or longer. Concerning BZ dependence, based on the Bendep-SRQ subscale scores,[33] the average severity of BZ dependence in our population was low. At the time of the interview, 41.5% of the total BCQ group ($n = 80$) had quit their use in the 3 months after receiving the letter from their GP.

Table 1 Subject characteristics of the BCQ sample

	Total BCQ sample	(n = 193)
	n/mean	%/SD
Background characteristics		
Age, mean (SD) years	62.9	12.0
Female	131	67.9%
Marital status		
No relationship	13	6.7%
Steady relationship (incl. married)	127	65.8%
Divorced	10	5.2%
Widowed	43	22.3%
Living alone	61	31.6%
Highest level of education		
Primary level	61	31.6%
Secondary level	123	63.7%
Advanced	9	4.7%
Financial income		
Income by profession	27	14.0%
Unemployment benefit	9	4.7%
Disability benefit	27	14.0%
Pension	90	46.6%
Partner's income	26	13.5%
Otherwise	14	7.3%
Smoking		
Smoking (cigarettes/cigars/pipe)	80	41.5%
Mean (SD) cigarettes/day among cigarette smokers (*n* = 79)	16.5	10.9
Alcohol use		
Drinking alcohol	98	50.8%
Mean (SD) units/week among drinkers	9.6	8.4
Problem drinkers among drinkers[a]	16	16.3%
Coffee use		
Coffee users	130	67.4%
Mean (SD) units/day among coffee users	4.4	2.8
Benzodiazepine use		
Quit after letter with advice to quit BZ use	80	41.5%
Daily dosage, mean (SD) in mg diazepam equivalents	6.9	8.1
Quartiles	2.9 - 5.0 - 7.8	
Duration of use, mean (SD) in months[b]	129.9	108.2
Quartiles	48.0 - 96.0 – 186.0	
Benzodiazepine dependence[c], mean (SD) total score		
Problematic use (*n* = 191)	1.2	1.2
Preoccupation (*n* = 192)	1.4	1.6
Compliance (*n* = 192)	0.3	0.7
Withdrawal (*n* = 178)	1.1	1.6

[a] Score ≥ 3 on Cornel Questionnaire[19]

[b] Based on patients who quit and did not quit in the previous three months.

[c] Based on the Bendep-SRQ[33]

Scalability

Visual inspection of the data and feedback from the interviewers indicated that many patients misinterpreted the reverse-keyed items as the opposite of their intended meaning, or simply did not understand these items. These items were left out of the analyses; 32 items remained.

Factor analysis

Principal axis factor analysis with the promax rotation method as conducted by Tiffany & Drobes[13] on the QSU data revealed six factors with eigen values greater than 1. The first factor accounted for 47.8% of the item variance and the remainder for a total of 19.6%, which suggested one main factor in our data. Kaiser–Meyer–Olkin measure of sampling adequacy was high (0.92), which indicated that our data were suitable for factor analysis. However, when we tried to confirm these one and six factor solutions with the aid of the maximum likelihood factor analysis, no factor solution with a non-significant goodness-of-fit test was found: all χ^2 df ratios were greater than 2. Goodness-of-fit was also significant for maximum likelihood factor analysis with eigen values greater than 1. These findings appeared to be caused by skewed data. Consequently, further interpretation of factor analysis data was not considered appropriate.

Rasch analysis

Data inspection showed that six patients had given mainly the same answer to all the items. They were omitted from the analyses, which left 187 patients. All items of the BCQ were dichotomized between option four and option five of the seven-point Likert scale. This procedure resulted in 59 subjects for Rasch analysis with non-zero variance. Investigating the dimensionality, initial analyses showed that several items made large contributions to R1 or R2, which disrupted the unidimensionality and local stochastic independence. These items were excluded from further Rasch analyses; final outcomes are shown in Table 2 for 20 items. The R1 and Q2 statistics were non-significant for all 20 items. (The Q2 statistic was used as an estimation of R2 due to the large number of items.) The results demonstrated that this 20-item BCQ meets the requirements for the Rasch model and can thus be considered a Rasch homogeneous scale. The English translation of the complete 20-item version of the BCQ, including the scale values for each item, is presented in the Appendix.

Reliability

Subject discriminability (internal consistency)

The KR-20 value was very high (0.94), which indicated that the BCQ has substantial differentiating power between patients.

Item discriminability

The high IDC value (0.86) and statistically significant results of Cochran's Q-test ($Q = 127.5$, $p < 0.001$) indicated good item discriminability.

Table 2 Test results of CML Rasch analysis on BCQ items by means of Rasch Scaling Program (RSP)[a]

Parameter	Value
No. of items in the scale	20
R1 (test statistic for equi-discriminability)	12.08
Degrees of freedom for R1	19
p-value R1	.8820
No. of subgroups formed by Rasch analysis	2
Q2 (test statistic for unidimensionality and local stochastic independence)	132.03
Degrees of freedom for Q2	approx. 170
p-value Q2	.9861
No. of patients remaining in the analysis	59

[a] Due to rounding-off error in the computational procedure of R2 using the original Rasch scores, the fit of the Rasch model is reported based on inverted Rasch scores (0 = 1 and 1 = 0). This inversion has no effect on the outcomes. The Q2 statistic was used as an estimation of R2 due to the large number of items.

Validity

Discriminative validity

The mean scores on the BCQ for the total population were low (mean = 1.2, SD = 3.2, median = 0.0). As reflected in Fig. 1a,b, patients who did not quit their BZ use after the letter from their GP (n = 113) scored significantly higher on the BCQ, i.e. experienced more severe craving, than patients who had quit (n = 80) (Mann–Whitney U = 3644.0, z = - 2.7, p = 0.006). Of the former group 40.7% (n = 46) reported craving to some extent, in contrast to 22.5% (n = 18) of the latter group. Patients still using BZ who experienced craving reported using significantly higher daily BZ dosages than patients who did not experience craving (9.3 mg (SD = 11.2) versus 5.2 mg (SD = 4.6) diazepam equivalents, p = 0.038).

With regard to the utility of the questionnaire we found eight items that distinguished bivariately current BZ users from patients who had recently quit their use with $p < 0.05$ (see Appendix items printed in bold). These items formed a reliable scale (KR-20 = 0.87) and yet covaried considerably with the non-discriminating items (r = 0.89). Not surprisingly, discriminative power was higher for these eight items (Mann–Whitney U = 3557.0, z = -3.6, p = 0.000). Apart from this, several individual items from the original 48-item version of the BCQ distinguished current BZ users from patients who had recently quit their use. These items did not constitute a scale; reliability was 0.58. Setting alpha to 0.001, three items remained: 'I could hardly feel better physically if I had taken a BZ' (χ^2 = 15.5, df = 1), 'Starting now, I could go without a BZ for a long time' (χ^2 = 42.1, df = 1), and 'If I took a BZ right now, I would hardly sleep better' (χ^2 = 18.3, df = 1). Patients who had recently quit their use scored higher on the single items than patients still using BZs, reflecting a higher perceived control to do without BZs. Only 'Starting now, I could go without a BZ for a long time' correlated significantly with the eight-item subscale (r = 0.21, $p < 0.01$).

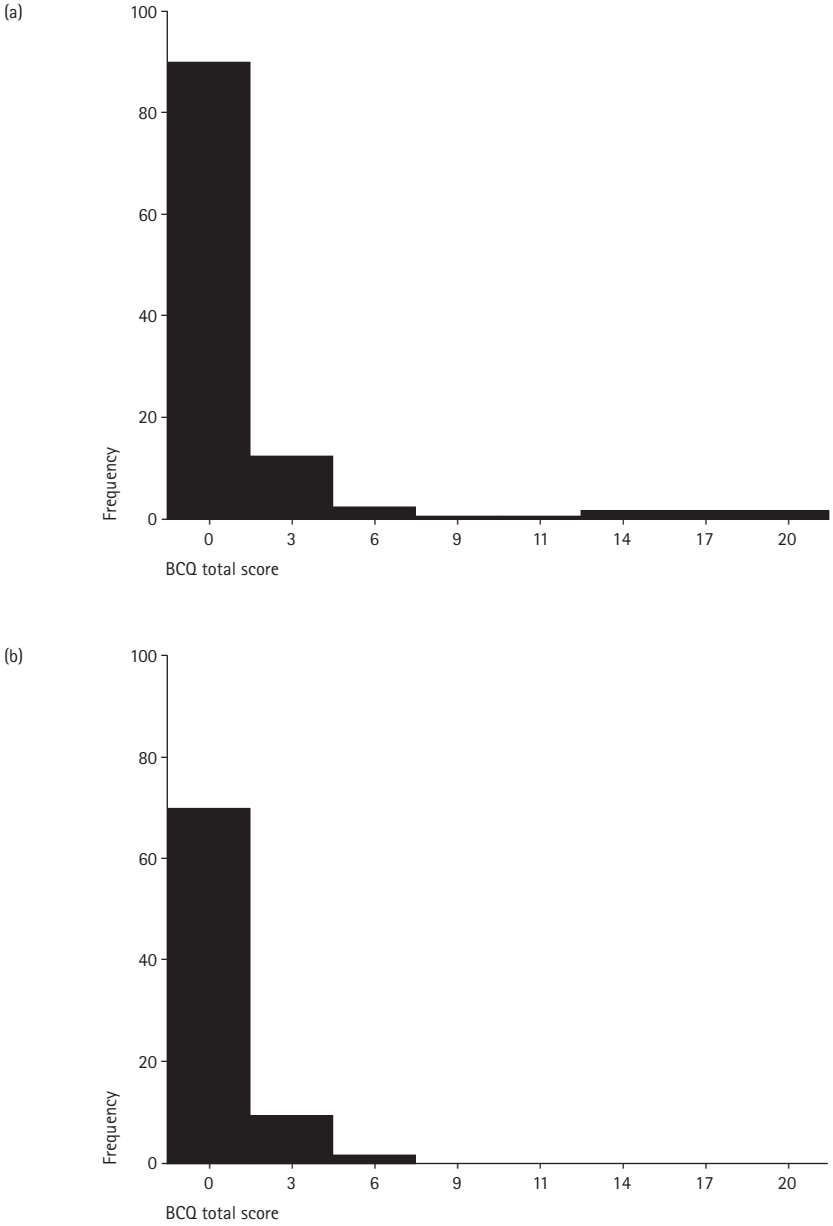

Figure 1 (a) Histogram of BCQ total scores for patients who had not quit their BZ use (n = 113; mean = 1.7; SD = 4.1; median = 0.0); (b) Histogram of BCQ total scores for patients who quit their BZ use (n = 80; mean = 0.5; SD = 1.0; median = 0.0)

Construct validity

In general the associations of the BCQ-scores with measures of related constructs were low (see Table 3). Highest significant associations were found with depression, negativism, GHQ-12 sum score, somatisation, preoccupation and withdrawal symptoms. The subset of eight items discriminating between BZ users and patients who had recently quit their use showed a significant association with anger, an increased association with preoccupation and withdrawal symptoms, and decreased associations with GHQ-12 sum score, negativism and depression. The two single items 'Starting now, I could go without a BZ for a long time' and 'If I took a BZ right now, I would hardly sleep better' were negatively associated with dependence measures (both items) and psychopathology ('..., I could go without a BZ for a long time' only).

Table 3 Associations between BZ craving and related constructs (Kendall's Tau-c)

Scale	A	B	C	D	E
BWSQ2 sum score	**.11**	**.12**	.02	**-.20**	.09
Bendep-SRQ					
Problematic use	.08	.10	-.11	**-.24**	**-.22**
Preoccupation	**.13**	**.18**	-.11	**-.36**	**-.23**
Lack of Compliance	.04	.05	.00	-.10	-.04
Dutch Shortened MMPI					
Negativism	**.14**	**.11**	.04	-.14	.01
Somatisation	**.13**	**.13**	-.09	-.17	-.03
Shyness	.07	.05	.04	-.13	.04
Psychopathology	.09	.08	.01	**-.21**	.08
Extraversion	.06	.03	.04	.10	.04
GHQ-12 sum score (Goldberg)	**.13**	**.12**	-.05	-.19	-.09
POMS					
Depression	**.15**	**.12**	-.07	-.19	.10
Anger	.10	**.11**	.03	-.15	.08
Fatigue	.11	.08	.03	.00	.15
Vigour	-.05	.00	.14	.06	-.05
Tension	.11	.11	-.05	-.17	.08
Coffee use	-.08	-.08	.00	-.00	-.14
Nicotine use	.01	.05	-.09	-.00	.02
Alcohol use	-.09	-.06	-.07	-.00	.04

Digits in bold represent $p < 0.01$

A = 20-item BCQ Rasch homogeneous scale. B = 8-item Rasch homogeneous subscale, distinguishing current BZ users from patients who had recently quit their use. C-E = single non-Rasch homogeneous items, distinguishing current BZ users and patients who had recently quit their use. C: 'I could hardly feel better physically if I had taken a BZ'; D: 'Starting now, I could go without a BZ for a long time'; E: 'If I took a BZ right now, I would hardly sleep better'.

DISCUSSION

To our knowledge, the BCQ is the first multi-item instrument that has been developed to assess BZ craving. In contrast with most existing craving measures for other substances,

the psychometric properties of the BCQ have been assessed in detail. The main findings of our study were:

1 The 20-item BCQ met the criteria for Rasch homogeneity and thus the items could be ranked according to 'craving intensity' on a unidimensional scale. This means that people who admit to an item indicating serious craving problems will also admit to the preceding 'less serious' items, i.e. the BCQ measures the extent to which people crave BZs. The sum score of the BCQ was a sufficient statistic of the underlying dimension, i.e. craving.
2 The BCQ proved to have good reliability. Construct validity, however, did not turn out as we had expected. Given the unidimensionality of the BCQ, it is possible that obsession with respect to the availability of BZs constitutes only a minor part of the craving dimension. Using a subset of items could increase the discriminative validity, maintaining sufficient reliability and validity.

Our finding that craving is a unidimensional construct indicates that craving can be defined as a continuum from (almost) none to very high. Although the 20-item BCQ appeared to be unidimensional, it contains items from the five conceptual craving categories: desire to use, anticipation of positive outcome, relief of withdrawal or (withdrawal-associated) negative affect, intention to use and lack of control. Roughly speaking, the items most commonly admitted to by the respondents were from the categories anticipation of positive outcome and anticipation of relief from withdrawal or negative affect. These items are located at the lower end of the Rasch rank order and reflect a moderate extent of BZ craving. This suggests that all subjects who experience craving expect BZs to modulate their emotions, suggesting cognitive reflection upon its effects. The items admitted to by the patients only with the most severe craving were from the categories intention to use, desire to use and lack of control. This suggests that in addition to the cognitive character high craving is explicitly goal-orientated.

Our study had several limitations. Differences in patients, item sets, language and substance may have contributed to the disparity between the results of the three studies (CCQ, QSU and BCQ). The BCQ sample consisted of long-term BZ users who had either quit their use recently or had failed to do so, but still appeared motivated to quit, as concluded from their willingness to visit their GP. The smokers and cocaine users studied by Tiffany & Drobes[13] and Tiffany et al.[26] were not selected on the intention to quit.

Although the items in the BCQ were similar to those in the QSU and CCQ, translation and modification of the items from the latter questionnaires resulted in a somewhat different item pool. Concerning the item formulation, we do not have an explanation for the misinterpretation of the reverse-keyed items. Sweeney, Pillitteri & Kozlowski explored the effect of item wording on responses to the QSU by Tiffany and colleagues.[34] Some negatively worded statements proved to be especially troublesome for their respondents. However, they could not detect any consistent patterns in their results that would provide an explanation either. Therefore, although the initial purpose of reverse-keyed items was to prevent response tendencies, we suggest for future research to avoid this methodology.

The fact that Tiffany & Drobes[13], Tiffany et al.[26] and Love et al.[12] did not use confirmatory factor analyses to test their factor models means that a unidimensional description of craving may also apply to other substances. They did find, however, that first-order nicotine, cocaine and alcohol craving factors all loaded strongly on single, second-order factors. Further evidence to suggest that craving (its structure) is roughly the same for all substances was reported by Bohn et al.[28] They developed the 49-item Questionnaire of Alcohol Urges (QAU), which was a preliminary version of the eight-item Alcohol Urge Questionnaire (AUQ) and based partly on the CCQ and QSU of Tiffany and colleagues. They found a reasonably good fit with a single-factor structure. The highest loading items of the QAU came from the categories that reflected high craving as measured by the BCQ (desire, lack of control), although used methods are incomparable.

Clearly, good psychometric characteristics may be considered only a basic requirement for usefulness of an instrument. Conclusions with respect to the predictive validity of the BCQ and its use in clinical practice (e.g. the ability to measure changes in craving) and scientific research cannot be made on the basis of the present cross-sectional data. Further research is needed to reveal the utility of the BCQ in terms of its contribution to the understanding of BZ dependence and the effectiveness of interventions. Follow-up data gathered at different stages of BZ reduction in our study may provide more insight in these matters.

As for clinical interpretation of the BCQ scores, the majority of patients hardly experience any craving at all, either while still using or after having quit. A tentative explanation for this low prevalence of craving may be that most BZs act slowly and have long half-lives. Upon cessation of quick- and short-acting stimulants, such as cocaine or nicotine, craving is reported to a much higher extent (e.g. [35-37]). Notwithstanding the above, the most reported (low) craving for BZs does seem to be dominated by outcome expectancies (anticipation of positive outcome and anticipation of relief from withdrawal or negative affect), whereas in a minority of patients who experience high craving it is characterized by lack of control, and intention and desire to use. Possibly, there is a subgroup of BZ users that is more sensitive to the craving inducing effects of BZs than others.

Concerning the discriminative power of the subset of eight items, which stem from the lower and middle regions of craving severity, the power of this study is too low for the high craving items to discriminate between BZ users and patients who had recently quit their use, given the low percentages of affirmative answers. From the construct validity analysis it appears that the subset of eight items refers more to preoccupation and less to negativism and depression. However, this conclusion may be premature with the differences being so small. Although the three single discriminating items do not constitute a scale, they seem to refer to a construct opposite to craving, comparable to behavioural control (e.g. [38]). This is reflected by negative associations with dependence and psychopathology. However, we should keep in mind the remarks by Sweeney et al. about possible misinterpretation of negatively worded statements.[34]

Cross-validation data may reveal these and other differences in experienced craving severity between general practice BZ users and BZ users from other settings.

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APPENDIX

Rasch-homogeneous BCQ items[c] with Rasch scale value estimates, standard errors, questionnaire of origin (QSU or CCQ) and item category of origin, and item number, placed in order of level of craving (high to low)

Item	B	SE(B)	Q/C, Cat	Item no.
I would hardly be able to stop myself from taking a BZ if I had some here now	-1.391	.690	C,5[a]	7
I crave a BZ right now	-.969	.617	Q,1	5
I must take a BZ now	-.969	.617	Q,1[a]	6
If I were offered a BZ, I would take it immediately	-.969	.617	Q,4	12
All I want right now is a BZ	-.969	.617	Q,1	17
I am going to take a BZ as soon as possible	**-.969**	**.617**	**Q,4**	**18**
I will take a BZ as soon as I get the chance	**-.969**	**.617**	**Q,4**	**20**
I would do almost anything for a BZ now	-.617	.559	Q,4	3
Nothing would be better than taking a BZ right now	-.617	.559	Q,2	9
I want to take a BZ now	**-.318**	**.514**	**Q,1[a]**	**13**
Right now I have an urgent need to take a BZ	**-.062**	**.478**	**Q,1[a]**	**11**
I would enjoy a BZ right now	**-.062**	**.478**	**Q,2[a]**	**15**
I would hardly be able to control how many BZ I took if I had some here	.357	.425	C,5[a]	4
If I took a BZ right now I would feel less inhibited	.691	.389	2[b]	16
I could control things better right now if I could take a BZ	**.835**	**.375**	**Q,3**	**14**
I would feel energetic if I took a BZ	**.835**	**.375**	**C,2**	**19**
I am missing my BZs right now	1.093	.353	Q,1[a]	2
Taking BZ right now would make me feel less tired	1.093	.353	Q,3	8
Taking a BZ would make me feel very good right now	**1.950**	**.301**	**Q,2**	**1**
Taking a BZ would make me feel less depressed	2.027	.297	Q,3	10

[a] Items 2, 13 and 15 were originally reverse-keyed items; items 4 and 7 were originally negatively worded items; items 6 and 11 were rephrased for clearer comprehension in Dutch.

[b] Item 16 was completely adapted for BZs, not present in QSU nor in CCQ.

[c] Respondents were instructed to substitute their specific benzodiazepine(s) for 'BZ'.

B: Rasch scale value estimate. Note that for purposes of analyses high values indicate low craving.

SE: standard error of the Rasch scale value estimate B.

Q/C: Q = item originated from Questionnaire on Smoking Urges; C = item originated from Cocaine Craving Questionnaire.

Cat: 1 = desire to use; 2 = anticipation of positive outcome; 3 = relief of withdrawal or negative affect; 4 = intention to use; 5 = lack of control.

Items printed in bold were univariately associated with abstinence/current use.

Chapter 3

Associations of benzodiazepine craving with other clinical variables in a population of general practice patients

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ABSTRACT

Background – The aim of this study was to (1) describe the characteristics of patients reporting craving for benzodiazepines (BZs) and (2) to search for associations between BZ craving and other clinical variables in a population of general practice (GP) patients who have made an attempt to discontinue their long-term BZ use.
Methods – The Benzodiazepine Craving Questionnaire (BCQ) and other self-report questionnaires were administered once to a population of 113 long-term and 80 former long-term GP BZ users participating in a large BZ reduction trial in GP. Cross-sectional data were gathered on self-reported BZ craving (BCQ), self-reported BZ dependence severity (Bendep-SRQ), psychopathology (General Health Questionnaire 12-item version; Medical Outcome Study Short-Form 36-item version), mood state (Profile of Mood States), personality (Dutch shortened MMPI), and lifestyle characteristics. Differences between patients who reported craving and patients who did not were analyzed univariately. Multivariate analyses were performed on variables significantly associated with craving, controlling for current use status.
Results – (1) Patients reporting craving differed significantly from patients not reporting craving on aspects of BZ dependence severity, psychopathology, negative mood state, and personality. (2) Negative mood and somatization were positively associated with BZ craving, although only the contribution of negative mood to craving was statistically significant for the total group of (former) BZ users (p = .002).
Conclusions – Self-reported negative mood and somatization are positively associated with BZ craving. In future BZ craving research, personality factors should be further explored.

INTRODUCTION

Craving is a psychobiological phenomenon that is regarded as an important aspect of dependence. In International Statistical Classification of Diseases, 10th Revision, but not in Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, a 'strong desire or compulsion' to use a drug is one of the diagnostic criteria for dependence.[1,2]

Empirical research and psychological theories and models on craving tend to focus on craving for alcohol, nicotine, cocaine, and opiates. From a theoretical perspective, the occurrence of craving has been associated grossly with (a) dependence and drug-use aspects (i.e., aversive aspects of the drug-withdrawal syndrome and positive reinforcing drug effects), (b) mood states, and (c) cognitive labeling (i.e., craving representing the cognitive labeling of physiological processes) (e.g. Refs [3-6]). Each theoretical model provides a different conceptualization of craving, but none of these models provide a full explanation of the craving phenomenon, suggesting that multiple mechanisms may be involved.[4,7] Experiments to compare theories with one another have not been conducted yet.

From an empirical perspective, there is evidence, although sometimes inconsistent, that craving is associated with (a) personality factors, such as sensation seeking, impulsiveness, neuroticism, extraversion;[11] (b) (situation specific) mood states;[8,10] (c) dependence;[9,10] (d) psychopathology (such as a general negative affective state, i.e. depressive symptomatology).[12]

Despite the accumulating evidence for benzodiazepines (BZs) to cause dependence e.g.[13,14]), and the fact that they are widely prescribed in the Western world,[15] craving research on BZs has hardly been done (for a discussion, see Ref [16]). In an attempt to fill this gap, the 32-item Benzodiazepine Craving Questionnaire (BCQ), the first multi-item instrument to assess BZ craving, was developed recently. The BCQ was based on the Questionnaire on Smoking Urges and the Cocaine Craving Questionnaire.[17,18] It proved to be a reliable and valid Rasch homogeneous self-report craving measure in a general practice (GP) population of long-term BZ users.[16]

The goal of the present study is (1) to expand our knowledge on BZ craving, that is, to describe the characteristics of patients experiencing BZ craving and to describe which subject-related variables were associated with BZ craving in a population of GP patients who recently discontinued their long-term BZ use or failed to do so. (2) We seek to determine to what length our data would support existing craving theories and empirical findings on craving occurrence. We used the BCQ as the measure for BZ craving. Based on associations frequently found with craving in other substances, associations with variables from the following domains were investigated with both univariate and multivariate approaches: BZ dependence (severity), psychopathology, mood state, personality, and lifestyle.

METHODS

Setting

Patients from a large study on the efficacy of a 2-part treatment intervention that aimed to reduce long-term BZ use in GP in the Netherlands completed a number of questionnaires.[19,20] The study was carried out between August 1998 and December 2001. Patients' responses to the BCQ at first assessment (baseline interview) formed the basis of the present study.

Subjects and procedure

We identified long-term BZ users (i.e., use for more than 3 months) by means of a computerized search for BZ prescriptions at 30 general practices with 55 GPs and a total of about 118000 patients. 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 a terminal illness. Furthermore, patients could be excluded specifically on the GPs request, because of severe comorbidity or for psychosocial reasons. Patients who met the definition of long-term use (n = 2004) were sent a letter by their GP with the advice to discontinue their BZ use gradually.[19,21] Three months later, they were invited to consult their GP to evaluate their current BZ use status and the preceding period. At this consultation, the GP asked the respondents (n = 1321) to participate in the study. After full explanation of the study procedures, 317 patients provided written informed consent to participate in the study.

Sample size

Of the 317 patients who enrolled in the study, 28 patients dropped out before the first assessment. The remaining 289 patients participated in the baseline interview. Not all the patients could be given the BCQ at baseline, because of a delay in the development of the questionnaire. However, analysis showed that there were no significant differences between the patients who received the BCQ at baseline (n = 193) and the patients who had not received the BCQ (n = 82) or had received the BCQ but had missing BCQ values (n = 14). At the time of the interview, about 42% of the patients who received the BCQ at baseline had discontinued their use in the 3 months after receiving the letter from their GP (80/193).

Measures

During the baseline interview, the BCQ was administered.[16] Information on lifestyle was obtained: sociodemographic characteristics, nicotine, alcohol and caffeine use, and data from a questionnaire measuring the extent of problem drinking (alcohol users only).[22] Dependence characteristics were obtained assessing BZ use features, severity of BZ dependence (Bendep-SRQ),[23,24] and BZ withdrawal symptoms during discontinuation (BWSQ2).[25,26] We used the Dutch shortened MMPI (NVM) to assess personality traits: negativism, somatization, shyness, psychopathology, and extraversion,[27] and the Profile of Mood States (POMS) Dutch shortened version, to measure 5 short-term changeable mood

states (depression, anger, fatigue, vigor, and tension).[28] Presence and severity of psychopathology were assessed with the General Health Questionnaire 12-item version (GHQ-12), a measure of psychological well-being,[29] and the Medical Outcome Study Short-Form 36-item version (MOS SF-36), a measure of health-related quality of life on 8 different health domains (physical functioning, role functioning - physical problem, role functioning - emotional problem, vitality, mental health, social functioning, pain, and general health).[30] All questionnaires were multi-item, self-report scales with satisfactory reliability and validity. Specially trained interviewers interviewed the patients at their homes

Data analyses

All data analyses were done using SPSS 10.0.5 (SPSS Inc, Chicago, Ill). To analyze differences on independent variables between patients who reported craving and patients who did not, we used Pearson χ^2 test and Mann-Whitney *U* test. After controlling for potential interaction effects of current use status via bivariate logistic regression analysis, variables still significantly associated with craving were entered into a multivariate logistic regression analysis using forward and backward elimination procedures, with craving yes/no as the dependent variable. For explorative purposes, all *p*-values were initially set at .05. For the final multivariate tests, α was set to .003, correcting for multiple testing (Bonferroni correction).

RESULTS

Characteristics of the study participants

Table 1 shows the characteristics of the study participants who received the BCQ at baseline. The majority of patients were elderly, female, married, had a secondary-education level, and were living on a pension. About half of the patients used alcohol and/or nicotine, and the majority used caffeine. On average, BZ dosage did not exceed the therapeutic dosage recommended by the World Health Organization. Given the skewed distribution of the craving data, momentary craving for BZs was coded as a dichotomous variable: 0 if a patient reported no craving for BZs at all, and 1 if any craving for BZs was present. About 33% of the patients indicated experiencing craving to some extent.

However, the average BCQ score (i.e., the average craving severity) was low. Scores on the withdrawal symptoms questionnaire were lower than those found by Tyrer et al[25] in a population of putative pharmacological dependent patients. The overall average severity of BZ dependence in our population was low. Based on the norm scores of the Dutch Shortened MMPI for the general Dutch population, our patients scored high on somatization, above average on shyness, and below average on extraversion. Patients rated their overall health-related well-being or functioning about 10 to 20 points lower than the averages of the Dutch population.[31] Based on a cutoff rate of two third on the GHQ-12, 26% of the patients could be classified as 'psychiatric cases'.[32] As for the POMS

subscales, the proportion of patients in the fifth quintile was 40% for depression, 25% for anger, 36% for fatigue, 28% for having no vigor, and 29% for tension, based on the sex-adjusted norm scores for the Dutch population.[28]

Table 1 Subject characteristics of the BCQ population

	Total group (n = 193)	
	n/mean	%/SD
Background and lifestyle characteristics		
Female	131	67.9%
Age, mean (SD) in years	62.9	12.0
Marital status		
No relationship	13	6.7%
Steady relationship (including married)	127	65.8%
Divorced	10	5.2%
Widowed	43	22.3%
Living alone	61	31.6%
Highest level of education		
Primary level	61	31.6%
Secondary level	123	63.7%
Advanced	9	4.7%
Financial income		
Income by profession	27	14.0%
Benefit (unemployment or disability)	36	18.7%
Pension	90	46.6%
Partner's income	26	13.5%
Otherwise	14	7.3%
Nicotine use		
Nicotine users	80	41.5%
Mean (SD) cigarettes per day among cigarette smokers (n = 79)	16.5	10.9
Alcohol use		
Drinking alcohol	98	50.8%
Mean (SD) units per week among drinkers	9.6	8.4
Problem drinkers among drinkers[a]	16	16.3%
Cornel score (n = 98), mean (SD) total score	1.0	1.7
Caffeine use		
Caffeine users	130	67.4%
Mean (SD) units per day among caffeine users	4.4	2.8
Benzodiazepine use		
Duration, mean (SD) in months[b]	129.9	108.2
Daily dosage at assessment, mean (SD) in mg diazepam equivalents[c]	6.9	8.1
Daily dosage previous 3 months, mean (SD) mg diazepam equivalents[d]	6.7	6.9
Discontinued after letter from GP with advice to discontinue BZ use	80	41.5%
Craving		
Craving severity (BCQ), mean (SD) total score	1.2	3.2
No craving (total score = 0)	129	66.8%
Craving (total score > 0)	64	33.2%
Dependence characteristics		
Withdrawal symptoms (BWSQ2) (n = 191), mean (SD) total score	6.1	6.7
BZ dependence severity (Bendep-SRQ), mean (SD) total score		
Problematic use (n = 191)	1.2	1.2
Preoccupation (n = 192)	1.4	1.6
Lack of compliance (n = 192)	0.3	0.7
Withdrawal (n = 178)	1.1	1.6

Table continues on the next page

Table 1 continued	n/mean	%/SD
Personality characteristics		
Dutch Shortened MMPI (NVM), mean (SD) total score		
Negativism	12.2	7.5
Somatization	14.0	7.8
Shyness	10.5	7.1
Psychopathology	2.9	3.1
Extraversion	13.2	5.6
Psychopathology		
Psychological wellbeing (GHQ-12, Goldberg), mean (SD) total score (n = 192)	2.0	3.1
Health related quality of life (MOS SF-36), mean (SD) (range 0 - 100)		
Physical functioning	68	26
Role functioning – physical problem (n = 192)	60	41
Pain	64	25
General health perception	58	22
Vitality	58	23
Social functioning	66	21
Role functioning - emotional problem	69	40
Mental health	68	19
Mood state		
Short-term changeable mood states (POMS), mean (SD) total score		
Depression	12.8	6.2
Anger	11.0	5.1
Fatigue	12.2	5.9
Vigour	15.0	4.7
Tension	11.8	5.5

[a] Score ≥ 3 on Cornel Questionnaire.[22]

[b] Based on patients who discontinued and did not discontinue their BZ use in the previous 3 months.

[c] Current BZ users only.

[d] Based on recorded consumption extracted from the GP's clinical database.

Associations with BZ craving

The Bendep-SRQ subscale withdrawal was left out of the analyses because patients only filled in the withdrawal section of the Bendep-SRQ if they had ever discontinued or attempted to discontinue their BZ use in the past.

As many as 16 variables were found to be significantly correlated with craving in univariate analyses at $p < .05$. In the group that reported craving for BZs (n = 64), significantly fewer patients had discontinued their BZ use in the 3 months after receiving the letter from their GP than in the group that did not report craving (n = 129). Craving was reported by 22.5% (18/80) of the patients who had discontinued their use vs 40.7% (46/113) of those who had not. Of all patients who experienced craving, 71.8% (46/64) were still using BZs compared with 51.9% (67/129) of all patients who did not experience craving (see Table 2A). With respect to the subgroup that failed to discontinue its use (n = 113), patients reporting craving used BZs in significantly higher daily dosages than patients not reporting craving (see Table 2B).

Patients reporting craving scored significantly higher on the withdrawal symptoms

questionnaire and were significantly more often preoccupied with the availability of BZs. They also scored significantly higher on Dutch Shortened MMPI subscales negativism (respectively average vs below average as compared with the general Dutch population), somatization (very high vs high), and psychopathology (high vs average) than did patients who did not report craving. Patients reporting craving rated their health-related quality of life significantly lower on 4 of 8 subscales and about 15 to 30 points lower than the averages of the Dutch population. Thirty-nine percent of the patients reporting craving could be classified as 'psychiatric cases' vs 20% in the nonreporting group. Patients reporting craving scored significantly higher on POMS subscales depression, anger, fatigue, and tension. The proportions of patients in the fifth quintile were respectively 48% vs 36% for depression, 33% vs 21% for anger, 45% vs 31% for fatigue, and 39% vs 23% for tension (see Table 2B).

As about 42% of the population had discontinued their BZ use, which led to missing data on BZ dosage for these patients, mean daily BZ dosage was left out of further analyses. Patients who had discontinued BZ use and patients who were still using BZs differed significantly on BCQ sum scores. Therefore, it was important to rule out the potential interaction effect of current use status. Using bivariate logistic regression analyses, we did not detect an interaction effect. Subsequently, 8 variables were still significantly associated with craving (at $p < .05$ for explorative purposes) after correcting for current use status (see Table 2B).

These 8 variables were entered in a logistic regression analysis forward stepwise (Wald) procedure ($n = 192$) with craving yes/no as the dependent variable. Block I consisted of current use status (discontinued BZ use yes/no) and block II of the 8 variables. This analysis yielded 1 independent 'predictor': POMS depression (see Table 3A). We attempted to confirm this finding in a logistic regression analysis backward stepwise (Wald) procedure, with block I the current use status (discontinued BZ use yes/no) and block II the 8 variables. Two nonsignificant 'predictors' of craving were yielded: POMS subscale depression and Dutch Shortened MMPI subscale somatization (see Table 3B). After omitting depression from the list of variables and conducting another logistic regression forward stepwise (Wald) procedure analysis as described above, somatization remained as the sole significant 'predictor' of craving (see Table 3C). Reversed, after omitting somatization from the list of variables, depression remained as the sole 'predictor' of craving (see Table 3D).

Further analysis revealed a high and significant correlation between depression and somatization (Pearson = 0.51, $p < .001$). As the influence of block I current use status was not significant at $\alpha = .003$, we cannot pronounce upon its influence on depression, respectively, somatization, and craving.

Table 2A 2 × 2 table of results for craving yes/no and benzodiazepine use yes/no

n = 193			Benzodiazepine use		
			No	Yes	
Craving	**No**	n	62	67	*n* = 129
		Row %	48.1	51.9	
		Column %	77.5	59.3	
		Table %	32.1	34.7	
	Yes	n	18	46	*n* = 64
		Row %	28.1	71.9	
		Column %	22.5	40.7	
		Table %	9.3	23.8	
			n = 80	*n* = 113	

Table 2B Differences between patients reporting craving ('cravers') and patients not reporting craving ('noncravers')

	'noncravers' (n = 129)		'cravers' (n = 64)		
	n/mean	%/SD	n/mean	%/SD	significance
Benzodiazepine use					
Discontinued BZ use after letter from GP	62	48.1%	18	28.1%	Pearson = 7.006, *df* = 1 *p* = .008
Daily dosage, mean (SD) mg diazepam equiv. (*n* = 67 vs. *n* = 46)[a]	5.2	4.6	9.3	11.2	*z* = -2.075 *p* = .038[b]
Dependence characteristics					
BWSQ2 mean (SD) total score (*n* = 128 vs *n* = 63)	5.4	6.3	7.5	7.2	*z* = -2.200 *p* = .028
Bendep-SRQ, mean (SD) total score					
Preoccupation (*n* = 128 vs *n* = 63)	1.2	1.5	1.8	1.7	*z* = -2.491 *p* = .013
Withdrawal (*n* = 117 vs *n* = 61)[b]	.8	1.5	1.7	1.7	
Personality characteristics					
Dutch Shortened MMPI, mean (SD) total score					
Negativism	11.1	6.8	14.3	8.5	*z* = -2.598 *p* = .009[c]
Somatization	12.7	7.0	16.6	8.7	*z* = -2.906 *p* = .004[c]
Psychopathology	2.6	2.8	3.6	3.6	*z* = -2.053 *p* = .040
Psychopathology					
GHQ-12, mean (SD) total score (*n* = 128 vs *n* = 64)	1.6	2.9	2.8	3.5	*z* = -2.799 *p* = .005[c]
MOS SF-36, mean (SD) (range 0 – 100)					
General health perception	60	21	54	21	*z* = -2.064 *p* = .039
Social functioning	68	20	60	22	*z* = -2.438 *p* = .015[c]
Role functioning - emotional problem	73	38	60	42	*z* = -2.209 *p* = .027[c]
Mental health	71	19	63	19	*z* = -3.406 *p* = .001[c]
Mood state					
POMS, mean (SD) total score					
Depression	11.7	5.2	14.9	7.3	*z* = -3.143 *p* = .002[c]
Anger	10.3	4.5	12.3	6.0	*z* = -2.156 *p* = .031[c]
Fatigue	11.6	5.8	13.4	6.0	*z* = -2.372 *p* = .018
Tension	11.2	5.2	13.1	5.9	*z* = -2.086 *p* = .037

[a] Current BZ users only.

[b] Left out of the analyses because of missing data and potential selection bias.

[c] These variables remained significant at p = .05 after correcting for current use status.

Table 3A Logistic regression forward stepwise (Wald) method

N = 192		Wald	df	Sig.	Exp(B)	95% CI for Exp(B)
Block 1	current use status	4.938	1	0.026	2.121	[1.093 – 4.118]
Block 2	depression	9.350	1	0.002	1.086	[1.030 – 1.144]
Step χ^2 = 10.1; *df* = 1; *p* = .001						
Block χ^2 = 10.1; *df* = 1; *p* = .001						
Model χ^2 = 17.5; *df* = 2; *p* < .001						

Table 3B Logistic regression backward stepwise (Wald) method

N = 192		Wald	df	Sig.	Exp(B)	95% CI for Exp(B)
Block 1	current use status	4.529	1	0.033	2.066	[1.059 – 4.029]
Block 2	somatization	3.015	1	0.082	1.042	[0.995 – 1.091]
	depression	3.643	1	0.056	1.059	[0.998 – 1.124]
Step 7:						
Step χ^2 = -1.2; *df* = 1; *p* = .268						
Block χ^2 = 13.1; *df* = 2; *p* = .001						
Model χ^2 = 20.6; *df* = 3; *p* < .001						

Table 3C Logistic regression forward stepwise (Wald) method without depression

N = 192		Wald	df	Sig.	Exp(B)	95% CI for Exp(B)
Block 1	current use status	5.252	1	0.022	2.168	[1.118 – 4.201]
Block 2	somatization	8.933	1	0.003	1.064	[1.022 – 1.108]
Step χ^2 = 9.4; *df* = 1; *p* = .002						
Block χ^2 = 9.4; *df* = 1; *p* = .002						
Model χ^2 = 16.8; *df* = 2; *p* < .001						

Table 3D Logistic regression forward stepwise (Wald) method without somatization

N = 192		Wald	df	Sig.	Exp(B)	95% CI for Exp(B)
Block 1	current use status	4.938	1	0.026	2.121	[1.093 – 4.118]
Block 2	depression	9.350	1	0.002	1.086	[1.030 – 1.144]
Step χ^2 = 10.1; *df* = 1; *p* = .001						
Block χ^2 = 10.1; *df* = 1; *p* = .001						
Model χ^2 = 17.5; *df* = 2; *p* < .001						

DISCUSSION

To the best of our knowledge, this is the first study in which the characteristics of a population of (former) BZ users reporting BZ craving are described. It is also the first study in which clinical variables associated with BZ craving are identified on the basis of cross-sectional data, gathered through self-report questionnaires in a GP population.

We found that patients who reported craving differed from patients who did not on aspects of 4 of the 5 examined domains (namely, BZ dependence, psychopathology, negative mood state, and personality). Patients reporting craving were worse off on all 4 domains. One apparent characteristic of patients reporting craving was the very high tendency to react to psychological strain with physical complaints (somatization) compared

with the general Dutch population. If patients had not discontinued their use in the previous 3 months, it was more likely that they reported craving at the time of the interview. Among patients who had not discontinued their BZ use and reported craving, the average BZ consumption at the time of the interview was higher than among patients who had not discontinued but did not report craving.

The second finding of this study was that self-reported depression and somatization, after correcting for BZ use status, were most strongly associated with BZ craving, although not statistically significant in the group as a whole. The fact that no single factor emerged appeared to be due to the high correlation between somatization, depression, and also current BZ use status. However, in the group as a whole, depression seemed to be the major contributor to BZ craving. This meant that patients with a negative mood going together with a feeling of personal inadequacy, unworthiness, and feelings of guilt have a higher chance in reporting craving and vice versa.

Our findings are in line with some laboratory and field studies that have looked at the influence of negative mood state on experienced craving and craving severity. For example, Litt et al[33] found that the presence of negative mood states alone appeared to be sufficient to elicit desire for alcohol in some subjects, regardless of other cues. Moreover, negative affect, both as a dispositional characteristic (e.g., neuroticism) and as a transient mood state, seems to play a key role in craving.[10]

In explanation of the relationship between somatization and BZ craving, we can turn to the cognitive labelling theories (e.g., Refs [34-36]), which are based on the cognition-arousal theory of emotion and applied to drug craving.[37] These theories state that craving represents the operation of an attributional process whereby physiological reactions are interpreted as desires to use the drug.[38] However, because of the absence of a formally developed cognitive labeling model of dependence, more specifically of craving, there are no published studies so far that directly test any predictions derived from such a model.[3]

We found a strong positive association between negative affect and somatization. Watson and Pennebaker[39] found negative affect to be associated with a broad range of subjective complaints, reflected in high scores on health complaint scales. One can hypothesize that patients with negative affect have an elevated bodily awareness, thus perceiving physical symptoms more quickly. In the case of BZ dependence or long-term use, patients may tend to focus on adverse bodily feelings and label them as a need for a BZ. Our study has stressed the need to specify the cognitive labeling model in craving research.

There are some limitations to our study. Because of a cross-sectional design, statements about causal relationships between craving and somatization or depression cannot be made. Future studies should make clear whether somatization and depression are predictors of BZ craving in longitudinal research. Secondly, a high score on the Dutch Shortened MMPI subscale somatization can be obtained when a patient has a somatic illness, without true somatization. Somatic comorbidity was not taken into account in this study. As the sum scores of the MOS SF-36 physical illness subscales are comparable for patients

experiencing craving and patients not experiencing craving, it is unlikely that the very high scores on somatization in patients who crave are primarily caused by physical illness. Thirdly, although we found somatization and depression as 2 joint associations with BZ craving, odds ratios are low, indicating modest relevance for clinical practice and some caution with respect to statements about applicability of existing craving theories and comparability to other studies. As our study took place in the patient's natural environment, it is difficult to compare our results to cue-reactivity studies that mainly took place in laboratories. Fourthly, the fact that craving could not be explained convincingly may be related to the fact that relatively few patients in our population reported BZ craving (33%) and that the average severity was low. This might be explained by some selection bias as patients experiencing higher craving and dependence on BZs may have refused to participate in the study. Possibly, more and more severe craving can be found in a (clinical) population with more (severe) affective complaints and lower physical and psychological well-being. On the other hand, the fact that all our patients expressed the wish to discontinue their BZ use makes it a clinically relevant population. Moreover, in contrast to some other studies that use single-item questionnaires or visual analogue scales with unknown psychometric properties to assess craving (e.g., Ref [10]), we used a multi-item Rasch homogeneous questionnaire with satisfactory psychometric properties.[16]

To conclude, our study has made a small but valuable contribution to filling the gap in BZ-craving research. As proposed by some researchers, personality may be seen as an important explanatory construct in many conceptualizations of craving and may account for individually different manifestations of craving.[7] Future research should be directed at concretizing this relationship between personality and BZ craving.

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Chapter 4

The absence of benzodiazepine craving in a general practice benzodiazepine discontinuation trial

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ABSTRACT

Aim – This study aimed to assess benzodiazepine craving longitudinally and to describe its time course by means of the Benzodiazepine Craving Questionnaire (BCQ).
Setting and participants – Subjects were long-term benzodiazepine users participating in a two-part treatment intervention aimed to reduce long-term benzodiazepine use in general practice in the Netherlands.
Measurements – Four repeated measurements of benzodiazepine craving were taken over a 21-month follow-up period.
Findings – Results indicated that (1) benzodiazepine craving severity decreased over time, (2) patients still using benzodiazepines experienced significantly more severe craving than patients who had quit their use after one of the two interventions, and (3) the way in which patients had attempted to quit did not influence the experienced craving severity over time, however, (4) patients who had received additional tapering off, on average, reported significantly more severe craving than patients who had only received a letter as an incentive to quit.
Conclusions – Although benzodiazepine craving is prevalent among (former) long-term benzodiazepine users during and after discontinuation, craving severity decreases over time to negligible proportions. Self-reported craving can be longitudinally monitored and quantified by means of the BCQ.

INTRODUCTION

'Craving' is often regarded as a central phenomenon related to substance dependence. In ICD-10, but not in DSM-IV, a 'strong desire or compulsion' to use a drug is one of the diagnostic criteria for dependence.[1,2] Craving has been proposed as a factor in maintaining continued use or relapse in substance-dependent subjects, although, study results have been ambiguous (e.g. [3-6]). In a cross-sectional study Bohn et al. found that the scores on the Alcohol Urge Questionnaire (AUQ) showed significant negative correlations with the duration of abstinence before completing the questionnaire, suggesting a decrease of craving over time in abstinent patients.[7] Nevertheless, subjects attempting to remain abstinent from drugs frequently complain about craving and describe it as having a disruptive effect on their daily functioning (e.g. [8] in cocaine abusers). Dependent subjects may continue to experience craving years after their last drug use (e.g. [8-10]) and regular substance users describe experiencing craving even when they are not attempting to abstain from drug use (e.g. [11,12]).

Also, other findings about the longitudinal course of craving are ambiguous. For example, Gawin and Kleber[8] and also Halikas et al.[13] found craving in cocaine users undergoing treatment as a phenomenon to be episodic, waxing and waning over time. Others have found relatively stable average craving scores over time. McMillan and Gilmore-Thomas, for example, asked opiate addicts on methadone maintenance not attempting to remain abstinent to rate their 24-h recall of peak craving scores, as measured with a visual analogue scale (VAS), on weekdays during a 4-week study period.[14] Although average craving scores over time were relatively stable, there were large individual differences in subjects' weekly scores and day-to-day variability within subjects was quite high for many subjects. Anton, Moak and Latham, on the other hand, found that all alcohol-dependent subgroups (abstinent, 'slip' drinking and relapse drinking) showed a reduction in scores on the Obsessive Compulsive Drinking Scale (OCDS), assessing the craving experience of the previous week during the course of a 12-week pharmacological and cognitive-behavioural treatment trial.[15] Although relapsed patients showed an increase in the OCDS scores after a period of improvement, scores did not return to baseline prestudy levels. Treatment may have allowed these patients to stabilise at a lower level of alcohol craving.[15] Weddington et al. also found statistically significant decreases in cocaine craving during short-term abstinence, as measured with VAS, in a 28-day study among male long-term cocaine-dependent subjects.[16] West, Hajek and Belcher have found similar results among abstinent smokers chewing nicotine gum.[17] The frequency of experiencing the urge to smoke was highest at 24 h and 1 week, and then declined over a 4-week period of abstinence. However, the average strength of urges did not decline until the fourth week.

Taking into account the various substances discussed, no clear picture emerges about the time course of craving, the association with various use patterns, or its relationship with different treatment modalities.

In benzodiazepine (BZ) research, studies on craving are scarce and have shown contradicting results about the occurrence of BZ craving. For example, Lucki, Volpicelli

and Schweizer found that treated chronic users of therapeutic doses of BZs after 3 months of abstinence expressed little craving for the drug.[18] Whereas, Linden, Bar and Geiselmann argued that the refusal of about two-thirds of their general practice patients with long-term low-dose BZ dependence to accept a short drug-free intermission, provided evidence for drug-seeking or craving behaviour, regarding craving to be the equivalent of drug insistence.[19]

Recent research has shown that in a sample of Dutch general practice patients about 33% of the long-term BZ users or former users experienced craving. However, the average craving severity was limited.[20] Patients still using BZs had significantly higher craving scores than patients who had recently quit their BZ use.[21]

Craving has been defined in physiological and behavioural terms, but the assessments most widely used in substance abuse research have been subjective.[15] In most studies on craving simple visual analogue scales to quantify craving or single-item ratings of craving of unknown reliability and validity are used. In recent years, however, several multi-item craving questionnaires have been developed (e.g. [7,11,12]). One of them is the Benzodiazepine Craving Questionnaire (BCQ), a self-report instrument to assess BZ craving.[21]

The present study is the first study to assess BZ craving longitudinally. Repeated measures of the BCQ were taken over a 21-month study period in a group of long-term BZ users participating in a two-part treatment intervention aimed to reduce long-term BZ use. Research questions were: (1) Does the reported craving severity differ among the several assessments in time? (2) Does the overall experienced craving severity differ between patients who have quit their BZ use, patients who continue using BZs and those with intermittent use patterns, over the study period? (3) Is the way in which patients have attempted to quit their use (of own accord vs. with help from their general practitioner) related to the severity of craving they experience over time?

METHODS

Setting and design

This study was conducted as part of a large study on the efficacy of a two-part treatment intervention that aimed to reduce long-term BZ use in general practice in the Netherlands. Participants were known to their general practitioner (GP) to be long-term BZ users. They received a letter from their GP (first intervention) with the advice to gradually cut down the use of BZs by themselves and if possible to stop using them altogether. The letter also informed patients about the drawbacks of long-term BZ use and provided information on (how to deal with) withdrawal symptoms.[22] The letter from the GP was used as a pre-selection for the second part of the study: a randomised controlled discontinuation trial (second intervention), comparing tapering off alone (TO) with tapering off with additional group cognitive-behavioural therapy (CBT), and with a control group receiving usual care (UC).[23]

The study received ethical approval from the University Medical Centre Nijmegen, and took place from 1998-2001. Patients' responses to the Benzodiazepine Craving Questionnaire[21] at four assessments in a 21-month time span formed the basis of present study.

Subjects and procedure

We identified long-term BZ users by means of a computerised search for BZ prescriptions at 30 general practices. Long-term use was defined as BZ use for at least 3 months with a 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, psychosis in medical history, epilepsy, insufficient mastery of the Dutch language, or terminal illness. Patients could also be excluded specifically on the GPs request, because of severe co-morbidity or for psychosocial reasons. Two thousand and four patients met the definition of long-term use and were sent a letter by their GP (first intervention). Three months after receipt of the letter with the advice to gradually discontinue their BZ use, patients were invited to consult their GP to evaluate their current BZ use status and the preceding period. Patients who did not succeed in discontinuing on their own accord were asked to participate in the second part of the study (discontinuation trial). The tapering off procedure was based on Schweizer et al., transferring participants to an equivalent dose of diazepam and reducing dosages by 25% a week during four weekly visits to the GP.[24] The last visit took place 2 weeks after the last reduction step. GPs were allowed to extend the tapering period if necessary. Group cognitive-behavioural therapy consisted of five weekly 2-h sessions, starting halfway through the tapering off period and ending 2 weeks thereafter. It aimed to support the participants during tapering off and to prevent relapse afterwards. The usual care control group did not receive any help with BZ reduction and GPs were instructed to give care as usual. Patients who did not quit BZ use after the first intervention were randomised for the second part of the study in a ratio of 2:2:1 (TO:CBT:UC) to achieve maximum discriminative power between the two experimental groups (TO and CBT).[23]

Measurements

In this study the course of craving is described by means of four assessments during a 21-month study period. The baseline assessment (T1) was carried out after receiving informed consent. It took place approximately 3 months after the start of the first intervention (letter from the GP). Three months after the start of the second intervention (discontinuation trial) patients received a short-term outcome assessment (T2), followed by two follow-up assessments (T3 and T4), 6 and 18 months, respectively, after the start of the discontinuation trial. All four assessments consisted of structured interviews and were carried out at the patients' homes by trained interviewers.

Measures

BCQ

The Benzodiazepine Craving Questionnaire (BCQ) was developed by our research group.[21] It is a reliable and psychometrically sound Rasch homogeneous self-report questionnaire to assess BZ craving in a general practice sample of long-term BZ users. Patients completed the original version of the BCQ according to their current experience, by indicating the

extent to which they agreed or disagreed with each item on a seven-point Likert-type scale. The endpoints of the scale were labelled 'strongly disagree' (1) and 'strongly agree' (7). For analysis, items of the BCQ were dichotomised between response options four and five of the Likert-type scale. Sum scores could range from 0 to 20.

Other measures

In addition to BZ craving, data were gathered concerning, among others, lifestyle characteristics (T1 only), BZ use, BZ withdrawal symptoms and BZ dependence. Number and severity of BZ withdrawal symptoms during discontinuation were assessed with the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ), a 20-item self-report questionnaire.[25,26] Severity of BZ dependence was assessed with the Benzodiazepine Dependence Self-Report Questionnaire (Bendep-SRQ), a 20-item self-report questionnaire consisting of four Rasch homogeneous scales, namely, problematic use, preoccupation, lack of compliance and withdrawal.[27] All questionnaires show good reliability and validity for the Dutch population. Results from the Bendep-SRQ, BWSQ and other variables at first assessment are used to describe the study sample.

Sample size

Of 1321 patients consulting their GP 3 months after the first intervention, 317 patients gave their informed consent to participate in the discontinuation trial. Patients who had quit their use of their own accord are also included in this number. They gave informed consent for follow-up assessments (as described above). For a graphic representation of the patient flow and dropout we refer to Oude Voshaar et al..[22,23] Of the 317 patients providing informed consent, 28 patients dropped-out before the first assessment, leaving 289 patients for the baseline interview. The BCQ was developed shortly after the study had started. Due to this delay in the development of the BCQ, 193 patients (of 317) filled in the BCQ at baseline. There were no significant differences in background and BZ use characteristics between patients who had received the BCQ at baseline and patients who had not or had missing BCQ values.[21] Of 193 patients who filled in the BCQ at baseline, 117 completed the BCQ at four assessments. The remaining 76 patients had missing BCQ values at one or more of these assessments and were left out of the analyses. There were no significant differences in background and BZ use characteristics between patients who had completed the BCQ at four assessments and patients who had not or had missing values. Oude Voshaar et al. have mentioned that some patients allocated to the treatment groups had already quit their BZ use before the treatment had started.[23] Since we were particularly interested in patients' actual BZ use behaviour, we did not commit to Intention to Treat analyses based on randomisation outcome. We distinguished three main subgroups in our data, based on patients' self-reported BZ use behaviour or 'pattern', namely, (1) BZ users, (2) former users, who had discontinued their BZ use, and (3) intermittent users, who were using and abstinent, respectively, at one assessment, and abstinent and using, respectively, at another assessment. These three groups could then be subdivided according to the

intervention the patients had received: (A) the letter from the GP only (first intervention) and (B) a discontinuation trial additional to the first intervention (second intervention, only for patients who had not quit their use after the first intervention). Interim analyses showed that BCQ scores did not differ significantly between patients receiving tapering off alone and patients receiving tapering off with additional group CBT, irrespective of their BZ use status (quit or using). Consequently, these two patient groups (tapering off alone and additional group CBT) were combined for the purpose of analysis. For an overview of the patient subgroups and numbers, we refer to Table 2.

Statistical analysis

To check for baseline differences between the patients who had quit and had not quit their use after the letter from the GP, SPSS 10.0.5 (SPSS Inc, Chicago, IL) was used to perform a series of univariate *t*-tests or non-parametric equivalents on socio-demographic and BZ use variables. For purpose of analysis, as described above, all 117 subjects were classified into six categories based on their actual self-reported BZ use 'pattern' (1 = quit, 2 = using, 3 = using intermittently) and the treatment they had received (A = first intervention (letter) only, B = additional second intervention (discontinuation trial)). The six categories were: (A1) patients who only received the first intervention (letter), had quit BZ use thereafter and remained abstinent for the duration of the study (n = 36); (A2) patients who only received the first intervention, but continued using BZs thereafter (n = 8); (A3) patients who only received the first intervention, had quit BZ use at a certain assessment but relapsed at another assessment (n = 19); (B1) patients who received the additional second intervention (discontinuation trial), had quit their BZ use thereafter and remained abstinent for the duration of the study (n = 20); (B2) patients who received the additional second intervention and continued using BZs (n = 23); (B3) patients who received the additional second intervention, had quit BZ use at a certain assessment but relapsed at another (n = 11).

We performed analysis of variance with three factors and first-order interactions. Square root transformation was performed to normalise the skewed data. Untransformed data are reported in the text. Scheffe's ratio, a method of post hoc comparison, was calculated on the transformed means to identify where the significant differences occurred.

RESULTS

Baseline characteristics of the patients who completed all four assessments (n = 117) are presented in Table 1. The majority of patients was female, elderly, married, had a secondary education level and was living on a pension. About 40% of the patients were smokers, about half used alcohol, and the majority used caffeine. The average BCQ score indicated a relatively low craving severity. On average, BZ dosage did not exceed the therapeutic dosage recommended by the WHO. Mean duration of BZ use exceeded 10 years. The overall

average severity of BZ dependence in our patient group was low.

Patients who had not quit their BZ use after the letter from their GP (first intervention) had used BZs for a significantly longer period of time (11.7 vs. 8.1 years; Mann–Whitney $U = 117.5$, $z = -2.4$, $p = .016$), had used BZs in significantly higher daily dosages prior to the intervention (7.8 vs. 2.2 mg of diazepam equivalents; Mann–Whitney $U = 1145.5$, $z = -2.6$, $p = .009$), scored significantly higher on three of four BZ dependence severity subscales, namely, problematic use (mean total score 1.7 vs. 0.6; Mann– Whitney $U = 746.5$, $z = -4.8$, $p < .0001$), preoccupation (2.2 vs. 0.5; Mann–Whitney $U = 670.0$, $z = -5.4$, $p < .0001$), and withdrawal (1.6 vs. 0.8; Mann–Whitney $U = 933.5$, $z = -3.2$, $p = .002$), and had significantly higher mean BCQ sum scores (1.9 vs. 0.3; Mann–Whitney $U = 1231.5$, $z = -2.5$, $p = .013$) compared to patients who had quit their BZ use after the discontinuation letter.

Data analysis for the course of BZ craving was based on 117 patients categorised as described above. Mean BCQ sum scores for the six subgroups at four assessments are shown in Table 2. There was no significant correlation between reported craving severity and BZ dosage. Percentages of patients experiencing BZ craving (BCQ sum score > 0) are presented in Table 3.

To answer our research questions we performed analysis of variance with three factors and first-order interactions. We found a main effect of time on the BCQ sum scores ($F_{3,450} = 9.9$, $p < .0001$). There was an overall decrease in BCQ sum scores during the course of the study (first research question). Scheffe's Test revealed a significantly lower mean BCQ sum score at the long-term follow-up assessment (T4) 18 months after the start of the second intervention, compared to all other assessments. In addition, there was a main effect of BZ use ´pattern´ (quit, use, intermittent) on the BCQ sum scores ($F_{2,450} = 3.7$, $p = .025$). On average (independent of time and intervention), there was a significant difference in self-reported craving severity between patients who had quit their BZ use, were still using and patients who were using intermittently (second research question). This ´effect of self-reported behaviour´ could be explained with Scheffe's Test by a significant difference in mean BCQ sum scores between patients who had quit their BZ use and patients who were still using BZs, users reporting more severe craving overall. The answer to our third research question was negative. There was no interaction between time and intervention, i.e., the way in which patients attempted to quit their BZ use (letter only or additional discontinuation trial guided by the GP) did not influence the BZ craving they experienced during the course of the study. However, on average (independent of time and BZ use pattern) there was a significant difference in experienced craving severity between patients who only received the letter as an incentive to quit their BZ use and patients who also completed the discontinuation trial (main effect of intervention: $F_{1,450} = 15.3$, $p = .0001$), suggesting that craving does play a role in discontinuing BZ use. Patients who had received the additional intervention reported significantly more severe craving (overall mean BCQ sum scores .55 vs. .25). Although marginally significant, the effect of BZ use pattern on the reported craving differed for each intervention (BZ use pattern * intervention effect: $F_{2,450} = 3.1$, $p = .045$), in other words, craving reported by the three groups (quit, use,

intermittent) had a different course for the patients who received only the letter (first intervention) compared to patients who received additional tapering off (second intervention). Scheffe's Test could not be performed on a compound variable. Additional analyses showed that the patients still using after the additional second intervention had significantly higher BCQ sum scores than patients who had quit after the additional second intervention and patients who had already quit or were using intermittently after the first intervention. There was no interaction effect between time and BZ use pattern.

Table 1 Baseline characteristics of the study sample

	Total group (n = 117)	
	n/mean	%/SD
Demographic variables		
Gender (female)	75	64.1%
Age (years)	62.4	12.0
Marital status		
Steady relationship (incl. married)	72	61.5%
Living alone	40	34.2%
Highest level of education		
Secondary level	81	69.2%
Financial income		
Pension	57	48.7%
Benzodiazepine usage		
Duration of benzodiazepine use (months)[a]	124.1	100.4
Quartiles	48.0 – 96.0 – 180.0	
Daily dose at first assessment (mg diazepam equivalents)[b]	7.4	9.5
Quartiles	2.9 – 5.0 – 8.3	
Daily dose 3 months previous to first intervention (mg diazepam equivalents)[c]	7.0	6.9
Quartiles	3.0 – 6.0 – 9.0	
Craving		
Craving severity (BCQ sum score)	1.3	3.5
Quartiles	0.0 - 0.0 – 1.0	
Benzodiazepine dependence characteristics		
Dependence severity (Bendep-SRQ sum score)		
Problematic use (*n* = 115)	1.3	1.2
Preoccupation (*n* = 116)	1.6	1.6
Lack of compliance (*n* = 117)	0.2	0.7
Withdrawal (*n* = 109)	1.3	1.7
Withdrawal symptoms (BWSQ sum score)	6.4	6.7
Substance/drug use		
Nicotine use		
Nicotine users	49	41.9%
Number of cigarettes/day among cigarette smokers (*n* = 48)	14.2	7.9
Alcohol use		
Drinking alcohol	58	49.6%
Units of alcohol/week	10.0	8.5
Caffeine use		
Caffeine users	75	64.1%
Units of caffeine/day	4.4	2.9

[a] Based on patients who discontinued and did not discontinue their BZ use in the previous 3 months.

[b] BZ users only.

[c] Based on recorded consumption extracted from the GP's clinical database.

Table 2 Mean BCQ sum score and standard deviation (SD) per patient subgroup, overall and at four assessments separately

		First intervention only (letter from GP)			Second intervention (additional) (discontinuation trial)*		
Self-reported BZ use pattern:		**Quit**	**Use**	**Intermittent**	**Quit**	**Use**	**Intermittent**
N (total = 117):		36	8	19	20	23	11
BCQ sum scores							
Assessment 1**	**Mean (SD)**	.33 (.83)	1.13 (2.03)	1.26 (3.89)	1.30 (2.94)#	2.48 (5.37)	2.64 (4.61)
Assessment 2	**Mean (SD)**	.33 (.72)	.25 (.71)	.26 (.56)	.60 (1.19)	1.78 (3.15)	1.27 (1.79)
Assessment 3	**Mean (SD)**	.67 (1.93)	.13 (.35)	.42 (.77)	.15 (.37)	1.48 (2.89)	2.55 (5.52)
Assessment 4	**Mean (SD)**	.28 (1.19)	.00 (.00)	.00 (.00)	.00 (.00)	.65 (2.35)	.09 (.30)
Overall BCQ sum scores	**Mean (SD)**	.24 (.59)	.25 (.57)	.27 (.65)	.30 (.65)	.71 (1.05)	.68 (1.10)

* This intervention includes only patients who did not quit their BZ use after the first intervention (letter). Before the start of the second intervention these patients were randomised either for tapering off alone or for group CBT. In this study the usual care control patients were considered as only receiving the first intervention and were placed in the use-group of the first intervention.

** Assessment 1: 3 months after the sending of the letter from the GP (first intervention); assessment 2: 3 months after the start of the discontinuation trial; assessment 3: 6 months after the start of the discontinuation trial; assessment 4: 18 months after the start of the discontinuation trial.

Since assessment 1 took place before the second intervention these patients were still using BZs at assessment 1.

Table 3 Percentage of patients experiencing craving in each patient subgroup*

		First intervention only (letter from GP)			Second intervention (additional) (discontinuation trial)#		
Self-reported BZ use pattern:		**Quit**	**Use**	**Intermittent**	**Quit**	**Use**	**Intermittent**
Assessment 1	%	19.4	50.0	31.6	45.0#	47.8	36.4
Assessment 2	%	22.2	12.5	21.1	25.0	52.2	54.5
Assessment 3	%	19.4	12.5	26.3	15.0	52.2	45.5
Assessment 4	%	5.6	0.0	0.0	0.0	13.0	9.1

* BCQ sum score > 0.

Since assessment 1 took place before the second intervention these patients were still using BZs at assessment 1.

DISCUSSION

This is the first study in which the long-term course of BZ craving has been described. The main findings of our study were:

1 Over the 21-month study period the reported craving severity decreased for all patient subgroups, regardless of their use status and the intervention they had received (main effect of time). At the long-term follow-up assessment 18 months after the start of the second intervention, the overall reported craving severity was significantly lower than the craving severity reported at earlier assessments for all subgroups, and negligible from a clinical point of view. Since patients who had only received the first intervention (letter) showed a decrease as well, the decrease in craving severity could not be due to the intensive GP guided tapering off (second intervention). Cue-reactivity studies might offer an explanation for this finding. Some of these studies have demonstrated that

craving can be highly stimulus specific (e.g. [28,29]). The two treatment phases of our study and the process of abstaining from BZs, focus patients on different kinds of discontinuation and withdrawal cues that may lead them to experience craving. At the fourth assessment, 18 months after the start of the second intervention, involvement from the GP has worn off as might have the patient's focus on BZ-related (withdrawal) cues, everything returning back to normal. Hence, less severe craving is being reported. Gritz et al. have found similar decreases over time, although, methods are not completely comparable since they asked their subjects to rate how frequently they experienced a craving.[30] After unaided smoking cessation on a self-determined target quit date, frequency of craving (varying from ´never´ through ´constantly´) gradually declined from months 1 to 12 among subjects who were abstinent at all follow-ups.[30]

2 Overall, patients still using BZs reported significantly more severe craving than patients who had quit their BZ use during the study (main effect of BZ use pattern). Possibly, continued use fosters BZ craving, or vice versa. Bordnick and Schmitz have found similar results in cocaine users.[3] Craving intensity during the past week of their outpatient treatment and 24-week follow-up was lowest among abstinent subjects and highest among subjects with moderate and heavy levels of cocaine use, as measured with the visual analogue scale of the Cocaine Craving Scale (CCS). In our study, however, there was no significant association between changes in experienced craving and changes in BZ dosage. Possibly, the fact that our subjects were all low-dose therapeutic BZ users may have accounted for this latter result.

3 The way in which patients had attempted to quit BZ use (of their own accord only or with additional GP guided tapering off with or without additional group CBT) did not influence the experienced craving severity over time (there was no interaction effect between time and intervention). However, patients who had received the additional tapering off intervention, on average, reported significantly more severe craving than patients who had only received the letter from the GP (main effect of intervention). In addition, patients who had received the additional second intervention but kept on using BZs experienced the most severe craving overall. Patients who had quit BZ use after the letter (first intervention) experienced the least severe craving. These findings suggest that for patients trying to discontinue their BZ use who are reporting more severe craving a ´minimal intervention´ alone may not be sufficient and a more intensive intervention, such as GP guided tapering off, may be appropriate. We have also found that patients who did not quit after the first intervention were more severely dependent on their BZs.

From a methodological point of view our study is in line with Linden et al.[19] They found that two-thirds of their GP patients with low-dose BZ dependence refused to accept a short drug-free intermission, referring to this drug insistence as craving. Kan et al. found that 40% of all those prescribed BZs in GP were dependent according to DSM-III-R criteria.[31] Craving and/or dependence might be an explanation for the relatively low participation rate in our study. However, Oude Voshaar et al. have mentioned that success rates for the

first intervention were fairly comparable to success rates reported by others.[22] This suggests that the patients who responded to the evaluation with the GP 3 months after sending the letter were representative of all patients who received the discontinuation letter with respect to BZ use.

One apparent finding in our study was that, although we found a considerable percentage of patients that experienced craving, the severity of the reported craving over time was relatively low for all subgroups. The majority of (former) BZ using GP patients hardly experienced any craving at all, either during or after their discontinuation process. Mol et al. have offered a tentative explanation in their earlier report, referring to the long half-lives and slow onset of action of most BZs compared to other substances of abuse in which craving is reported to a much higher extent.[21] Since our study sample consisted primarily of long-term, low-dose BZ users with the intention to quit, as they expressed this intention by giving informed consent to participate in a BZ discontinuation trial, future research needs to be conducted to evaluate the nature of BZ craving in untreated BZ users and in heavy users. Another possible explanation for the low BCQ scores over time might be a potential retest effect of the BCQ. Further longitudinal research, however, needs to provide more insight in these matters.

There is one major strong point compared to most other studies assessing self-reported craving. While in most other studies craving is assessed with VAS or single-item rating scales of unknown psychometric quality, we have assessed craving using a psychometrically sound multi-item questionnaire.

Since this is only the first study to describe the course of BZ craving longitudinally, one should be cautious in generalising and interpreting the results. However, this study further supports the notion that BZ craving is prevalent among (former) long-term BZ using GP patients, although it seems that severe or intense craving is almost absent.

The BCQ proved to be an instrument sensitive in discriminating the course of craving between different subgroups. Although data of other populations, e.g., BZ using psychiatric patients and (multi-)drug users, can further substantiate the validity of the BCQ, current data have shown that the BCQ is an instrument capable of quantifying craving for BZs longitudinally in (former) long-term general practice BZ users. The BCQ sum scores may give direction to the advisable treatment intensity, in terms of interference by the GP, when a patient is trying to abstain from BZs.

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Chapter 5

Benzodiazepine craving revised: a comparison of two conceptualisations of benzodiazepine craving

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ABSTRACT

Aim - This study aims to advance our understanding of craving for benzodiazepines (BZs) by comparing two conceptualisations of BZ craving: 1) a broad conceptualisation of BZ craving, represented by the Benzodiazepine Craving Questionnaire (BCQ), a 20-item Rasch homogeneous self-report questionnaire with promising psychometric qualities, and 2) a narrow conceptualisation, represented by the Benzodiazepine Desire Scale (BDS), three single-item Likert-type scales assessing frequency, global and peak intensity of the desire for BZs.
Setting and participants - Data were gathered from a sample of 113 long-term and 80 former long-term general practice BZ users participating in a large BZ reduction trial in general practice in the Netherlands.
Measurements - Sum scores of the BCQ and the BDS were entered in a Maximum Likelihood factor analysis together with other (BZ dependence) variables in order to test our hypothesis that both conceptualisations of BZ craving would load on one dependence factor different from other variables.
Findings - BCQ sum scores loaded on a factor representing negative affect, while BDS sum scores loaded on a dependence factor. Low craving intensity, as measured by the BCQ, and the selected time frame of craving measurement (current experience versus over the past week) are the most likely explanations of these findings in our sample of long-term low dose BZ users.
Conclusions - Low craving intensity, as measured with the BCQ, is associated with negative affect and reflects the anticipation of positive outcome of BZ use and of relief from negative affect or withdrawal. Both conceptualisations of BZ craving contribute to our understanding of the potential significance and meaning of craving in BZ use.

INTRODUCTION

In addiction literature some elaborate and thorough surveys have been published on the definitions of craving according to various theoretical models (eg [1-6]). There are still some unsolved definitional issues, among which is the scope of the craving definition.[4,7] While some researchers restrict the craving definition to a (strong) desire for use of an addictive substance, others use definitions with a broader focus. Both approaches have advantages and disadvantages from a theoretical point of view.

Researchers in support of a narrow conceptualisation of craving stick to dictionary definitions and have argued to use the term craving only for strong desires to take addictive substances.[1] However, there is evidence that a substantial percentage of persons with substance use and misuse disorders use the word craving to mean any urge or desire to take a drug, even a weak one (e.g. [8,9]). Furthermore, there is considerable diversity in the specific terms patients use to describe their craving. For example, smokers used significantly more affective descriptors than physiological descriptors to characterise their craving and significantly fewer synonym words (e.g. urge) than affective, behavioural, and cognitive descriptors.[10] Researchers in favour of a broad conceptualisation of craving include not only desires to use, but also behavioural intentions, lack of control over use, and anticipation of positive outcome and of relief from negative affect.

As a consequence of the many different definitions and conceptualisations of craving, craving measurement has been diverse. Sayette and colleagues, among others, evaluated different methodological approaches of the measurement of craving. Single-item measures, such as visual analogue scales, which often rate craving intensity from none to maximum, have face validity.[4] However, reliability of a single-item may be low, and unless administered with other items sampling the same content area, difficult to estimate.[4,11,12] Furthermore, single-item ratings may lack the breath required to capture the various semantic dimensions used by people to describe their craving.[10,13]

A broader range of items is advantageous if we take the position that we do not know which types of items are the purest indicators of craving.[13] When a broad definition of craving is applied, questionnaires designed to assess craving can be categorised as presenting craving as a single 'factor' or as a multi-factorial construct.[14] One of the advantages of the use of composite craving scores over single-item scales is that they might yield a more reliable estimate of the individual's craving report. A scale comprised of several items addressing desire for an addictive substance as well as other urge-relevant categories could provide a substantially more comprehensive representation of the semantic organisation of craving report and might also allow for the identification of its multidimensional aspects.[12] Moreover, reliability and power can be increased with the use of multi-item, relative to single-item, scales. It is also likely that increasing the number of items on the self-report measure would increase the reactivity of the measure.[4] However, the fundamental issue regarding the use of multi-item scales is whether items referring to expectancies about the effects of substance use and to the intention to use an addictive

substance, can be considered to be distinct components of a broad construct of craving.

Tiffany and colleagues have set the marker for the development of multi-item scales that aim to capture a broad range of conceptualisations of craving for different substances, by developing the Questionnaire on Smoking Urges (QSU) and the Cocaine Craving Questionnaire (CCQ), covering current craving theories as widely as possible.[9,13] Numerous questionnaires to assess craving for other substances have been adapted from these questionnaires, but most researchers found inconsistent results in terms of number and content of factors retained from factor analyses (e.g. Alcohol Craving Questionnaire,[15] Questionnaire of Alcohol Urges and Alcohol Urge Questionnaire,[16] Tobacco Craving Questionnaire,[17] Marihuana Craving Questionnaire,[18] Questionnaire of Cocaine Use,[19] and recently the Benzodiazepine Craving Questionnaire.[20])

Little research has focussed on craving for benzodiazepines (BZs), although these drugs have a high prevalence of use in the Western world and there have been many reports on their dependence liability.[21-23] A psychometrically sound instrument to measure BZ craving was lacking until recently. Mol and colleagues have developed the Benzodiazepine Craving Questionnaire (BCQ), a unidimensional multi-item questionnaire with promising reliability and validity, to measure the construct of craving in long-term BZ users.[20]

In this paper the issue concerning the scope of craving is addressed empirically by comparing a broad conceptualisation of BZ craving, as represented by the BCQ, and a narrow conceptualisation, as represented by the Benzodiazepine Desire Scale (BDS), consisting of three one-item Likert-type scales assessing the frequency, global intensity and peak intensity of desire for BZs when not using (derived from Schippers and colleagues[24]). To assess the effect of these two distinct conceptualisations, data on their associations with other (BZ dependence) related variables were gathered. We hypothesise that in a factor analysis the BCQ, the BDS and BZ dependence related variables load on a single factor, different from psychopathology, personality factors, quality of life and mood variables.

METHODS

Setting and design

Patients from a large study on the efficacy of a two-part treatment intervention that aimed to reduce long-term BZ use in general practice in the Netherlands received a number of questionnaires.[25,26] Patients' baseline responses to the Benzodiazepine Craving Questionnaire (BCQ) formed the basis of the present study.[20] The study received ethical approval from the Radboud University Nijmegen Medical Centre and took place from 1998 to 2001.

Subjects and procedure

We identified long-term BZ users by means of a computerised search for BZ prescriptions at 30 general practices. Patients were regarded as long-term users when they were using BZs for at least three months with a prescribed amount sufficient for at least 60 days of

consumption according to the prescription rules. Exclusion criteria and procedures, and participation rates are described elsewhere.[20] For a graphic representation of the patient flow and dropout of the whole study we refer to Oude Voshaar and colleagues and to Gorgels and colleagues. [25,26]

Two hundred and eighty-nine patients participated in the baseline interview. About 42% had quit their use since receiving a discontinuation letter from their GP (i.e. first intervention). The BCQ was developed shortly after the study had started. Due to this developmental delay, 193 patients (of 289) filled in the BCQ at baseline. There were no significant differences in background and BZ use characteristics between patients who had received the BCQ at baseline and patients who had not or had missing BCQ values.[20]

Measurement

The baseline assessment was carried out after receiving informed consent. It took place approximately three months after the start of the first intervention (discontinuation letter).

Measures

Benzodiazepine Craving Questionnaire

The Benzodiazepine Craving Questionnaire (BCQ) was developed by our research group and was based on items from the Questionnaire on Smoking Urges (QSU) and the Cocaine Craving Questionnaire (CCQ) by Tiffany and colleagues.[9,13] Items reflect five distinct conceptualisations of craving: 1) desire to use, 2) anticipation of positive outcome from BZ use, 3) anticipation of relief from withdrawal or withdrawal associated negative affect, 4) intention to use, and 5) lack of control over use. Patients indicated the extent to which they agreed or disagreed with each item on a seven-point Likert-type scale according to their current experience. The endpoints of the scale were labelled 'strongly disagree' (1) and 'strongly agree' (7). For analysis, items of the BCQ were dichotomised between response options four and five of the Likert-type scale. The BCQ proved to be a 20-item Rasch homogeneous self-report questionnaire to assess craving for BZs with promising reliability and validity.[20]

The BCQ was considered to be a good operationalisation of BZ craving since it consisted of items reflecting most common craving theories (cognitive, affective and behavioural aspects) and it allowed for the measurement of the subjective experience of BZ craving independent of the BZ using experience itself. Previous research has shown that the BCQ is able to discriminate between patients who have quit their BZ use recently and continuous BZ users.[20] Furthermore, the BCQ is able to monitor and quantify self-reported craving longitudinally.[27] Patients completed the original 32-item version of the questionnaire.

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: craving). Although in factor analysis sum scores are often used, different information is contained in the item scores, thereby obscuring the associations under investigation (e.g. population characteristics are well known confounders of factor structures).[28] Furthermore,

in questionnaire research continuous single peaked item characteristic curves (ICC's) may occasionally occur, which do not justify the use of sum scores.[29]

Although the use of questionnaire sum scores is generally accepted in research, this is only justified if the Rasch model holds true, as reflected by the goodness of fit statistics R1 and R2.[30] Rasch homogeneity implicates that the items can be rank ordered according to craving intensity or severity on a unidimensional scale, which presents another advantage over questionnaire development by means of factor analysis. This means that people who admit to an item indicating serious craving problems will also admit to the preceding 'less serious' items. The extent to which patients crave BZs is reflected by the total score on the instrument.

For more detailed information on the assumptions from which the Rasch model can be derived, we refer to e.g. Fisher,[31] Kan and colleagues[32] and Van der Ven and Ellis.[33]

Benzodiazepine Desire Scale

Patients also completed three one-item Likert-type scales assessing the frequency, global intensity and peak intensity of desire for BZs, respectively, by checking the box of their choice. 1) Frequency scale: 'How often during the last week did you experience a desire for BZs? (That is the desire for a BZ, while you were not using.)' Response options ranged from 1 (never) to 10 (constantly); 2) Global intensity scale: 'In general, how intense was your desire for BZs during the last week? (That is the desire for a BZ, while you were not using.)' Response options ranged from 1 (hardly any desire to none) to 10 (very strong desire); 3) Peak intensity scale: 'Please try to remember the moment during the last week that your desire for BZs was most intense. (That is the desire for a BZ, while you were not using.) How strong was the desire you felt by then?' Response options ranged from 1 (hardly any desire or none) to 10 (irresistible desire). This scale has been adopted from Schippers and colleagues who used the items for further development of their Obsessive Compulsive Drinking Scale.[24]

Other measures

During the baseline interview data were gathered on BZ use and sociodemographic characteristics. Severity of BZ dependence was assessed by means of the 20-item Benzodiazepine Dependence Self-Report Questionnaire (Bendep-SRQ). This questionnaire consists of four Rasch homogeneous scales with good reliability and validity, namely, Problematic use, Preoccupation, Lack of compliance and Withdrawal.[32,34] Presence and severity of psychopathology were assessed with the General Health Questionnaire 12-item version (GHQ-12), a measure of psychological wellbeing.[35] To assess personality traits we used the Dutch Shortened MMPI (NVM) consisting of the sub scales Negativism, Somatisation, Shyness, Psychopathology and Extraversion,[36] and mood variables were assessed by means of the Profile of Mood States Dutch shortened version (POMS), a questionnaire to measure five short-term changeable mood states (Depression, Anger, Fatigue, Vigour and Tension).[37] We also added a measure of health related quality of life,

the Medical Outcome Study Short-Form 36-item version (MOS SF-36). 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) that all have been related to BZ use in the general population. The Dutch version of the SF-36 was previously tested and validated.[38,39] All questionnaires show satisfactory reliability and validity for the Dutch population. Specially trained interviewers interviewed the patients at their homes.

Statistical analysis

All data analyses were conducted using SPSS 12.0.1 for windows. To assess the correlation between BCQ sum scores and BDS sub scale scores we performed crosstabs procedures (Kendall's tau-c, with correction for nodes). Maximum Likelihood factor analysis, which includes a Goodness of fit test for the factor structure found, with Varimax rotation was performed on our data. To normalise the skewness of the BCQ data we performed logarithmic transformation on the sum scores. Separate Maximum Likelihood analyses were performed on data from patients who had quit and had not quit their use, respectively. Correlations between the factors found were assessed using crosstabs procedures (Kendall's tau-c, with correction for nodes). To assess the possibility of confounding by the purpose of use status (anxiolytic and/or hypnotic) we performed posthoc univariate analyses of variance on our data.

RESULTS

Table 1 shows the baseline characteristics of our study sample. At the time of the interview, 41.5% of the total BCQ group (80/193) had quit their use in the three months after receiving the discontinuation letter from their GP. The average craving severity as measured with the BCQ was low. Concerning BZ dependence, based on the Bendep-SRQ sub scale scores, the overall average severity of BZ dependence in our population was low. Average scores on the BDS sub scales were also relatively low. Psychopathological dysfunction was relatively mild. Based on a cut-off point of 2/3 on the General Health Questionnaire 12-item version, 26% of the patients were classified as 'psychiatric case'. Sample characteristics have been described in more detail elsewhere.[20,40]

Table 1 Baseline characteristics of the total BCQ sample

	Total sample	(n = 193)
	n/mean	%/SD
Demographic variables		
Age (years)	62.9	12.0
Gender (female)	131	67.9%
Marital status		
Steady relationship (incl. married)	127	65.8%
Living alone	61	31.6%
Highest level of education		
Secondary level	123	63.7%
Financial income		
Pension	90	46.6%
Profession	27	14.0%
Benzodiazepine usage		
Quit after letter with advice to quit benzodiazepine use	80	41.5%
Duration of benzodiazepine use (months)[a]	129.9	108.2
Quartiles	48.0 – 96.0 – 186.0	
Daily dose (mg diazepam equivalents) (*n* = 113)[b]	6.9	8.1
Quartiles	2.9 – 5.0 – 7.8	
Daily dose 3 months previous to first intervention (mg diazepam equivalents) (*n* = 190)[c]	6.7	6.9
Quartiles	3.0 – 4.5 – 9.0	
Benzodiazepine Craving Questionnaire		
Craving severity (BCQ sum score) (range 0 - 20)	1.2	3.2
Quartiles	0.0 – 0.0 – 1.0	
Benzodiazepine Desire Scale		
Frequency (*n* = 190) (range 1 - 10)	3.7	2.9
Quartiles	1.0 – 3.0 – 6.0	
Global intensity (*n* = 191) (range 1 - 10)	3.5	3.0
Quartiles	1.0 – 2.0 – 6.0	
Peak intensity (*n* = 191) (range 1 - 10)	3.7	3.0
Quartiles	1.0 – 2.0 – 6.0	
BDS sum score (*n* = 190) (range 0 - 30)	10.9	8.4
Quartiles	3.0 – 8.5 – 17.0	
Bendep-SRQ		
Problematic use (*n* = 191) (range 0 - 5)	1.2	1.2
Quartiles	0.0 – 1.0 – 2.0	
Preoccupation (*n* = 192) (range 0 - 5)	1.4	1.6
Quartiles	0.0 – 1.0 – 3.0	
Lack of compliance (*n* = 192) (range 0 - 5)	0.3	0.7
Quartiles	0.0 – 0.0 – 0.0	
Withdrawal (*n* = 178) (range 0 - 5)	1.1	1.6
Quartiles	0.0 – 0.0 – 2.0	
Dutch shortened MMPI		
Negativism	12.2	7.5
Somatisation	14.0	7.8
Shyness	10.5	7.1
Psychopathology	2.9	3.1
Extraversion	13.2	5.6
Profile Of Mood State		
Depression	12.8	6.2
Anger	11.0	5.1

Table continues on the next page

Table 1 continued	n/mean	%/SD
Fatigue	12.2	5.9
Vigour	15.0	4.7
Tension	11.8	5.5
Short-Form 36 (range 0-100)		
Physical functioning	68.3	26.0
Role functioning – physical problem	59.6	40.5
Pain	64.1	25.1
General health perception	57.9	21.7
Vitality	57.6	22.9
Social functioning	65.5	20.8
Role functioning – emotional problem	68.9	39.6
Mental health	68.4	19.4
General Health Questionnaire-12		
Sum score (n = 192)	2.0	3.1

[a] Based on patients who discontinued and did not discontinue their BZ use in the previous three months.

[b] BZ users only.

[c] Based on recorded consumption extracted from the GP's clinical database.

Correlations between BCQ sum score and the BDS sub scales were low (Kendall's tau-c = .17, p = .000 for the Frequency scale; Kendall's tau-c = .14, p = .002 for the Global intensity scale; Kendall's tau-c = .13, p = .004 for the Peak intensity scale, respectively). Analysis of the internal consistency of the BDS showed a very high reliability coefficient (Cronbach's alpha = .93), suggesting that all three single-item sub scales are measuring the same construct, most obviously, desire for BZs. Given this finding, it seemed justified to combine the three separate rating scale sum scores into one overall BDS sum score in further analyses. The correlation between the BCQ sum score and this BDS sum score was also low (Kendall's tau-c = .15, p = .001).

Subsequently, we performed Maximum Likelihood factor analysis with Varimax rotation on the BCQ sum scores, BDS sum score, Bendep-SRQ sub scale scores, Dutch Shortened MMPI sub scale scores, GHQ-12 sum scores, SF-36 sub scale scores and POMS sub scale scores. Bendep-SRQ sub scale Withdrawal was left out of the analyses due to missing data (patients only had to fill in this section if they had attempted to quit their BZ use in the past half year). The scree plot recommended a five factor solution with eigen values of greater than one, which accounted for 64.5% of the explained variance. However, no variables were allocated to the fifth factor. Additional Maximum Likelihood factor analysis with the model set to extract four factors with eigen values of greater than one accounted for 59.9% of the explained variance. The results of the Goodness of fit Test were satisfactory, with Chi-square/df ratio < 2 (χ^2 = 352.5, df = 186, p = .000).

The BCQ sum score loaded on the first factor together with POMS sub scales Depression, Anger and Tension, GHQ-12 sum score, SF-36 sub scale Mental health, and Dutch Shortened MMPI sub scale Negativism (see table 2). This factor was named the 'negative affect-factor'. The second factor consisted of the SF-36 sub scales (except for sub scales Mental health and Role functioning – emotional problem) and was named the '(physical) quality of life-factor'. Bendep-SRQ sub scales Preoccupation and Problematic use, and the

BDS sum score made up the third factor, the 'dependence-factor'. Factor four ('extraversion-factor') consisted solely of Dutch Shortened MMPI sub scale Extraversion.

Table 2 Rotated factor matrix of Maximum Likelihood factor analysis with Varimax rotation on a matrix consisting of scale scores (n = 185)[a]

Factor:	1	2	3	4
BCQ sum score	**.34**			
BDS sum score			**.58**	
Bendep-SRQ				
Problematic use			**.64**	
Preoccupation			**.93**	
Lack of compliance[b]	(.41)		(.40)	
Dutch shortened MMPI				
Negativism	**.61**			(.38)
Somatisation[b]	(.44)	(-.51)		
Shyness[b]				
Psychopathology[b]	(.43)			(.39)
Extraversion				**.50**
GHQ-12 sum score (Goldberg)	**.71**		(.31)	
SF-36				
Physical functioning		**.63**		
Role functioning – physical problem		**.79**		
Pain		**.62**		
General health perception		**.64**		
Vitality		**.79**		(.36)
Social functioning	(-.32)	**.64**		
Role functioning – emotional problem[b]	(-.38)	(.56)		
Mental health	**-.69**	(.34)		
POMS				
Depression	**.86**			
Anger	**.81**			
Fatigue[b]	(.54)	(-.55)		
Vigour[b]		(.36)		(.45)
Tension	**.79**			

[a] n = 185 due to missing values in questionnaires other than the BCQ.

Note. The model was set to extract four factors. A variable was assigned to a factor if it loaded .30 or greater on a given factor and there was at least .20 difference with another factor. Factor loadings in parenthesis indicate that a variable loaded .30 or greater on a factor, but was not allocated to that specific factor.

[b] Variable could not be allocated to a single factor. Factor loadings of smaller than .30 are not noted in the table.

Correlations between the four factors were rather low (Kendall's tau-c ranging from -0.22 through 0.27), suggesting that the factors represent distinct domains, indicating good factor analysis quality. The negative correlation between the 'negative affect-factor' and the '(physical) quality of life-factor' was modest (Kendall's tau-c = -0.22, $p < 0.001$). The correlation between the 'negative affect-factor' and 'dependence-factor' was also modest (Kendall's tau-c = 0.27, $p < 0.001$). There was a very modest correlation between the

'(physical) quality of life-factor' and the 'extraversion-factor' (Kendall's tau-c = 0.14, p = 0.005), and a marginally significant negative correlation between the '(physical) quality of life-factor' and the 'dependence-factor' (Kendall's tau-c = -0.12, p = 0.02). All other correlations were non-significant.

Since patients who were still using BZs had significantly higher craving scores than patients who had quit their use recently,[20] we repeated the factor analyses on the sub sample of non-quitters (n = 113) and quitters (n = 80), separately. Due to the small sub sample size of quitters and the large number of variables in the factor analysis, no stable factor solution was found. Therefore, no interpretation of the factor structure will be presented here. The analyses in non-quitters yielded a similar factor structure to the one found for the sample as a whole, and accounted for 64.9% of the explained variance. The results of the Goodness of fit Test were satisfactory, with Chi-square/df ratio < 2 (χ^2 = 212.3, df = 166, p = .009). Associations between the factors were also similar to the ones found above.

Since BCQ assessment took place at daytime and our population included both individuals who were using the BZs as an anxiolytic drug and/or as a hypnotic drug, we performed a posthoc univariate analysis of variance with purpose of use status as independent variable and BCQ sum score as dependent variable. Results showed that BCQ sum scores did not differ significantly between the three groups (sedative, hypnotic or both) ($F_{2,123}$ = .925, p = .399). Entering current use status (i.e. quit or still using BZs) as a second independent variable did not change these results, nor did correcting for the time span between last BZ intake and moment of filling in the BCQ.

DISCUSSION

This study has focussed on the scope of the craving definition, by comparing two distinct conceptualisations of craving for BZs, a broad one versus a narrow one. The Benzodiazepine Craving Questionnaire (BCQ), a 20-item Rasch homogeneous scale, represented a broad craving conceptualisation, with items covering current craving theories as best as possible. Three one-item Likert-type scales, comprising the Benzodiazepine Desire Scale (BDS), represented a narrow conceptualisation of craving, assessing the frequency, global intensity and peak intensity of desire for BZs over a one-week period when not using.

Factor analysis revealed that the structure of our data was best represented by four factors, which represent negative affect, (physical) quality of life, dependence and extraversion. The BDS together with the sub scales Preoccupation and Problematic use of the Bendep-SRQ loaded on the 'dependence factor'. Although BCQ factor loadings indicated some relationship with this factor, the BCQ was designated to the 'negative affect factor', which refuted our hypothesis. Apparently, in our general practice population of (former) long-term, low dose, low dependence BZ users the chosen conceptualisation of craving is of importance.

One possible explanation for our findings is the low intensity of craving in our study

population, as measured with the BCQ. The items located at the lower end of the Rasch rank order of the BCQ reflect anticipation of positive outcome and anticipation of relief from withdrawal or negative affect, whereas items at the higher end of the Rasch rank order reflect intention to use, desire to use and lack of control.[20] This means that in case of low craving, as measured with the BCQ, the emphasis is on (cognitive aspects of) affect regulation, as one can deduct from the contents of the BCQ items that are confirmed first in case of craving.

Preoccupation, Problematic use and the BDS seem to refer to more obvious dependence dynamics. This has been amply demonstrated for the Preoccupation and Problematic use sub scales of the Bendep-SRQ.[32,34] Apparently Peak intensity, Global intensity and Frequency of BZ desire are better linked to BZ dependence than to BZ craving as measured with the BCQ. As mentioned, items referring to the desire to use BZs are also present in the BCQ, yet in the higher regions of the Rasch rank order, indicating higher craving intensity. Patients in our population hardly confirmed these BCQ items. Results of the sub sample of patients who were still using BZs (non-quitters) were very similar to the results described above, whereas an insufficient amount of quitters was included for separate analyses in that group.

Associations between craving and negative affect have been found in numerous other studies for different substances. Childress and colleagues, for example, found that hypnotically induced depression produced significant increases in drug craving for opiates in 10 male opiate abuse patients.[41] They also found a trend for induced anxiety to increase self-rated craving. Robbins and colleagues found significant pre- and post-cue correlations between craving and POMS sub scales Anger, Confusion, Depression, Fatigue, Tension and Vigour (the latter was negatively correlated), with the highest correlation found for Depression in a sample of 81 cocaine-dependent outpatients.[42] Rabois and Haaga found that in their sample of 89 regular light smokers who were not necessarily trying to quit or interested in quitting, sad mood predicted higher temptation to smoke.[43] Singleton and colleagues also found that the subjective experience of craving in nicotine users had a negative emotional valence.[44] They found a pattern of increased negative mood, decreased positive mood and increased craving under different craving conditions, as realised through imagery scripts. Based on results from other craving studies one can hypothesise that negative mood states can become conditioned stimuli capable of triggering craving (see also[41]). Based on the importance of cognitive aspects of craving in our study, one can also hypothesise that patients might have attributed the negative affect to craving (e.g. I feel miserable because I have no BZs).

The fact that our patients experience some 'desire' for BZs as indicated on the BDS, but not on the BCQ, might be explained by the differences in the inquired time frame of the craving experience: patients had to indicate their current feelings on the BCQ, whereas for the BDS patients had to evaluate their feelings over the past week when not using. Questions referring to prior craving experience are subject to recall bias, potentially leading to overestimation of the amount of craving.[45,46] This might account for the discrepancies found between the BCQ and BDS in current study.

In addition to the difference in time frame of craving measurement between both craving measures, some methodological issues must be addressed. Patients used BZs for different purposes: anxiolytic, hypnotic or both. Although purpose of use status could have confounded BZ craving severity, post-hoc analyses on the BCQ did not show differences in craving between hypnotic users and anxiolytic users. Furthermore, our results are representative for the majority of long-term BZ users, i.e. general practice patients of older age and female sex with low-dose use and low dependence (cf [21]). Consequently, in other populations, such as multiple drug users and BZ dependent psychiatric patients, the outcome might be significantly different in terms of factor structure. We hypothesise that these patients would confirm the items in the higher regions of the Rasch rank ordering and thus experience more severe craving in a sense of desire, intention to use and possible lack of control.

The measurement of craving has received considerable research attention over the years. Unfortunately, only a few studies have assessed the psychometric properties of self-report instruments. In view of the importance of anticipated outcomes in almost all theoretical accounts of craving, it may be preferable for research purposes to use instruments that provide measures of anticipated outcomes for use, such as the BCQ, in addition to the pure measure of desire to use.[47] Nonetheless, our study clearly shows that using multiple measures of craving contributes to our understanding of the significance and meaning of this construct in BZ use. Based on findings from the present study, future research should be directed at achieving a more precise understanding of negative affect (both as state and trait manifestations) as a possible cue for BZ craving. If certain mood states are modulators of BZ craving they demand treatment attention.

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Chapter 6

The role of craving in relapse after discontinuation of long-term benzodiazepine use

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ABSTRACT

Objective – Craving for benzodiazepines has never been examined as a factor of relapse after successful benzodiazepine discontinuation. In this study, we examined the predictive value of craving on benzodiazepine relapse.
Methods – A stepped-care intervention trial aimed to discontinue long-term benzodiazepine use in general practice. The first step was the sending of a letter to users with the advice to gradually quit their use by themselves (i.e. minimal intervention). The second step, a supervised tapering off programme, was offered to those unable to discontinue by themselves. Craving was assessed by means of the Benzodiazepine Craving Questionnaire (BCQ). Multiple Cox-regression analyses were performed to examine the effect of craving on subsequent relapse during a 15-month follow-up period in patients who had successfully quit their benzodiazepine use by themselves after the minimal intervention (n = 79) and in those patients who had successfully quit after the supervised tapering off programme n = 45). Data were collected from August 1998 to December 2001.
Results – Thirty-five (44%) and 24 (53%) patients had relapsed after the minimal intervention and tapering off programme, respectively. Patients able to quit by themselves hardly experienced any craving. In this sample, craving was not related to relapse (p = 0.82). In patients who needed an additional supervised tapering off programme, higher craving scores were significantly related to relapse (HR = 1.26 [95% CI: 1.02 – 1.54], p = 0.029), when corrected for benzodiazepine characteristics, psychopathology and personality characteristics.
Conclusion – Craving is an independent factor of subsequent relapse after successful benzodiazepine discontinuation in long-term benzodiazepine users who are not able to quit their usage of their own accord.

INTRODUCTION

Craving is generally considered as an important variable in substance dependence. Empirical results, however, are not consistent suggesting that craving is neither sufficient nor necessary for continued use or relapse to the use of addictive substances (for an overview see e.g.[1]). The concept of craving has been studied frequently in substance dependence for various substances, but hardly in case of benzodiazepine use. Although benzodiazepines have the potential to cause all aspects of dependence even in low dosages,[2] only one study has examined the prevalence of benzodiazepine dependence according to ICD-10 and DSM-III-R criteria. That study has found that approximately half of all benzodiazepine users in general practice met the criteria for benzodiazepine dependence.[3] Recently, the concept of craving for benzodiazepines has been examined within a benzodiazepine discontinuation project,[4,5] which has resulted in the development of the Benzodiazepine Craving Questionnaire (BCQ).[6] Up till now, benzodiazepine craving has never been examined prospectively in relation to benzodiazepine relapse after successful benzodiazepine discontinuation.

Several factors, e.g. benzodiazepine dosage, dependence characteristics, psychopathology and personality, have been related to successful benzodiazepine discontinuation,[7-11] but almost exclusively concern short-term outcome programmes. Although 2 out of 3 patients successfully quit their use by means of these programmes, relatively high relapse rates have been reported,[11,12] stressing the need to identify patients at risk for relapse. The only two studies that have evaluated relapse after a supervised benzodiazepine tapering off programme have found treatment condition (cognitive-behaviour therapy for insomnia, a supervised medication taper program, or a combined approach), end of treatment insomnia severity and psychological distress, respectively, self-efficacy in coping without benzodiazepines, as predictors of relapse.[13,14] Two other papers have examined predictors of relapse in benzodiazepine users who had quit their use by themselves after receiving a letter containing the advice to discontinue their use. Baseline characteristics that predicted relapse in this population were a higher dosage, use of more than one benzodiazepine, lower general health perception, and hypnotic type benzodiazepine.[15,16]

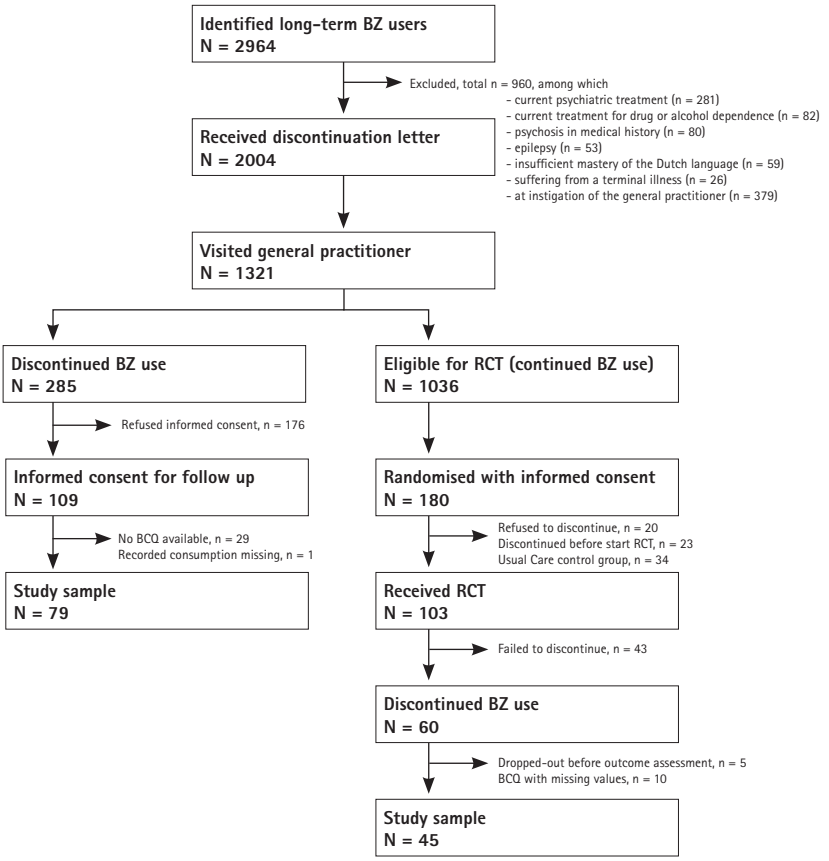
This study was conducted to test the hypotheses that craving is an independent predictor of relapse in long-term benzodiazepine users who successfully quit their use after 1) a minimal intervention, respectively, 2) after an additional supervised benzodiazepine tapering off programme in general practice.

METHODS

Study design and participants

This study was conducted as part of a larger study on the efficacy of a stepped-care model aimed to reduce long-term benzodiazepine use in general practice in the Netherlands. Participants were long-term benzodiazepine using general practice patients from 30 general practices with 55 general practitioners (GPs). Long-term users were selected on the basis of the following criteria: (1) having received benzodiazepine prescriptions for at least 3 months, and (2) having received prescriptions in an amount sufficient for at least 60 days in the 3 months prior to this study. Patients were excluded if benzodiazepine discontinuation could have a negative impact on their additional psychiatric treatment or underlying (major psychiatric) disorder (e.g. bipolar disorder, schizophrenia). For details on the exclusion criteria see figure 1.

Figure 1 Flowchart patient recruitment



The first step of the study was a minimal intervention strategy, i.e. a letter from the general practitioner (GP) with the advice to discontinue benzodiazepine use by themselves. Patients who had successfully quit their benzodiazepine use by themselves after receiving this letter, were the first group of interest for the present study. Patients who had continued benzodiazepine consumption after this intervention were approached to participate in the consecutive, more intensive step, i.e. a randomised controlled benzodiazepine discontinuation trial with three conditions: 1) tapering off alone, 2) tapering off with simultaneous group cognitive-behaviour therapy and 3) a usual care control group. Patients who had successfully quit their usage after participation in one of the two active conditions of this randomised controlled trial were the second group of interest for the present study. Since patients in both active treatment conditions were equally successful with similar rates of relapse, this group was treated as one cohort.[11,12] Written informed consent was obtained from all participants after full explanation of the study procedures.

The study received ethical approval from the Radboud University Nijmegen Medical Centre and was carried out between August 1998 and December 2001. It has been described in detail previously.[4,5] Figure 1 presents the recruitment process for the present study.

Measurements

The use of benzodiazepines and other prescribed drugs was monitored prospectively in the GPs medical records for a 15-month follow-up period. Drug prescription data were extracted on patient level from the GPs computerized medical records. In the Netherlands every patient is linked to only one GP who collects all medical information, including the use of prescribed medication. Moreover, more than 90% of the GPs use commercially available electronic medical dossiers enabling reliable data collection. Relapse was defined as receiving a benzodiazepine prescription during follow-up (for details, see[11]).

In addition to the computerized benzodiazepine prescription records, we assessed patients immediately after they had quit their benzodiazepine use after the first, respectively, the second intervention.

The primary variable of interest, benzodiazepine craving, was assessed by means of the Benzodiazepine Craving Questionnaire (BCQ), developed by our research group.[6] The BCQ is a unidimensional 20-item self-report questionnaire with good psychometric properties to assess benzodiazepine craving according to the patients' current experience. Sum scores can range from 0 to 20. In a previous report on the BCQ it was shown that patients who reported craving (sum scores of greater than zero) differed significantly from patients who did not report craving on the BCQ, concerning aspects of dependence severity, psychopathology, negative mood state, and personality.[17]

Additionally, we assessed the use of caffeine, nicotine, and alcohol, and the following self-report questionnaires were administered: severity of benzodiazepine dependence (Bendep-SRQ: Benzodiazepine Dependence Self-Report Questionnaire),[18,19] psychological well-being (GHQ-12: General Health Questionnaire 12 item version),[20] mood (POMS: Profile of Mood States),[21] quality of life (MOS SF-36: Medical Outcome Studies short-form),[22,23] and personality characteristics (NVM: Dutch shortened MMPI).[24]

Analyses

Both patient groups of interest, i.e. the group that had successfully quit after the first minimal intervention and the group that had quit after the additional supervised tapering off programme, were analysed separately. Since the BCQ sum scores were quite low, we first explored the data by comparing patients who did not report any craving (BCQ sum score = 0) and patients who reported craving to some extent (BCQ sum score ≥ 1), using cross-tabs.

Predictors of relapse were analyzed separately by means of Cox-regression analyses with time to relapse as the dependent variable and each of the following as the independent variable: BCQ sum score (range 0 - 20), daily benzodiazepine dosage (dichotomised at 10 mg diazepam equivalent), half-life (dichotomised at 24 hours), potency (presence of a 4-aryl group), hypnotic or anxiolytic use (dummy variable defined as self-reported (a) night-time use, (b) daytime use, (c) use at both night-time and daytime), use of antidepressants, use of pain medication, use of psychotropic drugs other than benzodiazepines, and finally, all variables measured at the baseline assessment. Patients lost to follow-up were analysed until the moment of loss to follow-up as censored observations. After the univariate Cox-regression analyses, variables with a Wald χ^2 statistic of $p < 0.15$ were entered into a multivariate Cox regression model using a forward, conditional procedure. Crude and adjusted hazard ratios (HR) with 95% confidence intervals (95% CI) are reported. A p-value of < 0.05 was considered significant in the final model. The output of the Cox-regression analysis was checked for instability by influential cases and for violation of the proportional hazards assumption. We used SPSS version 10.0 (SPSS Inc, Chicago, IL) to perform all analyses.

RESULTS

First intervention: discontinuation letter

Seventy-nine patients who had quit after the discontinuation letter were included in the present analyses (see figure 1). The mean (SD) age of these patients was 63 (13) years old and 68% was female. Patients used benzodiazepines for a mean (SD) duration of 6.9 (7.2) years in a mean (SD) daily dosage of 5.9 (6.0) mg diazepam equivalent.

The mean (SD) BCQ sum score was 0.5 (1.0) (quartiles: 0 – 0 – 0, range 0 - 6). Eighteen patients reported craving to some extent, as indicated by a BCQ sum score of greater than zero. The proportion of relapse did not differ between patients with and without craving (27/61 (44%) versus 8/18 (44%), $p = 0.99$). As shown in table 1, the BCQ sum score had no predictive value with respect to relapse in the univariate nor in the multivariate Cox-regression analyses ($p = 0.82$, respectively, $p = 0.67$).

Table 1 Univariate and independent predictors of relapse in successful quitters after a minimal intervention

	Univariate[a]		Multivariate[b]	
Variables	**Hazard Ratio [95% CI]**	**p-value**	**Hazard Ratio [95% CI]**	**p-value**
BCQ[c] sum score (range 0 – 20)	0.82 [0.55 – 1.20]	.82	0.93 [0.65 – 1.32]	.67
Benzodiazepine dosage (> 10mg)	3.00 [1.43 – 6.27]	.004	4.17 [1.87 – 9.30]	< .001
Duration of BZ use (years)	0.04 [0.00 – 0.77]	.042		
Age (years)	1.03 [1.00 – 1.06]	.055		
Stable relationship	0.49 [0.25 – 0.96]	.036		
Living alone	1.93 [0.98 – 3.70]	.057		
Use of alcohol	1.83 [0.92 – 3.58]	.083		
Vitality (SF-36 sub scale)	0.99 [0.97 – 1.00]	.054		
Extraversion (NVM sub scale)	0.94 [0.88 – 1.01]	.004	0.92 [0.87 – 0.98]	.008
		Model:	$\chi^2 = 17.2$; $df = 3$; $p < 0.001$	

[a] Only independent variables that had p-values of less than 0.15 in the univariate regression analyses are shown in the table.
[b] All univariate predictors were entered in the first block, using a forward Wald procedure, where after the BCQ score was added in the second block.
[c] Benzodiazepine Craving Questionnaire

Second intervention: supervised tapering off

Of the 180 patients who participated in the randomised controlled trial, 60 were of interest, as they successfully discontinued their benzodiazepine use with the aid of the tapering off protocol. Forty-five patients were included for analyses (5 patients withdrew from treatment, and 10 patients provided incomplete data (see figure 1)). In- and excluded patients were comparable with respect to age, gender, benzodiazepine dosage before the start of tapering off, and duration of use (all p-values > 0.18). The mean (SD) age of the 45 participants was 66 (12) years old and 67% was female. Patients used benzodiazepines for a mean (SD) duration of 12.8 (9.5) years in a mean (SD) daily dosage of 7.5 (4.7) mg diazepam equivalent.

The mean (SD) BCQ sum score was 1.2 (2.9) (quartiles: 0 – 0 – 1, range 0 - 18). Nineteen patients reported craving to some extent as indicated by a BCQ sum score of greater than zero. The proportion of relapse was higher in patients reporting craving versus patients reporting no craving at all (13/19 (68%) versus 11/26 (42%), which approached significance ($p = 0.08$)). Figure 2 shows the survival curves for relapse to benzodiazepine use for cravers (BCQ sum score of 1 or higher) and non-cravers (BCQ sum score of zero) separately. When corrected for time till relapse by a Cox-regression analysis, the BCQ sum score (range 0 - 18) was significantly related to relapse (HR = 1.20 [95% CI: 1.07 – 1.36], $p = 0.003$). As this result was influenced by one outlier (BCQ sum score = 18, relapse into benzodiazepine use after 11 days), the sum score of this outlier was corrected for on the basis of z-scores. Allocation of a z-score of 3 yielded a corrected sum score of 10 on the BCQ, thus decreasing the outlier effect yet maintaining the extreme position in the data. The hazard ratio of the BCQ sum score remained significant after this correction (see table 2: HR = 1.28 [95% CI: 1.07 - 1.55], $p = 0.009$). After correction for other significant independent predictors of relapse, the BCQ sum score still accounted for unique variance (HR = 1.26 [95% CI: 1.02 – 1.54], $p = 0.029$).

Figure 2 Survival time untill relapse after successful discontinuation

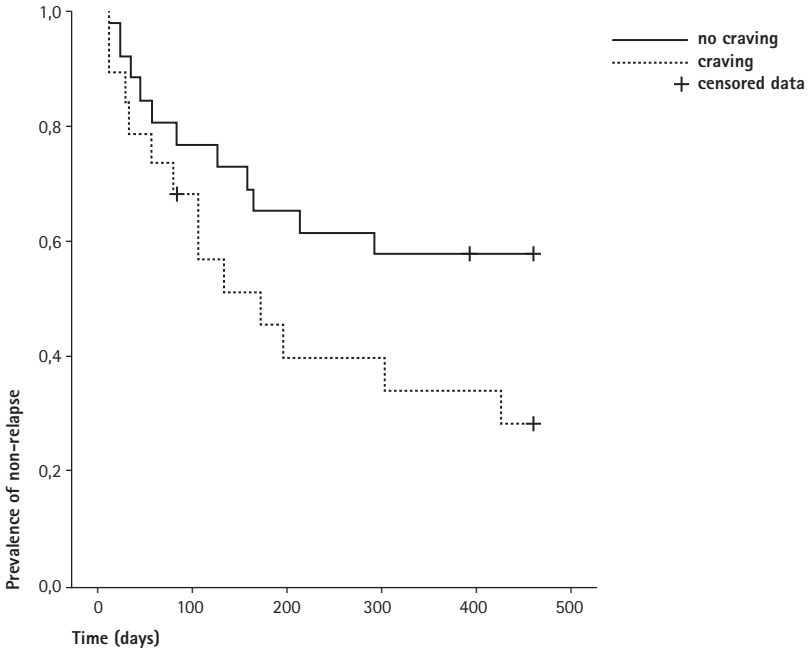


Table 2 Univariate and independent predictors of relapse in successful quitters after a tapering off programme

	Univariate[a]		Multivariate[b]	
Variables	**Hazard Ratio [95% CI]**	**p-value**	**Hazard Ratio [95% CI]**	**p-value**
BCQ[c] sum score (range 0 – 20)	1.28 [1.07 – 1.55]	.009	1.26 [1.02 – 1.54]	.029
Age (years)	1.04 [1.00 – 1.07]	.063	1.06 [1.02 – 1.11]	.007
Insurance status (1 = private; 0 = NHS)	0.43 [0.18 – 1.06]	.068	0.30 [0.11 – 0.77]	.013
Duration of benzodiazepine use (years)	1.00 [1.00 – 1.01]	.080		
Problematic use (Bendep-SRQ sub scale)	1.37 [0.92 – 2.06]	.125		
Preoccupation (Bendep-SRQ sub scale)	1.32 [0.96 – 1.80]	.085		
Lack of compliance (Bendep-SRQ sub scale)	6.42 [1.42 – 29.1]	.016	8.25 [1.71 – 39.9]	.009
Withdrawal (Bendep-SRQ sub scale)	1.25 [0.97 – 1.60]	.083		
Pain (SF-36 sub scale)	0.86 [0.74 – 1.00]	.055		
General health perception (SF-36 sub scale)	0.91 [0.84 – 1.00]	.039		
Vitality (SF-36 sub scale)	0.92 [0.85 – 1.00]	.039		
Mental health (SF-36 sub scale)	0.91 [0.85 – 0.98]	.017		
GHQ-12 sum score	1.15 [0.98 – 1.35]	.091		
Anger (POMS sub scale)	1.06 [0.99 – 1.13]	.099		
Fatigue (POMS sub scale)	1.06 [1.00 – 1.12]	.044		
Vigor (POMS sub scale)	0.93 [0.86 – 1.00]	.048		
Shyness (NVM sub scale)	0.95 [0.89 – 1.01]	.080		
Extraversion (NVM sub scale)	1.08 [1.00 – 1.16]	.039		
			Model: $\chi^2 = 22.6$; $df = 4$; $p < 0.001$	

[a] Only the independent variables that had p-values of less than 0.15 in the univariate regression analyses are shown in the table.

[b] All univariate predictors were entered in the first block, using a forward Wald procedure, where after the BCQ score was added in the second block.

[c] Benzodiazepine Craving Questionnaire

DISCUSSION

This is the first study examining the effect of benzodiazepine craving on relapse after successful discontinuation. We found different results in our two groups of interest: in patients able to discontinue on their own after receiving a discontinuation letter, we did not detect any effect of craving on subsequent relapse. However, in long-term benzodiazepine users who needed additional treatment to discontinue successfully, i.e. a supervised tapering off protocol, a higher extent of craving, as measured with the Benzodiazepine Craving Questionnaire (BCQ), predicted relapse during a 15-month follow-up period, independent of other predictors. This differential effect of craving was probably best explained by population characteristics. Patients who were able to discontinue relatively easy, i.e. with the aid of a discontinuation letter, probably lacked the significant influence of dependence characteristics and therefore hardly experienced any craving, as supported by the low BCQ sum scores and lack of variance herein.

Interpretation of our results is hampered by the lack of previous benzodiazepine relapse studies to compare with. To our knowledge, only two studies specifically examined relapse after successful discontinuation by means of a supervised benzodiazepine tapering off programme, but none of them included measures of benzodiazepine craving.[13,14] The study of Morin et al[13] was limited to long-term benzodiazepine users suffering from insomnia (n = 47). They found end of treatment insomnia severity and psychological distress as predictors of relapse, analogous to univariate effects of mental health characteristics in our study (subscale mental health of the SF-36, respectively, anger, fatigue, and vigour of the POMS). However, in our multivariate model, these characteristics lost significance after correction for age, socioeconomic status and benzodiazepine dependence severity (subscale lack of compliance of the Bendep-SRQ) of which the latter variable had not been included by Morin et al.[13] The other study reported a negative association between self-efficacy in coping without benzodiazepine use and relapse after successful supervised tapering off, based on a small study of 12 patients with anxiety or insomnia of which 3 had relapsed at 3-months follow-up.[14] In various studies on smoking, higher levels of self-efficacy are consistently associated with decreased craving (e.g.[25,26]), whereby findings from O'Conner et al[14] appear to be in line with our findings. Similar to our results, Morin et al[13] and O'Connor et al[14] did not find an effect of benzodiazepine dosage, suggesting that this variable is only important for achieving successful discontinuation after supervised tapering off but not in subsequent relapse.[11]

Since the study was conducted in primary care, mainly elderly low-dose users were included, thereby limiting generalisation to high-dose benzodiazepine users. In previous reports on the second step of this study, i.e. the randomised controlled trial, we have shown that the participants were representative of all long-term benzodiazepine users unable to discontinue by themselves after receiving a discontinuation letter, with respect to age, gender, and benzodiazepine dosage (for details and discussion see[4]). Nevertheless, even if our recruitment process has led to significant selection bias, this bias is probably

comparable to clinical practice in which most likely only motivated patients will be referred for benzodiazepine discontinuation treatment.

The concept of low-dose benzodiazepine dependence has been criticised by some researchers, mainly for two reasons: (i) the number of benzodiazepine users who escalate their dosage beyond therapeutic levels is low,[27] and (ii) long-term, low-dose benzodiazepine usage is considered as 'normal physical dependence' necessary for the long-term treatment of chronic anxiety and should therefore not be considered abuse or addiction.[28] Advocates of the concept of low-dose benzodiazepine dependence emphasise that (a) the withdrawal syndrome for benzodiazepine includes unique symptoms that can be distinguished from rebound anxiety,[29] that (b) withdrawal symptoms are identical for low-dose and high-dose users,[30] and finally, (c) that approximately half of all low-dose users fulfil DSM-III-R criteria for dependence.[3] Our results contribute to these latter arguments by showing that craving, a concept specifically associated with the use of addictive substances, predicts relapse after successful discontinuation of low-dose benzodiazepine usage.

Our findings point to a potentially important role for craving in subsequent relapse after successful benzodiazepine discontinuation, but only for the subgroup of low-dose benzodiazepine users who need specific treatment for benzodiazepine discontinuation in clinical practice. If these results hold true in subsequent studies, they should guide relapse prevention programmes, including treatment elements with a focus on (coping with) craving experiences.

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Chapter 7

General discussion

DISCUSSION

The focus of this thesis has been on the development and initial validation of the Benzodiazepine Craving Questionnaire (BCQ). The BCQ was developed within a population of long-term and former long-term general practice benzodiazepine users participating in a large benzodiazepine discontinuation trial in the Netherlands. With this study we have made an attempt to fill a gap in craving research and we have contributed to the understanding of craving for benzodiazepines.

In this chapter we address the strengths and limitations of this study on the basis of the results and present the major conclusions of this thesis. Adaptations and ideas for further research are suggested in order to further substantiate the psychometric properties of the BCQ. Finally, some potential clinical implications are discussed.

STRENGTHS AND LIMITATIONS

The results of our study have already been discussed in the previous chapters of this thesis. Below, the (methodological) strengths and limitations of our study are addressed, together with their implications for the interpretation of the results.

Study participants: generalisability of our results

The development of the BCQ took place within the Benzoredux project, a two-part treatment intervention aimed at reducing long-term benzodiazepine use in general practice. Patients from rural and urban general practices were selected a priori by means of a computerised search with benzodiazepine use for more than three months as the principal criterion. Patients also had to meet our other inclusion criteria. The attrition rate was fairly high for both treatment interventions (about 35% of the patients turned down the invitation to evaluate their cut down attempt after the discontinuation letter from their general practitioner, and only 17% took part in the tapering off trial, respectively).[1,2] Although high-dose benzodiazepine users were not excluded beforehand, the average benzodiazepine dose levels were rather low and within the therapeutic range. Nevertheless, this low participation rate was comparable with another Dutch general practice study.[3] For users of high dosages of benzodiazepines any intervention may appear aversive. These users possibly are not ready to undertake action to change at all.[4] Stages of change research into other substances of abuse has suggested that attrition and drop-out rates are significantly higher for users who are not ready to change their behaviour than for users who are.[5-7] In that respect the results of our study seem to be in line with previous work.

We also expect that, among others, dependence might have played a role in the low participation rate and the use of low benzodiazepine dosages among participants, implicating that the more severely dependent patients possibly refused to take part in our study. Research has shown that 40% of all benzodiazepine users in general practice meet

dependence criteria according to DSM-III-R.[8] This suggestion was supported by our own Bendep-SRQ cross-validation study, although Bendep-SRQ subscale scores were significantly lower in our study (which supports the hypothesis that the more severely dependent patients refused to participate).[9] In addition, craving might have played a role as well. Linden et al.[10] labelled the refusal of two-thirds of their long-term low-dose benzodiazepine users to take a short drug-free intermission as craving. Nonetheless, our findings are of interest for and reflect daily clinical practice since our study selectively recruited those patients who were prepared to try to discontinue their usage, whereas the non-participants probably will never be treated in day-to-day practice to reduce their benzodiazepine use.

The abovementioned has influenced the degree of generalisability of our BCQ data. Ideally, one would draw a random, stratified or a multi-stage sample from a 'sampled population' in order to get a good enough representation of the population. For administrative and logistic reasons, it was not possible to get the most optimal sample for the development of the BCQ. However, the choice to develop the BCQ within this Benzoredux population was acceptable because of the existing lack of research into benzodiazepine craving and the fact that we applied population independent Rasch analyses. Furthermore, the Benzoredux project aimed to include as many benzodiazepine users as possible and it was a minimal extra strain for participants to fill in the BCQ. The abovementioned, however, calls for replication of our study in a comparable, but less selective sample.

Development of the BCQ

Rasch scaling model

The design of the Benzoredux project implicated the use of (self-report) questionnaires. There was no valid benzodiazepine craving instrument available, so we had to develop one and examine its psychometric properties.

Questionnaires are usually developed in accordance with 'classical test theory'. One of the major problems with classical test theory is its population dependence.[11] Drawbacks of scale construction by means of factor analysis have been described in chapters 2 and 5 (e.g. population characteristics are well known confounders of factor structures). Furthermore, common questionnaires use sum scores as an indicator of craving severity, however, the conceptual homogeneity of the items in a scale is not addressed by the classical test theory.[12]

'Item response theory' or 'latent trait theory', however, addresses both issues. This theory was developed without any reference to any population (i.e. it is population independent) and it has provided a theoretical framework to assess the consistency between the latent trait, i.e. the underlying construct, and the specific responses on a set of items.[11] The main reason for choosing a model based on item response theory (i.c. Rasch scaling model) in this study, therefore, was to be able to properly use the sum scores of the BCQ as a sufficient statistic for the underlying construct, i.e. craving.

Although the advantages of the item response theory over classical test theory have been

outlined (see chapters 2 and 5 and [13] for an elaboration on Rasch analysis) there are some limitations to the use of the Rasch scaling model caused by the limitations of the computer program used to analyse the data, the Rasch Scaling Computer Program (RSP). This program requires dichotomisation of the BCQ items, implicating the loss of valuable information contained in the data, possibly causing reduction in scale discriminability.

Theories on the polytomous Rasch model have been described,[11] in which the sum score of the original item scores are a sufficient parameter for the subject parameter. Computerised programs that can be applied on polytomous items became available in the last few years.

There are other modern measurement models available that are based on item response theory and do not require dichotomisation of the data, e.g. the nonparametric Mokken models. Some authors advise to use not just one model for analysing data but to use several, because of the different measurement properties and different methods for data analysis.[14] Compared with the Mokken models, the Rasch scaling model is best applied when the number of items is rather high (e.g. greater than 20).[15] Furthermore, the Rasch scaling model is more restrictive. In other words, it is easier to meet the assumptions of a nonparametric model than it is to meet those of a parametric model. The Rasch scaling model gives more profound information about scale and item properties. Only with parametric information about the latent trait and the responses of the subjects to items it is possible to provide standardized test scores.[16] Future research should be directed at Latent Trait Standardisation of the BCQ, on the basis of a normative population of general practice benzodiazepine users.

Unidimensionality of benzodiazepine craving

The way Tiffany et al.[17,18] approached the development of the Questionnaire on Smoking Urges (QSU) and the Cocaine Craving Questionnaire (CCQ) appealed to us as a starting point for the BCQ, because of the broad scope of their craving definition. The QSU contains items from four different conceptual areas relevant to cigarette craving, in order to cover current craving theories as widely as possible: 1) desire to use, 2) anticipation of positive outcome, 3) anticipation of relief of withdrawal or (withdrawal-associated) negative affect, and 4) intention to use. We derived an additional fifth category, 'lack of control over use' from the CCQ.

Tiffany et al. propose that craving should be considered as a multidimensional construct. Many researchers have shared this view and have supported it with evidence through their research (e.g.[19-23]). They found that at a primary level their questionnaires had two to four dimensions, representing different aspects of craving report. Nonetheless, these dimensions were themselves moderately to strongly intercorrelated, suggesting the presence of one higher-order general craving factor.[17,18,20,24]

For reasons described above, we have chosen a different test methodology for the development of the BCQ, by applying the Rasch scaling model on our data. The Rasch scaling model held true, leading to a 20-item unidimensional scale, implicating that benzodiazepine craving could be defined as a continuum from (almost) none to very high.

Although unidimensional as a construct, all conceptual areas described above were represented in the BCQ. In other words, looking at the item contents, benzodiazepine craving still incorporated a variety of features, including not only the desire to use, but also aspects of anticipation of positive outcome, anticipation of relief of withdrawal or (withdrawal-associated) negative affect, intention to use, and lack of control (see the appendix of chapter 2 for an overview of the Rasch-homogeneous BCQ items; see appendix C for an overview of the original 48 items of the BCQ, in Dutch).

Due to the differences in research methodology and substances under investigation, comparability of the abovementioned studies with our study is limited. Further research should reveal whether or not the structure of craving is essentially unidimensional for all substances of abuse.

Low BCQ sum scores

Average BCQ sum scores were very low. Bendep-SRQ sum scores were also relatively low, indicating that the majority of our study population was dependent on their benzodiazepines only to a fairly limited extent. We found moderate associations between these two variables. Craving and dependence do not seem to be big issues for the majority of our study population.

An additional explanation for the low sum scores was given in chapter 2, referring to long half-lives and slow onset of action of most benzodiazepines compared with other substances of abuse in which craving is reported more often and to a higher extent. One might also argue that the lack of variance in the sum scores is due to the lack of sensitivity of our questionnaire to detect craving in this population. However, this does not seem to be the case, since the BCQ was sensitive enough to detect variation in craving over time (see chapter 4). Moreover, Rasch scale values indicated sufficient item-spacing in the lower regions of the BCQ (confirmed first in case of craving) (see the appendix of chapter 2).

Validity of the BCQ

By lack of a 'golden standard' for craving, the validity of the BCQ was assessed by comparing it with other (theoretically relevant) measures, in accordance with classical test theory. In chapter 2 construct validity was assessed by associating BCQ sum scores with potentially (theoretically) related constructs, resulting in modest construct validity.

Another approach to assess construct validity is by comparing it with a chosen external standard, such as an expert's clinical judgement. The specific item order, generated if the Rasch model holds true, based on increasing Rasch scale values reflecting increasing levels of craving, offers a new approach to assess construct validity. Two independent expert assessors (physicians) interpreted the specific item order and the contents of the items. This made it possible to formulate theoretical rationales that reflected a more thorough understanding of the latent trait, i.e. the underlying dimension, supposedly craving. Clearly, this interpretation was subjective and the theoretical rationales could be challenged by alternative ones.[13] However, the item order determined by the independent assessors

can be statistically compared to the item order empirically found in the Rasch analysis using Kendall's tau-c correlation coefficient, with correction for nodes. Substantial correlation coefficients were found between the item order given by the two independent assessors and the item order found using Rasch analysis (Kendall's tau-c = .59, $p < .0001$ and Kendall's tau-c = .37, $p = .005$, respectively). The intercorrelation between assessor 1 and assessor 2 was .65 ($p < .001$). These findings suggest that the underlying dimension (latent trait) is indeed benzodiazepine craving. *(personal communication of the author)*

Implications of our results in the light of (neuro)biological findings

In this study (neuro)biological approaches of craving were left aside. From these perspectives, theories on the concept and aetiology of craving have been described.

Many complex neurobiochemical mechanisms have been implicated in the aetiology of craving for substances of abuse other than benzodiazepines, involving several neurotransmitter systems. Results are mainly based on animal studies.[25-27] Benzodiazepines exert their effects by binding on the gamma-aminobutyric acid receptor type A ($GABA_A$ receptor) enlarging the inhibitory effects of GABA, the most frequently used inhibitory neurotransmitter in the central nervous system. Discontinuation of benzodiazepines leads to decreased inhibitory activity of GABA. One might hypothesise that this, in turn, leads to more arousal and results in increased desire (craving) for relief from this arousal. This is in line with one of the three pathways of the psychobiological model of alcohol craving proposed by Verheul et al.,[27] named 'relief craving' (i.e. a desire for the reduction of tension or arousal, associated with the GABAergic/glutaminergic system). We have found that patients who are still using benzodiazepines, but who are in the process of discontinuation, experience more severe craving than patients who have quit their use. In line with the abovementioned model, it is clear that the former subgroup continuously disturbs the GABAergic system with the ongoing process of quitting, causing arousal hence leading to 'relief craving'. However, the fact that the patients who experienced craving were more vulnerable in terms of dependence, withdrawal symptoms, personality traits, mood aspects, health-related quality of life, and psychopathology, suggests the involvement of other neurobiochemical mechanisms in the aetiology of craving as well. Further research should lead to a better insight into these matters.

EEG, PET and fMRI studies have indicated that craving involves several interacting brain regions (for a review, see e.g.[25,28,29]). Several PET/fMRI studies have found a consistent relationship between the degrees of brain activity and self-reported craving in other substances of abuse.[30,31] To our knowledge there has not been any research in this area directed at benzodiazepines.

Integrating psychological and neurobiochemical approaches offers opportunities to further expand our knowledge about the mechanisms underlying craving for benzodiazepines, its conceptualisation and its measurement.[25]

Implications of our results in the context of current psychological craving theories

With respect to the items that are confirmed first in case of craving, i.e. in cases of low craving severity, the emphasis is on (cognitive aspects of) affect regulation. These items are from the item categories anticipation of positive outcome and anticipation of relief of withdrawal or (withdrawal-associated) negative affect. In our study population, expectations of positive effects of benzodiazepine use constitute the first signs of benzodiazepine craving. BCQ items indicative of more severe craving, referring to the desire to use benzodiazepines, intention to use and lack of control over use, which are present in the higher regions of the Rasch rank order, were hardly confirmed in our study population. These items refer to more obvious dependence aspects. Further research into other, high-dose and high-dependence, benzodiazepine-using populations should reveal whether or not craving in these groups covers the entire spectrum of items. Up till now it is unclear whether different groups of users have different craving profiles.[26,27,32]

In this thesis we have referred to various cognitive craving theories to explain and compare our results with (e.g. the cognitive labelling model in chapter 3). Most of the cognitive theories are based on the cognitive social learning theory.[33] Although this is predominantly a theory of relapse, it has relevance to understanding craving (and its role in relapse). It incorporates both positive and negative affect states (whether or not in response to cues) and the expectancies of drug effects. In this theory craving is regarded as a 'desire for positive drug effects', which is in line with the description of benzodiazepine craving for our study population. The cognitive social learning theory also invokes conditioning theory: 'craving may be a conditioned response elicited by stimuli associated with past gratification'. This theory regards craving and self-efficacy reciprocally related (high craving undermines self-efficacy as it challenges the patient's coping skills). In chapter 6 we have briefly mentioned this possible undermining effect of craving on self-efficacy and coping, and thereby increasing the likelihood of relapse. In our opinion, treatment strategies should take these explicit drug expectancies into account and focus on coping without benzodiazepines.

Conditioning theories have taken up a central role in contemporary theories on addiction and craving. They have been influential in the development of cue exposure treatments. However, the efficacy of these cue exposure therapies as a treatment for addictive disorders has been questioned in recent studies (e.g.[34,35]). A recent review of human-nicotine-conditioning studies provided evidence for both (emotional) conditioning and expectancies in mediating addictive behaviour, among which was subjective craving.[36]

We believe it is too soon to draw definite conclusions. Results can be looked upon from different angles. In general, little research has been directed at testing specific craving theories. In addition, none of the theories seem to provide a full explanation of the phenomenon of craving.[37] As Sayette et al.[38] have argued: 'there is no single craving construct; there are as many craving constructs as there are craving theories. Construct validity is not derived from a single study; rather it is inferred from the accumulation of data through ongoing research'.

MAJOR CONCLUSIONS

- The benzodiazepine Craving Questionnaire (BCQ) is the first multi-item instrument to assess benzodiazepine craving of which the psychometric properties have been addressed in detail and have shown to be promising.
- Benzodiazepine craving, as assessed with the BCQ, can be regarded as a unidimensional construct (ranging from almost none to very high).
- High craving for benzodiazepines is characterised by desire to use, intention to use and lack of control.
- The first signs of craving in benzodiazepine use are represented by expectations of positive outcome and expectations of relief from withdrawal or negative affect.
- Patients who report craving for benzodiazepines are significantly less able to quit their benzodiazepine use after a minimal intervention (letter from their general practitioner). They are a more vulnerable subgroup (with respect to benzodiazepine dependence, withdrawal symptoms, personality traits, mood aspects, health-related quality of life, and psychopathology) than patients who do not report craving.
- BCQ sum scores may give direction to the advisable treatment intensity, in terms of type of intervention by the general practitioner, when a patient is trying to abstain from benzodiazepines.
- In long-term benzodiazepine users who receive additional treatment to discontinue benzodiazepine use successfully, i.e. a supervised tapering off protocol after a failed attempt to quit on their own, benzodiazepine craving predicts relapse during a 15-month follow-up period independent of other predictors.
- The BCQ is able to monitor and quantify self-reported benzodiazepine craving longitudinally.
- After taking part in a discontinuation trial, the severity of craving decreases over time for both patients who are able to quit their benzodiazepine use and patients who continue taking benzodiazepines.
- In our study the majority of long-term benzodiazepine users in general practice hardly experiences any craving at all, either while still using or after having quit. Nonetheless, about 33% of our patients indicated to experience benzodiazepine craving to some extent. In addition, the data suggested that the most severely dependent patients (with possibly the highest degree of craving) did not participate in the study.
- Benzodiazepine craving in our general practice population is associated with negative affect. This underlines the importance of achieving a more precise understanding of negative affect (both as state and trait manifestations) as a possible cue for benzodiazepine craving. If certain mood states are cues for benzodiazepine craving they demand treatment attention.

RECOMMENDATIONS FOR FUTURE STUDIES

The BCQ can be improved further. Firstly, reliability and validity could gain from adding new items to the BCQ. These should be formulated in line with the theoretical rationale (i.e. craving) of the BCQ. Formulating appropriate new items would contribute to the improvement of 'equal item spacing', especially in the higher regions of the BCQ (confirmed only in case of more severe craving). Removing items without item spacing will lead to a more efficient questionnaire.

Secondly, it is important to repeat our research in other populations, e.g. psychiatric inpatients, inpatients at drug centres (multi-drug users) and general hospital inpatients. Theoretically, the Rasch scaling model has been shown to be population-independent. It can therefore be expected to hold true in other benzodiazepine using populations as well. Repeating our study will contribute, however, to obtaining a better understanding of benzodiazepine craving.

Thirdly, future research should also be directed at Latent Trait Standardisation of the BCQ, on the basis of a normative population of general practice benzodiazepine users. Latent Trait Standardisation requires the Rasch scaling model with the additional assumption of a normally distributed latent trait. It would make raw BCQ scores clinically interpretable in relation to the normative general practice sample of benzodiazepine users.

Clearly, as stated in chapter 2 good psychometric characteristics may be considered only a basic requirement for the usefulness of an instrument. Further research is needed to reveal the clinical utility of the BCQ in terms of its contribution to the effectiveness of treatment interventions. Follow-up data gathered at the start and at different follow-up stages of benzodiazepine reduction trials in other populations may provide more insight in the role of craving in successful abstinence and relapse.

CLINICAL IMPLICATIONS

It has become clear from this study that, although not to a very large extent, craving for benzodiazepines can be an issue for some long-term general practice benzodiazepine users. Physicians should be aware of this.

At this stage of the development of the BCQ, we can only speculate about its future clinical implications. When the results of our study hold up in future research, a completed BCQ may give physicians information on how to proceed when a patient expresses the wish to discontinue benzodiazepine use. It may give direction to the appropriate treatment intensity (supervised tapering off or not). To some extent, it can inform physicians about the patient's vulnerability in terms of e.g. personality, especially negative affect. And finally, when a patient indicates to experience craving on the BCQ, physicians should be aware of the chance of relapse even after supervised tapering off. Furthermore, on the basis of the contents of the confirmed items, the physician could engage in a dialogue with

the patient about the expectations of the effects of benzodiazepines, and focus on how to cope without benzodiazepines. This could help the patient-physician working alliance and, in turn, the patient's motivation and self-efficacy to quit benzodiazepine use and cope with craving.

Finally, in clinical practice the utility of an instrument also depends on the amount of time that is required to administer the instrument. The amount of time it takes to complete the BCQ is limited and it does not require special training.

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APPENDIX A
Benzodiazepine Craving Questionnaire (BCQ)

A.J.J. Mol, M.H.M. Breteler, F.G. Zitman

Tijdstip invullen BCQ: |___|___|:|___|___| uur
Patiënt gebruikt BZ als slaapmiddel/kalmeringsmiddel/beide (omcirkel wat van toepassing is)

Datum laatste BZ gebruik: |___|___|-|___|___|-20|___|___|
Tijdstip laatste BZ gebruik: |___|___|:|___|___| uur

Instructie
Alle beweringen in deze vragenlijst gaan alléén over de slaap- en kalmeringsmiddelen (behorend tot de benzodiazepinen, afgekort als BZ) die u daarnet heeft opgegeven. Als het in de vragen gaat over "de BZ", "een BZ" of "BZ" dan worden alléén deze slaap- en kalmeringsmiddelen bedoeld.

Voorbeeld
De vraag "Als ik nu een BZ zou nemen dan zou ik me minder geremd voelen."
Als u bijvoorbeeld valium (diazepam) gebruikt(e) leest u: "Als ik nu valium zou nemen dan zou ik me minder geremd voelen."

Wilt u aangeven in welke mate u het eens of oneens bent met de volgende beweringen door een kruisje te zetten op iedere lijn tussen ERG MEE ONEENS en ERG MEE EENS.
Zo: |_X_|
Hoe dichter u uw kruisje zet bij "erg mee oneens", hoe meer u het met de bewering oneens bent. Hoe dichter u uw kruisje zet bij "erg mee eens", hoe meer u het met de bewering eens bent.

Vult u alstublieft iedere vraag in!
We willen graag weten wat u op dit moment, terwijl u de vragenlijst invult, denkt of voelt.

1 Het innemen van een BZ zou me nu gelukkiger maken.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

2 Ik bedenk manieren om aan BZ te komen.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

3 Als ik nu een BZ zou hebben ingenomen zou ik helderder kunnen denken.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

4 Als ik een BZ zou innemen zou ik me op dit moment erg goed voelen.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

5 Op dit moment mis ik de BZ.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

6 Ik zou op dit moment bijna alles doen voor een BZ.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

7 Ik zou me erg alert voelen als ik nu een BZ zou innemen.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

8 Ik zou nu minder prikkelbaar zijn als ik een BZ zou kunnen innemen.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

9 Ik zou de hoeveelheid BZ die ik gebruik nauwelijks in de hand kunnen houden als ik er enkele bij me had.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

10 Op dit moment snak ik naar een BZ.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

11 Ik moet nu een BZ innemen.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

12 Ik zou mezelf nauwelijks kunnen tegenhouden BZ te gebruiken als ik er nu hier wat had.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

13 Door het innemen van een BZ zou ik me nu minder vermoeid voelen.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

14 Niets zou beter zijn dan op dit moment een BZ innemen.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

15 Het innemen van een BZ zou me minder neerslachtig maken.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

16 Op dit moment heb ik dringend behoefte aan een BZ.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

17 Als ik een BZ aangeboden zou krijgen, zou ik hem onmiddellijk innemen.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

18 Nu een BZ innemen zou ervoor zorgen dat de dingen volmaakt lijken.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

19 Als ik op dit moment een BZ zou hebben ingenomen, zou ik me minder vervelen.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

20 Het zou moeilijk zijn om nu direct BZ af te slaan.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

vervolg op de volgende pagina

21 Mijn verlangen om een BZ te nemen lijkt overweldigend.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

22 Als er een BZ vlak voor me zou liggen zou het moeilijk zijn hem te laten liggen.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

23 Op dit moment verlang ik naar een BZ.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

24 Ik wil nu een BZ innemen.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

25 Ik zou de boel op dit moment beter onder controle hebben als ik een BZ kon innemen.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

26 Ik zou op dit moment van een BZ genieten.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

27 Als ik nu een klein beetje BZ zou gebruiken, zou ik mezelf er nauwelijks van kunnen weerhouden om meer in te nemen.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

28 Als ik nu een BZ zou nemen dan zou ik me minder geremd voelen.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

29 Het enige dat ik op dit moment wil is een BZ.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

30 Ik ga zo snel mogelijk een BZ nemen.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

31 Ik zou me energiek voelen als ik BZ zou innemen.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

32 Ik zal een BZ nemen zodra ik de kans krijg.
ERG MEE ONEENS |___|___|___|___|___|___|___| ERG MEE EENS

- Bedankt voor uw medewerking -

APPENDIX B
Benzodiazepine Desire Scale (BDS)

A.J.J. Mol, M.H.M. Breteler, F.G. Zitman

Instructie

Beantwoord de onderstaande beweringen op een schaal van 1 tot 10 door een kruisje te zetten in het hokje dat het meest voor u van toepassing is.

A Welk deel van de tijd ervoer u een verlangen naar benzodiazepinen in de afgelopen week?
(d.w.z. uw verlangen naar een slaap- of kalmeringsmiddel, terwijl u er geen had ingenomen.)

nooit |___|___|___|___|___|___|___|___|___|___| constant

B Hoe hevig was uw verlangen naar benzodiazepinen in de afgelopen week over het algemeen?
(d.w.z. uw verlangen naar een slaap- of kalmeringsmiddel, terwijl u er geen had ingenomen.)

weinig of geen verlangen |___|___|___|___|___|___|___|___|___|___| erg sterk verlangen

C Probeert u zich het moment in de afgelopen week te herinneren waarop uw verlangen naar benzodiazepinen het hevigst was. (d.w.z. uw verlangen naar een slaap- of kalmeringsmiddel, terwijl u er geen had ingenomen.) Hoe sterk was het verlangen op dat moment?

weinig of geen verlangen |___|___|___|___|___|___|___|___|___|___| onweerstaanbaar verlangen

- Bedankt voor uw medewerking -

APPENDIX C
Original 48 items of the BCQ (in Dutch)

Oorspronkelijke 48 BCQ items, geordend naar itemcategorie

	i	ii	iii
DESIRE TO USE			
Op dit moment mis ik de BZ.	x	1	c
Op dit moment snak ik naar een BZ.	x	1	
Ik moet nu een BZ innemen.	x	1	d
Op dit moment heb ik dringend behoefte aan een BZ.	x	1	d
Mijn verlangen om een BZ te nemen lijkt overweldigend.		1	
Op dit moment verlang ik naar een BZ.		1	c
Ik wil nu een BZ innemen.	x	1	c
Het enige dat ik op dit moment wil is een BZ.	x	1	
ANTICIPATION OF POSITIVE OUTCOME			
Het innemen van een BZ zou me nu gelukkiger maken.		1	
Als ik nu een BZ zou innemen zou ik nauwelijks beter slapen.			a, e
Als ik een BZ zou innemen zou ik me op dit moment erg goed voelen.	x	1	
Als ik nu een BZ zou innemen, dan zou ik de situatie nauwelijks beter in de hand hebben.			a, e
Als ik nu een BZ zou innemen zou ik me nauwelijks ontspannener voelen.			a, e
Ik zou me erg alert voelen als ik nu een BZ zou innemen.		2	
Een BZ zou nu weinig voldoening geven.		2	a
Niets zou beter zijn dan op dit moment een BZ innemen.	x	1	
Het innemen van een BZ zou onaangenaam zijn.		1	a
Nu een BZ innemen zou ervoor zorgen dat de dingen volmaakt lijken.		2	
Een BZ zou me op dit moment slecht bevallen.		1	a
Ik zou op dit moment van een BZ genieten.	x	1	c
Als ik nu een BZ zou nemen dan zou ik me minder geremd voelen.	x		e
Ik zou me energiek voelen als ik BZ zou innemen.	x	2	
ANTICIPATION OF WITHDRAWAL OR NEGATIVE AFFECT			
Ik zou me lichamelijk nauwelijks beter voelen als ik een BZ zou hebben ingenomen.		1	a, b
Het innemen van een BZ zou me nu nauwelijks helpen om rustiger te worden.		1	a, b
Als ik nu een BZ zou hebben ingenomen zou ik helderder kunnen denken.		1	
Ik zou nu minder prikkelbaar zijn als ik een BZ zou kunnen innemen.		1	
Door het innemen van een BZ zou ik me nu minder vermoeid voelen.	x	1	
Het innemen van een BZ zou me minder neerslachtig maken.	x	1	
Als ik op dit moment een BZ zou hebben ingenomen, zou ik me minder vervelen.		1	
Ik zou de boel op dit moment beter onder controle hebben als ik een BZ kon innemen.	x	1	
Als ik een BZ zou gebruiken zou mijn ergernis nauwelijks verminderen.			a, e

	i	ii	iii
INTENTION TO USE			
Ik bedenk manieren om aan BZ te komen.		2	
Vanaf nu zou ik het heel lang kunnen uithouden zonder BZ.		1	a
Op dit moment heb ik geen plannen om een BZ in te nemen.		1	a
Ik zou op dit moment bijna alles doen voor een BZ.	x	1	
Als ik de kans had om een BZ in te nemen, dan zou ik er waarschijnlijk van afblijven.		2	a
Als ik een BZ aangeboden zou krijgen, zou ik hem onmiddellijk innemen.	x	1	
Al had ik een tablet in de hand die net uit de strip was gedrukt, dan zou ik hem waarschijnlijk laten liggen.		1	a
Ik ga zo snel mogelijk een BZ nemen.	x	1	
Ik zal een BZ nemen zodra ik de kans krijg.	x	1	
LACK OF CONTROL OVER USE			
Ik zou de hoeveelheid BZ die ik gebruik nauwelijks in de hand kunnen houden als ik er enkele bij me had.	x	2	b
Ik zou mezelf nauwelijks kunnen tegenhouden BZ te gebruiken als ik er nu hier wat had	x	2	b
Ik zou makkelijk in de hand kunnen houden hoeveel BZ ik op dit moment zou gebruiken.		2	a
Ik denk dat ik de verleiding om een BZ in te nemen nu kan weerstaan.		2	a
Het zou moeilijk zijn om nu direct BZ af te slaan.		2	
Als er een BZ vlak voor me zou liggen zou het moeilijk zijn hem te laten liggen.		2	
Het zou gemakkelijk zijn om de kans om BZ te gebruiken te laten schieten.		2	a
Als ik nu een klein beetje BZ zou gebruiken, zou ik mezelf er nauwelijks van kunnen weerhouden om meer in te nemen.		2	b

i) De 20 items die de Rasch homogene schaal vormen

ii) Lijst van herkomst. 1=Questionnaire on Smoking Urges; 2=Cocaine Craving Questionnaire

iii) a. Reverse-keyed items die, naar aanleiding van pilotresultaten, uit de lijst zijn verwijderd en niet meededen in de analyses.
b. Oorspronkelijk item was negatief verwoord (in Engels: 'not')
c. Oorspronkelijk item was reverse-keyed
d. Oorspronkelijk item herschreven voor een beter begrip in het Nederlands
e. Item is niet aanwezig in QSU of CCQ

Summary

CRAVING FOR BENZODIAZEPINES
The development of the Benzodiazepine Craving Questionnaire

This thesis describes the development and initial validation of the Benzodiazepine Craving Questionnaire, a Rasch-homogeneous self-report questionnaire to assess craving for benzodiazepines. This questionnaire was developed as part of the Benzoredux project, which was designed to evaluate a stepped-care approach to reduce long-term benzodiazepine use in general practice.

In **chapter 1** some aspects of (long-term) benzodiazepine use are discussed, such as its definition and prevalence, and drawbacks of this use, e.g. dependence. Subsequently, we address the role of craving in dependence on addictive substances, and discuss some models of craving and recent developments in craving research. We find that benzodiazepine craving research is scarce and that a good benzodiazepine craving questionnaire is lacking. These observations are the starting point of the development of the Benzodiazepine Craving Questionnaire and of this thesis.

In **chapter 2** we describe the development and initial validation of a newly constructed self-report questionnaire assessing craving for benzodiazepines, the Benzodiazepine Craving Questionnaire (BCQ). The BCQ was administered to a sample of 113 long-term and 80 former long-term general practice benzodiazepine users participating in the Benzoredux project. The BCQ met the requirements for Rasch homogeneity, i.e. self-reported benzodiazepine craving as assessed by this questionnaire can be regarded as a unidimensional construct. Reliability, as indicated by the subject and item discriminability, was good. Construct validity was modest: correlations between BCQ sum scores and other variables (dependence, personality, and psychopathology) were low. Discriminative validity was satisfactory. The first signs of craving were represented by the acknowledgement of expectations of positive outcome and of relief of withdrawal or negative affect, whereas desire, lack of control over use and direct intention to use were only found in cases of high craving. The BCQ was found to be a reliable and psychometrically sound self-report instrument to assess benzodiazepine craving in a general practice population of (former) long-term benzodiazepine users.

Chapter 3 aims to describe characteristics of patients reporting craving for benzodiazepines and to search for associations between benzodiazepine craving and other clinical variables in a population of general practice patients who had made an attempt to discontinue their long-term benzodiazepine use. Patients reporting craving for benzodiazepines on the BCQ differed significantly from patients not reporting craving on aspects of benzodiazepine dependence severity, psychological well-being, aspects of health-related quality of life,

aspects of a negative mood state (depression and anger), and certain personality traits (somatisation and negativism). Furthermore, in a multivariate analysis, controlling for current use status, depression and somatisation were positively associated with benzodiazepine craving. However, only the contribution of depression to craving was statistically significant for the total group of (former) benzodiazepine users (p = .002). These results call for further research with respect to the relationship between personality and benzodiazepine craving.

Since craving for different substances of abuse has been described to fluctuate over time, it is important that craving questionnaires are sensitive to changes over time. Therefore, in **chapter 4** we have aimed to assess benzodiazepine craving longitudinally and have described its course by means of the BCQ. A subset of 117 (former) long-term benzodiazepine users received four repeated measurements of the BCQ, taken over a 21-month follow-up period. Results indicated that benzodiazepine craving severity decreased over time. Patients still using benzodiazepines experienced significantly more severe craving than patients who had quit their use after either a minimal intervention (letter from their general practitioner with the advice to quit their use) or after a subsequent randomised controlled trial (tapering off programme with or without additional group cognitive-behavioural therapy). The method of discontinuation did not influence the experienced craving severity over time. However, patients who had received the additional tapering off programme, on average, reported significantly more severe craving than patients who had only received a letter from their general practitioner as an incentive to quit. It was concluded that, although benzodiazepine craving was prevalent among (former) long-term benzodiazepine users in our study population during and after discontinuation, it decreased over time to minimal proportions. Nevertheless, the BCQ proved to be an instrument capable of monitoring and quantifying craving for benzodiazepines longitudinally and it was sensitive enough to discriminate between different subgroups. The BCQ sum scores may give direction to the advisable treatment intensity, in terms of type of interference by the general practitioner, when a patient is trying to abstain from benzodiazepines.

Chapter 5 addresses the scope of the craving definition (broad versus narrow). We compared a broad conceptualisation of benzodiazepine craving, as represented by the BCQ, with a narrow one, as represented by the sum score of three one-item Likert-type scales assessing the frequency, global intensity and peak intensity of the desire for benzodiazepines when not using (the Benzodiazepine Desire Scale, BDS). In a factor analysis the BCQ loaded on a factor representing negative affect, while the BDS loaded on a dependence factor. Apparently, low craving, as measured with the BCQ, is associated with negative affect and reflects the anticipation of positive outcome of benzodiazepine use and of relief from negative affect or withdrawal. The low BCQ sum scores in our study population and the selected time frame of the craving measurement (current experience versus over the past week) were the most likely explanations for our findings. Both

conceptualisations of benzodiazepine craving contribute to our understanding of the potential significance and meaning of craving in benzodiazepine use.

Chapter 6 presents a Cox-regression analysis used to identify independent predictors of relapse after benzodiazepine discontinuation, with time to relapse as the dependent variable. Potential predictors included benzodiazepine (usage) characteristics, psychopathological symptoms, personality traits and characteristics of benzodiazepine dependence, including craving as measured with the BCQ. The BCQ sum score had no predictive value with respect to relapse after a minimal intervention (letter from the general practitioner). However, independent predictors of relapse during a 15-month follow-up period after a tapering off programme included higher craving sum scores on the BCQ, higher age, public health insurance, and higher 'lack of compliance' with the therapeutic benzodiazepine regimen. These results should guide relapse prevention programmes by including treatment elements with a focus on (coping with) craving experiences.

Chapter 7 mainly considers points of discussion that have not been addressed in the previous chapters. Furthermore, the major conclusions are presented along with recommendations for further research and some clinical implications.

First of all, we examine the generalisability of our results further and conclude that generalisability was probably reduced due to the large amount of patients who refused to take part in the Benzoredux study. Mainly low-dose benzodiazepine users took part in the study. Benzodiazepine dependence might have played a role here. Our findings probably represent daily clinical practice, as particularly those patients will take part in a discontinuation trial who are prepared to try to discontinue their benzodiazepine taking. Therefore the present study should be repeated in a less selective sample.

With regard to the development of the BCQ, the pros and cons of the use of the Rasch scaling model as compared with 'classical test theory' are addressed. The 'item response theory' or 'latent trait theory' on which the Rasch scaling model is based, justifies the use of the BCQ sum score as a measure for the underlying unidimensional construct of craving. The BCQ sum scores were low on average, which indicates that craving did not seem to be a big issue in our study population.

Comparing our study results with (neuro)biological findings from craving research into other substances of abuse, we have found some similarities with 'relief craving', as described in the 'three-pathway psychobiological model of craving for alcohol'.[1] However, benzodiazepine craving research in this field of expertise is lacking.

In our study population, expectations of positive effects of benzodiazepine use constitute the first signs of benzodiazepine craving. This makes our study results interpretable from the perspective of different cognitive theories on craving, e.g. the cognitive social learning theory. Treatment strategies should take these explicit drug expectancies into account.

BCQ items indicative of more severe craving for benzodiazepines, referring to the desire to

use benzodiazepines, the intention to use, and lack of control over use, were hardly confirmed in our study population. Further research in other, high-dose and high-dependence benzodiazepine-using populations should reveal whether craving in these groups covers the entire spectrum of BCQ items. Up till now it is unclear whether different groups of users have different craving profiles.

In addition to repeating the present study in different populations, the usefulness of the BCQ can be further improved by means of Latent Trait Standardisation on the basis of a normative population of general practice benzodiazepine users. It would make raw BCQ scores clinically interpretable in relation to the normative population. This would increase the usefulness of the BCQ in benzodiazepine reduction programmes in general practice.

Reference

1 Verheul R, Van den Brink W, Geerlings P. A three-pathway psychobiological model of craving for alcohol. Alcohol & Alcoholism 1999;34(2):197-222

Samenvatting

CRAVING NAAR BENZODIAZEPINEN
De ontwikkeling van de Benzodiazepine Craving Questionnaire

Dit proefschrift beschrijft de ontwikkeling en een eerste psychometrische evaluatie van de Benzodiazepine Craving Questionnaire, een Rasch-homogene zelf-rapportage vragenlijst om de mate van craving (hunkering) naar benzodiazepinen in kaart te brengen. Deze vragenlijst werd ontwikkeld in het kader van het Benzoredux-project. Het Benzoredux-project was ontworpen om een getrapte benadering, gericht op het terugdringen van langdurig benzodiazepinegebruik in de huisartspraktijk, te evalueren.

In **hoofdstuk 1** worden enkele aspecten van (langdurig) benzodiazepinegebruik belicht, zoals de definitie, de prevalentie en de nadelen van dit gebruik, waaronder afhankelijkheid. Vervolgens wordt ingegaan op de rol van craving bij afhankelijkheid van verslavende middelen. Ook worden enkele cravingmodellen en recente ontwikkelingen op het gebied van cravingonderzoek besproken. Er wordt vastgesteld dat onderzoek naar craving bij benzodiazepinegebruik schaars is en dat een goede vragenlijst om benzodiazepinecraving in kaart te brengen ontbreekt. Deze constateringen vormen het vertrekpunt van de ontwikkeling van de Benzodiazepine Craving Questionnaire en van dit proefschrift.

In **hoofdstuk 2** wordt de ontwikkeling en eerste validering van een nieuwe zelf-rapportage vragenlijst beschreven die craving naar benzodiazepinen meet: de Benzodiazepine Craving Questionnaire (BCQ). De BCQ is afgenomen bij een groep van 113 langdurige gebruikers en 80 voormalige langdurige gebruikers, allen huisartspatiënten die meededen aan het Benzoredux-project. De BCQ voldeed aan de vereisten voor Rasch-homogeniteit. Dit betekent dat zelf-gerapporteerde benzodiazepinecraving, zoals gemeten met de BCQ, beschouwd moet worden als een unidimensioneel construct. De betrouwbaarheid van de BCQ, zoals bepaald werd door middel van de subject-discriminabiliteit en item-discriminabiliteit, kon als goed worden beschouwd. De constructvaliditeit was matig: de samenhang tussen de somscores van de BCQ en andere variabelen (afhankelijkheid, persoonlijkheid, psychopathologie) was laag. De discriminatieve validiteit was toereikend. Verwachtingen omtrent een positief effect van het gebruik van de benzodiazepine en verwachtingen omtrent de verlichting van ontwenningsverschijnselen of een negatief affect, konden worden beschouwd als de eerste tekenen van craving. Alleen in geval van een hoge mate van craving was er daarnaast ook sprake van verlangen, controleverlies en de directe intentie om te gebruiken. De BCQ bleek een betrouwbaar en psychometrisch deugdelijk zelf-rapportage instrument te zijn om benzodiazepinecraving te meten in een huisartspatiëntenpopulatie van (voormalige) langdurige benzodiazepinegebruikers.

Hoofdstuk 3 beschrijft de kenmerken van patienten die craving naar benzodiazepinen rapporteren. Daarnaast werd gezocht naar associaties tussen benzodiazepinecraving en andere klinische variabelen. Dit alles in een huisartspatiëntengroep die een poging deed om het benzodiazepinegebruik te staken. Patiënten die craving rapporteerden op de BCQ verschilden significant van patiënten die geen craving rapporteerden wat betreft de mate van afhankelijkheid, psychologisch welbevinden, aspecten van gezondheidsgerelateerde kwaliteit van leven, aspecten van een negatieve gemoedstoestand (depressie en boosheid) en bepaalde persoonlijkheidseigenschappen (somatisatie en negativisme). In een multivariate analyse, die controleerde voor de huidige gebruiksstatus, bleek, dat depressie en somatisatie positief samenhingen met craving. Echter, alleen de bijdrage van de variabele depressie aan craving was significant voor de gehele groep van (voormalige) langdurige gebruikers (p = .002). Deze resultaten in ogenschouw nemende, zou in toekomstig onderzoek de relatie tussen persoonlijkheid en benzodiazepinecraving verder onder de loep moeten worden genomen.

Uit de literatuur over craving bij andere verslavende stoffen is gebleken dat de mate van craving kan fluctueren over de tijd. Het is daarom belangrijk dat een cravingvragenlijst sensitief genoeg is om veranderingen in het verloop van craving over de tijd in kaart te brengen. Derhalve wilden we in **hoofdstuk 4** met behulp van de BCQ benzodiazepinecraving over een langere tijd beoordelen en het verloop ervan beschrijven. Een subgroep van 117 (voormalige) langdurige gebruikers kreeg viermaal de BCQ voorgelegd over een follow-upperiode van 21 maanden. De ervaren craving bleek af te nemen over de tijd. Patiënten die benzodiazepinen bleven gebruiken ervoeren significant meer craving dan patiënten die hun gebruik hadden gestaakt na een minimale interventie (brief met stopadvies van hun huisarts) of na een aansluitende 'randomised controlled trial' (afbouwprogramma met of zonder aanvullende cognitieve gedragstherapie in een groep). De methode van stoppen had geen invloed op de mate van craving die de patiënten over de tijd ervoeren. Echter, patiënten die meededen aan het aansluitende afbouwprogramma rapporteerden gemiddeld genomen meer craving dan patiënten die alleen de brief van hun huisarts hadden gekregen als een aanmoediging om te stoppen. Concluderend kan men stellen dat benzodiazepinecraving, hoewel het zowel tijdens als na het afbouwproces voorkomt onder de (voormalige) langdurige benzodiazepinegebruikers, afneemt over de tijd tot minimale omvang. Desalniettemin bleek de BCQ in staat om benzodiazepinecraving longitudinaal te monitoren en te kwantificeren. Bovendien was het instrument sensitief genoeg om een onderscheid te kunnen maken tussen verschillende subgroepen in het verloop van craving. De somscores van de BCQ kunnen richtinggevend zijn voor de aan te raden intensiteit van de behandeling, in termen van de mate van bemoeienis door de huisarts, wanneer een patiënt het benzodiazepinegebruik wil staken.

Hoofdstuk 5 gaat in op de 'reikwijdte' van de definitie van craving (breed versus smal). We vergeleken een brede en een smalle conceptualisatie van benzodiazepinecraving met

elkaar. De brede conceptualisatie werd gerepresenteerd door de BCQ en de smalle door de Benzodiazepine Desire Scale (BDS). De BDS bestaat uit drie één-item Likert-type schaaltjes, waarop de patiënt de frequentie, de globale intensiteit en de piekintensiteit van het verlangen naar benzodiazepinen moet aangeven, wanneer de patiënt op dat moment niet gebruikt. In een factoranalyse bleek de BCQ op een factor te laden die te labelen was als een 'negative affect'-factor, terwijl de BDS laadde op een 'afhankelijkheid'-factor. Klaarblijkelijk hangt een lage mate van craving, zoals gemeten met de BCQ, samen met negatief affect en weerspiegelt het de verwachting van een positief effect van het gebruik van benzodiazepinen en de verwachting van verlichting van negatief affect of ontwenningsverschijnselen. De lage somscores op de BCQ in onze studiepopulatie en de geselecteerde tijdspanne van het meten van craving (craving op dit moment versus gedurende de afgelopen week) waren de meest voor de hand liggende verklaringen voor deze bevindingen. Beide conceptualisaties van benzodiazepinecraving dragen bij aan het begrip van de potentiële betekenis van craving bij benzodiazepinegebruik.

Hoofdstuk 6 presenteert de uitkomsten van een Cox-regressie analyse ter identificatie van onafhankelijke voorspellers van terugval na het staken van benzodiazepinegebruik, met tijd tot terugval als afhankelijke variabele. Als potentiële voorspellers werden benzodiazepine(gebruiks)karakteristieken, psychopathology, persoonlijkheidskenmerken en karakteristieken van benzodiazepine-afhankelijkheid, waaronder craving zoals gemeten met de BCQ, meegenomen. De BCQ somscore had geen voorspellende waarde bij terugval na een minimale interventie (brief met stopadvies van de huisarts). Echter, onafhankelijke voorspellers van terugval gedurende een follow-upperiode van 15 maanden na een afbouwprogramma waren: hogere craving somscores op de BCQ, een hogere leeftijd, het hebben van een ziekenfondsverzekering, en een hogere score op de schaal 'gebrek aan therapietrouw' van de Bendep-SRQ. Deze resultaten zouden richting moeten geven aan relapsepreventieprogramma's door het includeren van behandelonderdelen die zich richten op het ervaren van en het omgaan met craving.

Hoofdstuk 7 geeft een algemene beschouwing die met name is gericht op punten van discussie die niet in de voorgaande hoofdstukken aan de orde zijn gekomen. Daarnaast wordt een opsomming gegeven van de belangrijkste conclusies uit dit onderzoek, worden aanbevelingen voor verder onderzoek gedaan en worden enkele klinische implicaties besproken.

Allereerst wordt ingegaan op de generaliseerbaarheid van de onderzoeksresultaten, waarbij geconcludeerd wordt dat deze mogelijk beperkt is door het grote aantal patiënten dat weigerde deel te nemen aan de Benzoredux-studie. Het waren vooral gebruikers van lage doseringen die deelnamen. Mogelijk speelde afhankelijkheid hierbij een rol. Hoewel de resultaten waarschijnlijk representatief zijn voor de dagelijkse klinische praktijk, omdat juist die patiënten deelnemen aan een afbouwtraject die bereid zijn om te stoppen, zou de studie moeten worden herhaald in een minder selectieve groep.

Met betrekking tot de ontwikkeling van de BCQ wordt ingegaan op de voordelen en nadelen van het gebruik van het Rasch-schaalmodel ten opzichte van de 'klassieke testtheorie'. De 'itemresponstheorie' ofwel 'latente-trektheorie' waarop het Rasch-schaalmodel is gebaseerd, rechtvaardigt het gebruik van de BCQ somscore als maat voor het onderliggende unidimensionele construct craving. De BCQ somscores waren over het algemeen laag, wat erop lijkt te duiden dat craving in onze studiepopulatie geen belangrijke rol speelt.

Wanneer we de resultaten van het onderzoek vergelijken met (neuro)biologische bevindingen op het gebied van craving bij andere middelen, vinden we overeenkomsten met 'relief craving' zoals wordt beschreven in het 'three-pathway psychobiological model of craving for alcohol'.[1] Onderzoek naar benzodiazepinecraving op dit gebied ontbreekt echter.

In onze studiepopulatie vormen verwachtingen van positieve effecten van benzodiazepinegebruik de eerste tekenen van craving naar benzodiazepinen. Onze studieresultaten zijn daarmee te interpreteren vanuit verschillende bestaande cognitieve cravingtheorieën, waaronder de cognitieve sociale leertheorie. Tijdens een (afbouw)behandeling zouden de expliciete verwachtingen van een patiënt over de effecten van benzodiazepinen aandacht moeten krijgen.

In onze studiepopulatie worden items van de BCQ die indicatief zijn voor een hoge mate van craving nauwelijks bevestigend beantwoord. Het zijn de items die verwijzen naar een verlangen om te gebruiken, de intentie om te gebruiken en het gebrek aan controle over het benzodiazepinegebruik. Onderzoek in patiëntenpopulaties die hogere doseringen gebruiken en/of een hogere mate van benzodiazepine-afhankelijkheid aangeven, zal moeten uitwijzen of craving in deze groepen het gehele spectrum van BCQ items beslaat. Momenteel is nog onduidelijk of verschillende gebruikersgroepen verschillende cravingprofielen hebben.

Behalve door het herhalen van onderhavig onderzoek in andere populaties, kan de bruikbaarheid van de BCQ verder worden verbeterd door 'Latent Trait Standardisation' op basis van een normatieve populatie van benzodiazepinegebruikers uit de huisartspraktijk. Door de ruwe BCQ somscores te vergelijken met deze normatieve groep worden ze klinisch interpretabel. Dit zal de toepasbaarheid van de BCQ bij benzodiazepine-afbouwprogramma's in de huisartspraktijk vergroten.

Referentie

1 Verheul R, Van den Brink W, Geerlings P. A three-pathway psychobiological model of craving for alcohol. Alcohol & Alcoholism 1999;34(2):197-222

Dankwoord

Toen ik in 1997 voor het eerst in aanraking kwam met benzodiazepinen, had ik nooit gedacht dat ik er tien jaar later pas mee zou kunnen stoppen.

Bovenstaande zou gezegd kunnen zijn door een benzodiazepinegebruiker, maar het is van toepassing op mijzelf. De 'verslavende' werking van benzo's was al die jaren evident: verschillende stoppogingen, terugval, veel tijd ermee kwijt zijn - soms ten koste van andere plezierige activiteiten, en niet te vergeten... craving.

Stoppen met benzo's bleek in mijn geval moeilijker dan gedacht. Gelukkig maar, want stug ermee doorgaan heeft het proefschrift opgeleverd dat voor u ligt. Het promotietraject was in vele opzichten een leerproces. 'Aún aprendo' ('ik leer nog steeds') was de titel van het schilderij van Francisco de Goya dat in 1997 de voorkant van mijn scriptie over chronisch benzodiazepinegebruik door ouderen sierde. Het is gelukkig nog steeds van toepassing!

Via deze weg wil ik graag iedereen bedanken die op één of andere manier betrokken was bij de totstandkoming van mijn proefschrift. Een aantal mensen wil ik in het bijzonder noemen.

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Het zit erop!

Tijd voor nieuwe dingen...

Curriculum vitae

Audrey Mol werd geboren op 21 april 1974 te Roosendaal en Nispen. In 1992 behaalde zij haar Gymnasium β diploma aan het St. Gertrudislyceum te Roosendaal. Die nazomer vertrok zij naar Nijmegen om psychologie te gaan studeren aan de Katholieke Universiteit Nijmegen. Ze studeerde in 1997 af in de klinische psychologie met de afstudeerscriptie 'Chronisch benzodiazepinegebruik door ouderen'. Haar scriptiebegeleider dr. Rien Breteler attendeerde haar op het Benzoredux-project. Van mei 1998 tot december 2001 werkte zij als onderzoeks-assistent mee aan dit project dat aan de afdeling Psychiatrie van het Universitair Medisch Centrum St Radboud te Nijmegen werd uitgevoerd. Prof. dr. Frans Zitman stelde haar in de gelegenheid om haar werkzaamheden als onderzoeks-assistent uit te breiden met het in dit proefschrift beschreven wetenschappelijk onderzoek. Van januari 2002 tot september 2003 combineerde zij haar onderzoekswerk met een parttime aanstelling als psycholoog op de kliniek van de afdeling Psychiatrie van het Universitair Medisch Centrum St Radboud. Aansluitend kon zij fulltime als psycholoog aan de slag bij Centrum Autisme te Leiden, waar zij in september 2005 aan de opleiding tot Gz-psycholoog begon. Thans is zij met veel plezier werkzaam bij Centrum Autisme als Gz-psycholoog in opleiding. In september van dit jaar hoopt zij haar diploma te ontvangen.

List of publications

Benzoredux publications

1 **Mol AJJ**, Oude Voshaar RC, Gorgels WJ, Breteler MH, Zitman FG. The role of craving in relapse after successful benzodiazepine discontinuation. Journal of Clinical Psychiatry, *in press*

2 Gorgels WJMJ, Oude Voshaar RC, **Mol AJJ**, Van de Lisdonk EH, Mulder J, Van den Hoogen H, Van Balkom AJLM, Breteler MHM, Zitman FG. Consequences of a benzodiazepine discontinuation programme in family practice on psychotropic medication prescription to the participants. Family Practice, *in press*

3 Oude Voshaar RC, Gorgels WJMJ, **Mol AJJ**, Van Balkom AJLM, Mulder J, Van de Lisdonk EH, Breteler MHM, Zitman FG. Predictors of long-term benzodiazepine abstinence in participants of a randomized controlled benzodiazepine withdrawal program. The Canadian Journal of Psychiatry, 2006;51:445-452

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