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## Craving for benzodiazepines : the development of the benzodiazepine craving questionnaire

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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.<sup>1</sup>). 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,<sup>2</sup> 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.<sup>3</sup> Recently, the concept of craving for benzodiazepines has been examined within a benzodiazepine discontinuation project,<sup>4,5</sup> which has resulted in the development of the Benzodiazepine Craving Questionnaire (BCQ).<sup>6</sup> 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,<sup>7-11</sup> 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,<sup>11,12</sup> 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.<sup>13,14</sup> 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.<sup>15,16</sup>

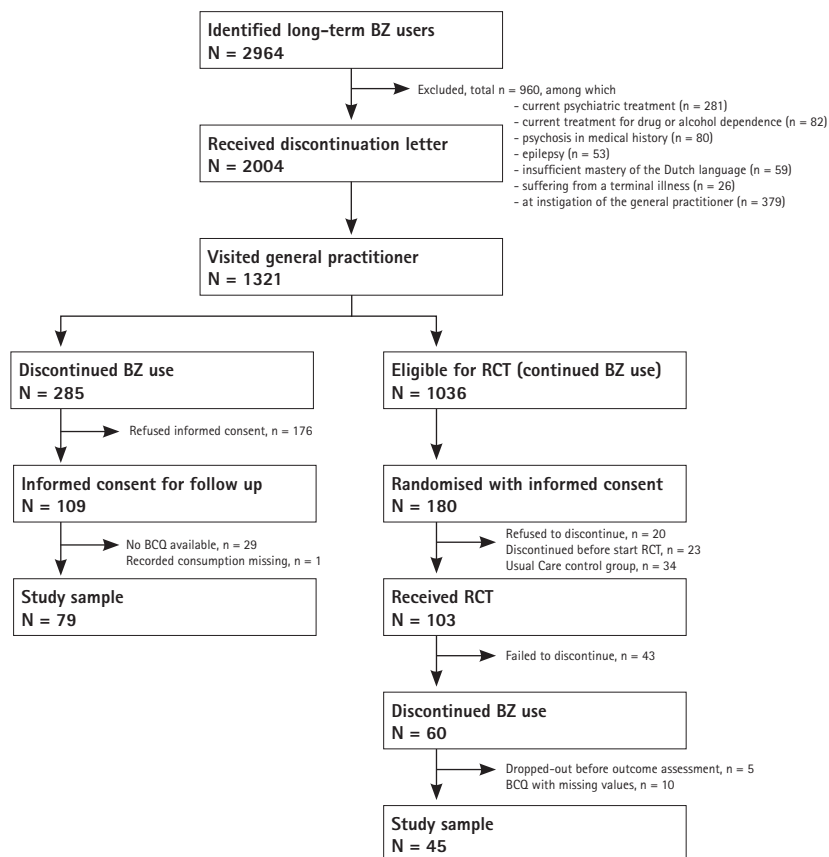
This study was conducted to test the hypotheses that craving is an independent predictor of relapse in long-term benzodiazepine users who successfully quit their use after 1) a minimal intervention, respectively, 2) after an additional supervised benzodiazepine tapering off programme in general practice.

## 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.<sup>11,12</sup> 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.<sup>4,5</sup> 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<sup>11</sup>).

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.<sup>6</sup> 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.<sup>17</sup>

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),<sup>18,19</sup> psychological well-being (GHQ-12: General Health Questionnaire 12 item version),<sup>20</sup> mood (POMS: Profile of Mood States),<sup>21</sup> quality of life (MOS SF-36: Medical Outcome Studies short-form),<sup>22,23</sup> and personality characteristics (NVM: Dutch shortened MMPI).<sup>24</sup>

### 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  $\geq 1$ ), 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  $\chi^2$  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**

Variables	Univariate <sup>a</sup>		Multivariate <sup>b</sup>	
	Hazard Ratio [95% CI]	p-value	Hazard Ratio [95% CI]	p-value
BCQ <sup>c</sup> 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: $\chi^2 = 17.2; df = 3; p < 0.001$				

<sup>a</sup> Only independent variables that had p-values of less than 0.15 in the univariate regression analyses are shown in the table.

<sup>b</sup> 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.

<sup>c</sup> 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 until relapse after successful discontinuation

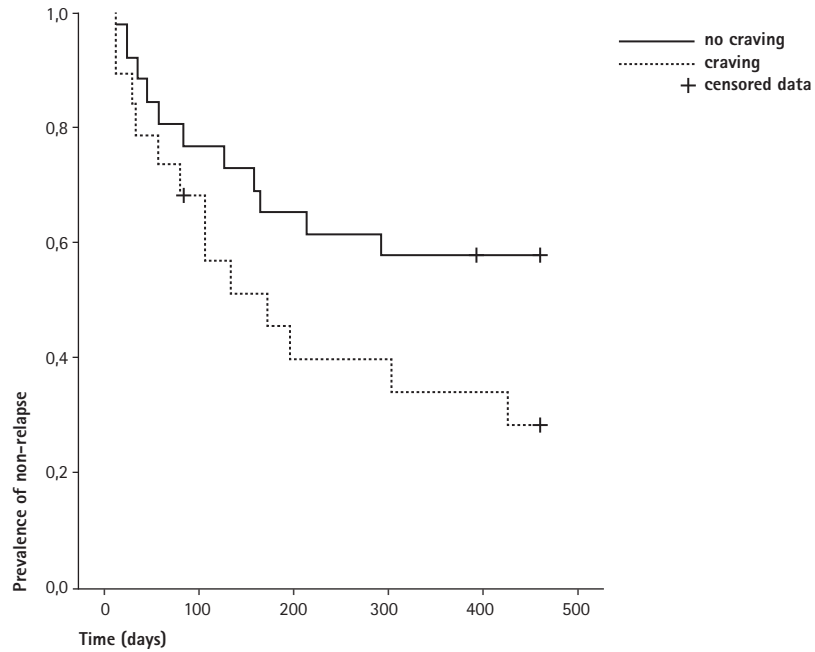


Table 2 Univariate and independent predictors of relapse in successful quitters after a tapering off programme

Variables	Univariate <sup>a</sup>		Multivariate <sup>b</sup>	
	Hazard Ratio [95% CI]	p-value	Hazard Ratio [95% CI]	p-value
BCQ <sup>c</sup> 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:  $\chi^2 = 22.6$ ;  $df = 4$ ;  $p < 0.001$

<sup>a</sup> Only the independent variables that had p-values of less than 0.15 in the univariate regression analyses are shown in the table.

<sup>b</sup> 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.

<sup>c</sup> 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.<sup>13,14</sup> The study of Morin et al<sup>13</sup> 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.<sup>13</sup> 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.<sup>14</sup> In various studies on smoking, higher levels of self-efficacy are consistently associated with decreased craving (e.g.<sup>25,26</sup>), whereby findings from O'Connor et al<sup>14</sup> appear to be in line with our findings. Similar to our results, Morin et al<sup>13</sup> and O'Connor et al<sup>14</sup> 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.<sup>11</sup>

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<sup>4</sup>). 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,<sup>27</sup> 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.<sup>28</sup> 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,<sup>29</sup> that (b) withdrawal symptoms are identical for low-dose and high-dose users,<sup>30</sup> and finally, (c) that approximately half of all low-dose users fulfil DSM-III-R criteria for dependence.<sup>3</sup> 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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