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

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# Chapter 1

## Introduction and thesis outline

## INTRODUCTION

Benzodiazepines belong to the most prescribed drugs in Western countries.<sup>1</sup> In the Netherlands they are registered for the symptomatic treatment of pathological anxiety, tension and severe insomnia.<sup>2</sup> Their use is indicated, with some reserve, for short-term treatment (two weeks or four weeks of intermittent use) of severe insomnia with poor day-time 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.<sup>3-5</sup>

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).<sup>6</sup>

In spite of the above mentioned guidelines and the lack of evidence concerning the effectiveness of benzodiazepines with prolonged treatment,<sup>7</sup> 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.<sup>1</sup> 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).<sup>8</sup> 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.<sup>8</sup> The demographic characteristics of these long-term benzodiazepine users show that half to two-thirds are female and half are aged 65 or over.<sup>1,8-10</sup> Most long-term users (89%) receive their benzodiazepine prescription from their general practitioner.<sup>8</sup>

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.<sup>11,12</sup>

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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.<sup>48</sup>

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.<sup>6</sup>).

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.<sup>13</sup> Not long thereafter physical dependence in normal-dose benzodiazepine usage was reported.<sup>14,15</sup> Research has shown that benzodiazepines have all the characteristics of drugs of dependence,<sup>16</sup> 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.<sup>19</sup> Long-term users make up the largest group of benzodiazepine-dependent patients.<sup>16</sup>

**Table 1** Criteria for benzodiazepine dependence according to DSM-IV<sup>17</sup> and ICD-10<sup>18</sup> criteria

Diagnostic and Statistical Manual of Mental Disorders, 4 <sup>th</sup> edition (DSM-IV)	International Classification of Diseases, 10 <sup>th</sup> edition (ICD-10)
<p>Three (or more) of the following, occurring any time in the same 12-month period:</p> <ul style="list-style-type: none"> <li>• Tolerance</li> <li>• Withdrawal</li> <li>• The substance is often taken in larger amounts or over a longer period than intended</li> <li>• There is a persistent desire or unsuccessful efforts to cut down or control substance use</li> <li>• A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects</li> <li>• Important social, occupational, or recreational activities are given up or reduced because of substance use</li> <li>• 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</li> <li>• -</li> </ul>	<p>Three or more of the following have been present together at some time during the previous year:</p> <ul style="list-style-type: none"> <li>• Tolerance</li> <li>• Physiological withdrawal state when substance use has ceased or been reduced</li> <li>• -</li> <li>• Difficulties in controlling substance-taking behaviour in terms of its onset, termination, or levels of use</li> <li>• 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</li> <li>• -</li> <li>• Persisting with substance use despite clear evidence of overtly harmful consequences</li> <li>• Craving: a strong desire or sense of compulsion to take the substance</li> </ul>

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

dependence,<sup>17</sup> there is still little consensus about its definition and theory, its causes and consequences, and its measurement.<sup>20-22</sup>

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.<sup>23</sup> 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.<sup>24-28</sup>.

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.<sup>21</sup> 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.<sup>29-32</sup>). Dependent subjects may even continue to experience craving years after their last drug use (e.g.<sup>33-35</sup>) and regular substance users describe experiencing craving even when they are not attempting to abstain from drug use (e.g.<sup>36,37</sup>).

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.<sup>24</sup> 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.<sup>23,38,39</sup>). 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.<sup>40</sup>), single-item Likert-type scales (e.g.<sup>41</sup>) to multi-item multidimensional questionnaires (e.g.<sup>36,37,42</sup>). 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)<sup>36</sup> and the Cocaine Craving Questionnaire (CCQ),<sup>37</sup> 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<sup>43</sup> 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,<sup>44</sup> 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,<sup>45</sup> 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<sup>19</sup> 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 BCO. For a more elaborate outline of the Benzoredux project and its study results, we refer to Gorgels et al.<sup>46</sup> and to Oude Voshaar et al.<sup>47</sup>.



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