Craving for benzodiazepines : the development of the benzodiazepine craving questionnaire

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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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