Chapter 1

Introduction, aim and outline of the study

INTRODUCTION

It has been recognized for many years that the use of benzodiazepines (BZDs) can lead to benzodiazepine dependence.[1-11] Especially long-term BZD use carries a high risk of dependence.[12-19] This also applies to normal-dose BZD use, which is referred to as low-dose BZD dependence.[6,10,20-23] There is no convincing proof that long-term BZD use has lasting therapeutic effects.[18,19,24,25] On the contrary, persistent cognitive deficits have been demonstrated after withdrawal from long-term BZD use.[26] In general, it is agreed that BZD use should be therapeutic and not maintain dependence. Guidelines with respect to the prescription of BZDs have been proposed, in order to prevent dependence as much as possible.[27-30] Nevertheless, in many reports the dependence risks have been played down or have been 'outweighed' by the desired therapeutic effects.[31-33] Some reports only addressed dependence in the case of non-medical BZD use. Objections have been made against this confinement to non-medical BZD use,[34,35] because it suggests that medical use rules out BZD dependence. Along these lines, the debate on BZD dependence has persisted, apparently maintained by a lack of consensus on the definition of BZD dependence.[10,36,37]

In contrast, during the past thirty to forty years, there has been a clear trend in psychiatry towards developing descriptive criteria for psychiatric disorders and reaching consensus on classification systems, such as the International Classification of Diseases (ICD) from the World Health Organization (WHO) and the Diagnostic Statistic Manual for Mental Disorders (DSM) from the American Psychiatric Association (APA). In the ICD-10, DSM-III-R and DSM-IV[38-41] criteria are defined for substance dependence,[42-45] which are based on the provisional criteria for alcohol dependence postulated by Edwards and Gross in 1976.[46,47] In the field of addiction, these substance dependence criteria have increasingly been applied to

alcohol and other psychoactive substances.[48-54]

Although the ICD and the DSM substance dependence criteria have gained worldwide recognition in psychiatry, they have been neglected in relation to BZD dependence in scientific reports. Linsen et al. (1995) assessed the definitions used for BZD dependence in 250 papers published between 1988 and 1991: the ICD and DSM criteria had only rarely been used.[37] In a review on historical developments in the diagnosis of BZD dependence, Tyrer (1993) did not mention the ICD and DSM criteria at all, but still concluded that the diagnosis remained shadowy.[10]

It can be concluded that the ICD and DSM substance dependence criteria have not yet become popular for the diagnosis of BZD dependence. The medical context in which BZDs are mostly used probably masks aspects of dependence. Therefore, these aspects are not taken into account during screening for ICD and DSM substance dependence symptoms. Most dependence-inducing drugs are bought in shops (alcohol) or acquired illicitly; the overt reasons for use are the induction of euphoria and/or a decrease in withdrawal symptoms. Their use is not labelled as medical. BZDs, on the other hand, are generally acquired on medical prescription and the overt reason for their use is labelled as medical. Within this medical context, it is more tempting to believe that BZD use relieves medical complaints instead of producing a state of dependence. Dependence symptoms like withdrawal and craving are therefore easily mistaken for relapsing disease symptoms.[21,55-57] Gratification of persistent appeals from patients by physicians who write repeat prescriptions in order to continue to suppress the symptoms can lead to neglect or denial of dependence symptoms. A compliant attitude of physicians with respect to prescribing BZDs can induce a false sense of security in patients and reinforce requests for repeat prescriptions. The medical context, particularly the interaction between the patient and physician, therefore appears to add an

extra dimension to dependence in the case of BZD use.[58]

To break this vicious circle, the logical step was to develop specific criteria for BZD dependence which would take the medical context into account. A provisional set of specific criteria for BZD dependence, formulated on the basis of a literature study and clinical experience, was briefly outlined by Linsen et al..[37] Subsequently, a delphi procedure was used to obtain feedback on these criteria from an international panel of experts; the feedback was used to modify the criteria.[59] The final set of criteria for BZD dependence is shown in Appendix A.[60]

The postulation of these specific criteria enabled a new structured approach to BZD dependence, in addition to the DSM and ICD classifications. A self-report instrument, the Benzodiazepine Dependence Self-Report Questionnaire (Bendep-SRQ), was developed with the aim of reflecting the severity of BZD dependence. The Bendep-SRQ is shown in Appendix B of this thesis. The criteria in Appendix A served as the main basis for the formulation of the Bendep-SRQ items.

This thesis made a structured approach to BZD dependence in a clinical study on several samples of outpatients who were using BZDs.

AIM OF THE STUDY

The purpose of this study was to evaluate some structured approaches to the assessment of BZD dependence that were based on the general criteria of the substance dependence syndrome and the specific criteria for BZD dependence (see Appendix A). In this evaluation, special attention was paid to the psychometric properties of DSM-III-R, ICD-10 and Bendep-SRQ dependence constructs when they are applied to BZD use. Thorough investigation of these psychometric properties guided a well-considered application of structured approaches as clinical instruments with the aim of facilitating the clinical management of non-indicated chronic BZD use.

OUTLINE OF THE STUDY

This thesis followed the two structured approaches described above. Chapters 2 and 3 focus on the application of the DSM-III-R and ICD-10 substance dependence criteria for the evaluation of BZD dependence, while Chapters 4, 5, 6 and 7 concentrate on the development of the Bendep-SRQ.

Chapter 2 evaluates the DSM-III-R and ICD-10 BZD dependence criteria using an epidemiological approach. The criteria were applied to outpatient BZD users to assess the prevalences of the past year and lifetime BZD dependence diagnoses based on the DSM-III-R and ICD-10 classifications. On the assumption that these prevalence figures reflected the risk of BZD dependence in outpatient BZD users, recommendations could be made for the clinical management of BZD use.

Chapter 3 takes a dimensional approach to the DSM-III-R and ICD-10 BZD dependence criteria; Rasch modelling was applied to a large sample of outpatient BZD users to assess the homogeneity of the DSM-III-R and ICD-10 BZD dependence criteria. The reliability of resulting the Rasch homogeneous sets of criteria was assessed in terms of subject and item discriminability. Taking the specific order and the contents of the items into account, theoretical rationales were formulated to support the construct validity of the Rasch homogeneous sets of criteria. Attention was paid to some differences between the DSM-III-R and ICD-10 constructs.

Chapter 4 describes a study in which the Bendep-SRQ was introduced and assessed in an outpatient sample of BZD users, consisting of General Practice (GP) patients, psychiatric outpatients and self-help patients. The composition of the Bendep-SRQ is described and potential Bendep-SRQ scales were extracted by means of factor analyses. Rasch analyses were carried out to assess the scalability of the Bendep-SRQ scales. Subsequently, the reliability of the Bendep-SRQ scales was evaluated in terms of subject discriminability, item discriminability and test-retest stability. A new measure emerged: the Item Discriminability Coefficient (IDC). To support the construct validity of the scales, theoretical rationales were drawn up to explain the specific item order provided by the Rasch scale values. To assess the concurrent and discriminant validity, a matrix consisting of Bendep-SRQ scales and supposed concurrent and discriminant measures was factor-analysed. In the light of the results, the utility of the Bendep-SRQ is discussed.

Chapter 5 presents a study on the assessment of BZD dependence in alcohol and drug dependent outpatients who were receiving treatment at Community-Based Addiction Centres (CBACs). The prevalences of the DSM-III-R and ICD-10 dependence diagnoses were determined with respect to BZDs and other psychoactive substances. Applying the

methodology of Chapter 4, the psychometric properties and the utility of the Bendep-SRQ were evaluated in this particular population.

Chapter 6 re-assesses the scalability, reliability and validity of the Bendep-SRQ scales in new samples of GP patients and psychiatric outpatients for the purpose of cross-validation. In the discussion of the results, differences between the new and original patient samples with respect to sociodemographic characteristics and aspects of BZD use were taken into account.

Chapter 7 applies a new methodology, referred to as Rasch latent trait standardization, to standardize the raw sumscores of the Bendep-SRQ scales into the normal form, using the total group of GP patients as a normative sample. This new method was compared to the classical method of standardization. Standard scores and corresponding percentile ranks were derived to facilitate the interpretation of the Bendep-SRQ sumscores in clinical practice.

Chapter 8 presents a general discussion on this study. The main topics include a global clinical impression, design and implementation, the psychometric methodology applied and the utility of the new structured approaches in clinical practice and scientific research. Some major conclusions are drawn and recommendations are made for further research.

REFERENCES

1. Lader M. Benzodiazepines--the opium of the masses? Neuroscience 1978;3:159-165.

2. Lader M. Dependence on benzodiazepines. J Clin Psychiatry 1983;44:121-127.

3. Tyrer PJ, Seivewright N. Identification and management of benzodiazepine dependence. Postgrad Med J 1984;60 Suppl 2:41-46.

4. Noyes R, Jr., Garvey MJ, Cook BL, Perry PJ. Benzodiazepine withdrawal: a review of the evidence. J Clin Psychiatry 1988;49:382-389.

5. Tyrer P. Risks of dependence on benzodiazepine drugs: the importance of patient selection. BMJ 1989;298:102, 104-5.

6. Tyrer P. Dependence as a limiting factor in the clinical use of minor tranquillizers. Pharmacol Ther 1988;36: 173-188.

7. Taylor FK. The damnation of benzodiazepines. Br J Psychiatry 1989;154:697-704.

8. American Psychiatric Association. Benzodiazepine dependence, toxicity and abuse. A task force report of the American Psychiatric Association. Washington, D.C.: American Psychiatric Association, 1990.

9. Lader M. History of benzodiazepine dependence. J Subst Abuse Treat 1991;8:53-59.

10. Tyrer P. Benzodiazepine dependence: a shadowy diagnosis. Biochem Soc Symp 1993;59:107-119.

11. Marriott S, Tyrer P. Benzodiazepine dependence. Avoidance and withdrawal. Drug Saf 1993;9:93-103.

12. Petursson H, Lader MH. Withdrawal from long-term benzodiazepine treatment. Br Med J Clin Res Ed 1981;283:643-645.

13. Schopf J. Withdrawal phenomena after long-term administration of benzodiazepines. A review of recent investigations. Pharmacopsychiatry 1983;16:1-8.

14. Busto U, Sellers EM, Naranjo CA, Cappell H, Sanchez Craig M, Sykora K. Withdrawal reaction after long-term therapeutic use of benzodiazepines. N Engl J Med 1986;315:854-859.

15. Ashton H. Risks of dependence on benzodiazepine drugs: a major problem of long term treatment. BMJ 1989;298:103-104.

16. Rickels K, Schweizer E, Case WG, Greenblatt DJ. Long-term therapeutic use of benzodiazepines. I. Effects of abrupt discontinuation. Arch Gen Psychiatry 1990;47:899-907.

17. Schweizer E, Rickels K, Case WG, Greenblatt DJ. Long-term therapeutic use of benzodiazepines. II. Effects of gradual taper. Arch Gen Psychiatry 1990;47:908-915.

18. Rickels K, Case GW, Winokur A, Swenson C. Long-term benzodiazepine therapy: benefits and risks. Psychopharmacol Bull 1984;20(4):608-615.

19. Michelini S, Cassano GB, Frare F, Perugi G. Long-term use of benzodiazepines: tolerance, dependence and clinical problems in anxiety and mood disorders. Pharmacopsychiatry 1996;29(4):127-134.

20. Landry MJ, Smith DE, McDuff DR, Baughman OL. Benzodiazepine dependence and withdrawal: identification and medical management. J Am Board Fam Pract 1992;5:167-175.

21. Smith DE, Wesson DR. Benzodiazepine dependency syndromes. Journal of Psychoactive Drugs 1983;15:85-95.

22. Schneider Helmert D. Why low-dose benzodiazepine-dependent insomniacs can't escape their sleeping pills. Acta Psychiatr Scand 1988;78:706-711.

23. Rickels K, Case WG, Schweizer EE, Swenson C, Fridman RB. Low-dose dependence in chronic benzodiazepine users: a preliminary report on 119 patients. Psychopharmacol Bull 1986;22:407-415.

24. Van Balkom AJ, De Beurs E, Koele P, Lange A, Van Dyck R. Long-term benzodiazepine use is associated with smaller treatment gain in panic disorder with agoraphobia. J Nerv Ment Dis 1996;184(2):133-135.

25. Rickels K, Schweizer E. Anxiolytics: indications, benefits and risks of short- and long-term benzodiazepine therapy: current research data. NIDA Res Monogr 1993;131:51-67.

26. Tata PR, Rollings J, Collins M, Pickering A, Jacobson RR. Lack of cognitive recovery following withdrawal from long-term benzodiazepine use. Psychol Med 1994;24(1):203-213.

27. Systematic review of the benzodiazepines. Guidelines for data sheets on diazepam, chlordiazepoxide, medazepam, clorazepate, lorazepam, oxazepam, temazepam, triazolam, nitrazepam and flurazepam. Committee on the Review of Medicines. Br Med J 1980;280:910-912.

28. Lader M, Russell J. Guidelines for the prevention and treatment of benzodiazepine dependence: summary of a report from the Mental Health Foundation. Addiction 1993;88:1707-1708.

29. Gabe J. Promoting benzodiazepine withdrawal. Addiction 1994;89:1497-1504.

30. Sussman N. Treating anxiety while minimizing abuse and dependence. J Clin Psychiatry 1993;54 Suppl:44-51.

31. Marks J. The benzodiazepines - for good or evil. Neuropsychobiology 1983;10:115-126.

32. Marks J. The Benzodiazepines. Use, overuse, misuse, abuse. Lancaster: MTP press, 1985.

33. Uhlenhuth EH, DeWit H, Balter MB, Johanson CE, Mellinger GD. Risks and benefits of long-term benzodiazepine use. J Clin Psychopharmacol 1988;8:161-167.

34. Miller NS, Gold MS. Abuse, addiction, tolerance and dependence to benzodiazepines in medical and nonmedical populations. Am J Drug Alcohol Abuse 1991;17:27-37.

35. Cole JO, Chiarello RJ. The benzodiazepines as drugs of abuse. J Psychiatr Res 1990;24 Suppl 2:135-144.

36. Miller NS, Mahler JC. Addiction to and dependence on benzodiazepines. Diagnostic confusion in clinical practice and research studies. J Subst Abuse Treat 1991;8:61-67.

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

38. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 3rd revised edition. Washington, D.C.: American Psychiatric Association, 1987.

39. World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders. Clinical descriptions and guidelines. Geneva: World Health Organization, 1992.

40. World Health Organization. The ICD-10 classification of mental and behavioural disorders: diagnostic criteria for research. Geneva: World Health Organization, 1992.

41. American Psychiatric Association. Diagnostic and Statistical Manual for Mental Disorders: DSM-IV, 4th

edition. Washington, DC: American Psychiatric Association, 1994.

42. Rounsaville BJ, Spitzer RL, Williams JBW. Proposed changes in DSM-III substance use disorders: description and rationale. Am J Psychiatry 1986;143:463-468.

43. Nathan PE. Substance use disorders in the DSM-IV. J Abnorm Psychol 1991;100:356-361.

44. Landry M. Addiction diagnostic update: DSM-III-R psychoactive substance use disorders. J Psychoactive Drugs 1987;19:379-381.

45. Rounsaville BJ, Kranzler HR. The DSM-III-R Diagnosis of Alcoholism. In: Tasman A, Hales RE, Frances AJ (eds): Annual Review of Psychiatry. Washington, D.C. American Psychiatric Press, 1989:323-340.

46. Edwards G, Gross MM. Alcohol dependence: provisional description of a clinical syndrome. Br Med J 1976; 1:1058-1061.

47. Edwards G. The alcohol dependence syndrome: a concept as stimulus to enquiry. Br J Addict 1986;81:171-183.

48. Kosten TR, Rounsaville BJ, Babor TF, Spitzer RL, Williams JB. Substance-use disorders in DSM-III-R. Evidence for the dependence syndrome across different psychoactive substances. Br J Psychiatry 1987;151:834-843.

49. Stripp AM, Burgess PM, Pattison PE, Pead J, Holman CP. An evaluation of the psychoactive substance dependence syndrome in its application to opiate users. Br J Addict 1990;85:621-627.

50. Hasin DS, Grant BF, Harford TC, Endicott J. The drug dependence syndrome and related disabilities. Br J Addict 1988;83:45-55.

51. Bryant KJ, Rounsaville BJ, Babor TF. Coherence of the dependence syndrome in cocaine users. Br J Addict 1991;86:1299-1310.

52. Hasin DS, Muthuen B, Wisnicki KS, Grant B. Validity of the bi-axial dependence concept: a test in the US general population. Addiction 1994;89:573-579.

53. Morgenstern J, Langenbucher J, Labouvie E, W. The generalizability of the dependence syndrome across substances: An examination of some properties of the proposed DSM-IV dependence criteria. Addiction 89(9): 1105 1113 1994;1105-1113.

54. Feingold A, Rounsaville B. Construct validity of the dependence syndrome as measure by DSM-IV for different psychoactive substances. Addiction 1995;90(12):1661-1669.

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

56. Ashton H. Benzodiazepine withdrawal: outcome in 50 patients. Br J Addict 1987;82(6):665-671.

57. Ashton H. Protracted withdrawal syndromes from benzodiazepines. J Subst Abuse Treat 1991;8(1-2):19-28.

58. Lilja J, Larsson S. Social pharmacology: unresolved critical issues. Int J Addict 1994;29(13):1647-1737.

59. Roosenboom JT, Zitman FG, Breteler MHM, Linsen SM. Criteria benzodiazepine afhankelijkheid, van onduidelijk begrip tot helder concept. (Unpublished, 1992).

60. Linsen SM, Breteler MHM, Zitman FG. Defining benzodiazepine dependence.(Abstract). New Research Program and Abstracts 1992;137.