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Original article

Defining benzodiazepine dependence: the confusion persists

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Summary – Little consensus exists on the risk of benzodiazepine (BZD) dependence. We investigated how often BZD dependence and related concepts have been defined in the literature on BZD effects in humans. In addition, the definitions of BZD dependence were compared in order to assess the similarity of contents. From a total of 250 papers (published between 1988 and 1991) 51 provided 126 dependence-related definitions. Six studies referred to the DSM definitions and one to the WHO definition. The obsolete concept of addiction was frequently defined ($n = 13$), with little consensus about its meaning. Psychological and physical dependence were defined fairly often ($n = 29$), also with low levels of consensus. We conclude that the discussion on the risk of BZD dependence would be well-served by attempting to improve consensus first. This may lead to more meaningful data on the incidence, prevalence and relevant co-factors of BZD dependence. An outline for criteria for benzodiazepine dependence is presented.

benzodiazepines / substance dependence / addiction / review

INTRODUCTION

Considerable controversy exists regarding the benefits of benzodiazepines (BZD) (Uhlenhuth *et al.*, 1988) and the risk of dependence (Lader, 1989). The debate on the risk of BZD dependence started in the seventies (Marks, 1978) and is likely to continue for some time yet. On a society level, this is illustrated by the fact that despite reassuring conclusions in influential overviews, such as the Task Force Report from the American Psychiatric Association (1990), the state of New York is currently running a tripartite prescription programme for benzodiazepines. It is hardly surprising that the debate has not yet come to an end, because as Miller and Gold (1990) suggested, the concepts of abuse, dependence and tolerance seem to be poorly understood by the majority of physicians. This, however, should not be considered as a shortcoming, because the concept of dependence has induced many leading scientists in the field of psychiatry to state their own personal

views, which range from the need for a broad definition (Marks, 1990) to quite the opposite (Jaffe, 1990). Recent contributions to this debate stress the need of recognizing patients that are vulnerable to dose escalation (Sussman, 1993) and adverse effects (Juergens, 1993).

In this paper, it is not our intention to take sides in the debate about the risks of benzodiazepine dependence and its prevalence. The aim of our study was 1) to investigate how often benzodiazepine dependence and related concepts, *eg* benzodiazepine euphoria, tolerance, rebound and withdrawal, have been defined in publications on the effects of benzodiazepines in humans; and 2) to analyse the contents of each definition in order to estimate the level of consensus.

METHODS

A search was carried out covering all the English literature published during a four-year period (1988 to mid

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1991) using Medline and PsychLit. Two keyword combinations were used as starting points: benzodiazepines and anxiety; and benzodiazepines and insomnia. These were then combined with any of the following: substance abuse, substance dependence, substance use disorder and substance withdrawal. In addition, we reviewed all the papers with these same keywords in the July to December 1991 issues of 18 psychiatric journals (published in English), because at the time of the investigation, these issues had not yet been added to Medline or PsychLit. The reference lists of all the resulting papers were screened manually for the same keywords to obtain additional papers published in the four-year period. Any papers which dealt with animal studies were excluded. The papers included in the study were divided into original research papers and reviews.

The publications were scanned for the concepts of addiction/dependence, tolerance, withdrawal symptoms/syndrome, euphoria, craving, rebound (symptoms) and relapse. An inventory was made of the definitions given for these concepts. Sentences which explained these concepts were operationalized as a definition. Definitions were considered to be 'identical' if the meaning was largely the same, based on a word-by-word content analysis. All three authors made an independent analysis of the (dis)similarity between the definitions and any differences in results were discussed. Consensus could be reached in all cases. The WHO and DSM-III criteria specific for dependence on hypnotics and sedatives and the aspecific DSM-III-R criteria for benzodiazepine dependence were also noted without any further content analysis.

RESULTS

Our search using Medline with the keyword combinations 'benzodiazepines and anxiety' and 'benzodiazepines and insomnia' produced a total of 550 papers. The secondary keywords reduced this number to 118. Twelve papers had been included twice, so the search yielded 106 papers. PsychLit and the keyword combinations mentioned above, produced 266 papers. The secondary keywords reduced this number to 3. None of these studies addressed a combination of BZD, insomnia and aspects of dependence. The search in the July to December 1991 issues of 18 psychiatric journals resulted in 40 papers. The lists of references in the 157 papers thus selected, yielded 101 new papers. We therefore reviewed a total of 250 papers published in the four-year study period: 161 original research papers and 89 reviews.

In the majority of the original research papers ($n = 124$, 77%) dependence was not the main topic although it was named as a keyword. Nevertheless,

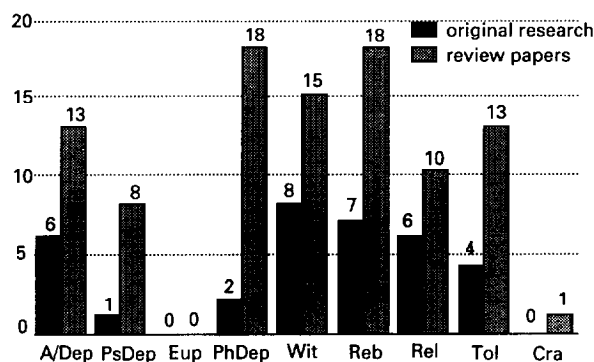


Fig 1. Number of explicit definitions in 161 original research and 89 review papers. A/Dep: addiction/dependence; PsDep: psychological dependence; Eup: euphoria; PhDep: physical dependence; Wit: withdrawal; Reb: rebound; Rel: relapse; Tol: tolerance; Cra: craving.

eight of these studies defined (aspects of) dependence. Of the remaining 37 studies (22.9%) another seven gave at least one explicit concept definition. The DSM-III criteria and DSM-III-R criteria were used in four and two other studies, respectively. The WHO criteria were not used. Therefore a total of 21 articles produced 33 definitions.

Comparable figures were found in the reviews, of which 74 (85.4%) were directed at, for example, anxiety disorders, epidemiological matters and controversies surrounding benzodiazepines, *ie* dependence was not the main topic. In 14 reviews, definitions of (aspects of) dependence were given. The remaining 15 (14.6%) reviews addressed aspects of dependence as the main topic. They all gave explicit definitions of (aspects of) dependence. The WHO criteria were used in one article, the DSM criteria concerning benzodiazepine dependence were not used. Thirty reviews provided at least one definition each, which amounted to a total of 93 definitions.

Figure 1 shows the number of articles in which one or more of the following concepts were defined: addiction/dependence, psychological dependence, physical dependence, tolerance, withdrawal symptoms, craving, rebound, relapse and euphoria.

After the WHO, DSM-III and DSM-III-R criteria for dependence (APA, 1980; 1987) had been excluded, considerable disagreement was found regarding the meaning of these concepts. The number of different (non-homogeneous) definitions per concept are given below, with the total number of definitions shown between parentheses: addiction 13 (13), psychological dependence 8 (9), physical

Table I. Analysis of definitions of addiction and dependence except DSM-III-R and WHO.

| Study | Criteria | | | | | | | | | | | | |
|----------------------------------|----------|---|---|---|---|---|---|---|---|---|---|---|---|
| | A | B | C | D | E | F | G | H | I | J | K | L | |
| Talley (1990) | A | B | - | - | - | - | - | - | - | - | - | - | - |
| Talley (1990) | - | - | C | - | - | - | - | - | - | - | - | - | - |
| Farnsworth (1990) | A | - | - | - | E | F | G | - | - | - | - | - | - |
| Rifkin (1990) | A | - | - | - | - | - | - | H | - | - | - | - | - |
| Miller and Gold (1990a) | - | - | - | - | E | F | - | - | I | - | - | - | - |
| Roache (1990) | - | - | C | - | - | - | - | - | - | J | - | - | - |
| DuPont (1990) | - | - | - | - | E | - | G | - | - | J | - | - | - |
| Miller and Gold (1990b) | - | - | - | - | - | F | G | - | I | J | - | - | - |
| Miller and Gold (1989) | - | - | - | - | - | F | G | - | - | J | - | - | - |
| Anitto (1989) | - | - | - | D | - | - | - | - | - | - | K | - | - |
| Ladewig and Grossenbacher (1988) | - | - | - | - | - | F | - | - | - | - | - | - | - |
| Rinaldi <i>et al</i> (1988) | - | - | - | D | - | - | G | - | - | J | K | - | - |
| Roy Byrne and Hommer (1988) | - | - | - | - | - | - | - | - | - | - | - | - | L |
| Total | 3 | 1 | 2 | 2 | 2 | 5 | 6 | 1 | 2 | 5 | 2 | 1 | |

A: abuse; B: substance capable of altering level of consciousness; C: self-indication, -medication; D: disease, disorder; E: behavior pattern; F: supply security, preoccupation with acquisition; G: compulsive use, loss of control, over-whelming involvement with use; H: dependence; I: relapse to use; J: adverse (social) consequences; K: chronic progressive course; L: withdrawal reaction.

Table II. Analysis of definitions of psychological dependence.

| Study | Criteria | | | | | | | | | | |
|----------------------------------|----------|---|---|---|---|---|---|---|---|---|---|
| | A | B | C | D | E | F | G | H | I | | |
| Teboul and Chouinard (1990) | A | - | - | - | - | - | - | - | - | - | - |
| Talley (1990) | - | - | - | - | - | - | - | - | H | I | |
| Farnsworth (1990) | - | B | - | D | - | - | - | - | - | - | |
| Roache (1990) | - | - | C | - | - | - | F | - | - | - | |
| Kräupl Taylor (1989) | - | B | C | - | - | - | - | - | - | - | |
| Ladewig and Grossenbacher (1988) | - | - | C | - | - | - | - | - | - | - | |
| Noyes <i>et al</i> (1988) | - | B | - | D | - | - | - | - | - | - | |
| Gottschalk (1988) | - | - | - | - | E | - | - | - | - | - | |
| Rinaldi (1988) | - | B | C | - | - | - | - | G | - | - | |
| Total | 1 | 4 | 4 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | |

A: subjective need; B: compulsive craving; C: reliance on and/or expectation of effect; D: drug seeking behavior; E: drug dependence; F: compulsive use; G: negative (withdrawal symptoms) avoidance; H: chronic disease; I: effective symptoms control.

dependence 14 (20), tolerance 11 (16), withdrawal symptoms 17 (22), craving 1 (1), rebound 12 (24), relapse 4 (15), euphoria 0 (0). The results for the definitions of the concept of addiction are illustrated in table I.

In the definitions of addiction, the highest consensus existed with regard to the presence of loss of control (48%), supply security (40%) and (socially) adverse consequences (40%). No combination of items occurred more than once. It can be concluded that each of the 13 papers provide a definition of addiction or dependence of their own.

The results for the definitions of psychological dependence are presented in table II. Compulsive craving and expectation of effect were most used, *ie* in 44% of the cases. Only two combinations of criteria were chosen more than once: the combina-

tion of compulsive craving and expectation of effect (two papers) and the combination of compulsive craving and drug seeking behavior (also two papers, in one case combined with a third criterion). It can be concluded that only a small proportion of the nine papers provide comparable definitions of psychological dependence.

In table III the results for the definitions of physical dependence are presented. In 50% of the papers the appearance of specific withdrawal symptoms after cessation/discontinuation was used in the definition. Biological or neuropharmacological adaptation (30%) was another requirement for physical dependence used fairly frequently. Contrary to what one might expect, papers using this criterion were not published in pharmacological, but in clinical journals. Chronic or repeated use was a criter-

Table III. Analysis of definitions of physical dependence.

| Study | Criteria | | | | | | | | | | | | |
|--------------------------------|----------|---|---|---|---|---|---|---|---|---|---|---|---|
| Teboul and Chouinard (1991) | - | - | - | - | - | - | G | - | - | - | - | - | - |
| Lader (1989) | A | B | - | - | - | - | - | - | - | - | - | - | - |
| Salzmann (1991) | - | B | C | - | - | - | - | - | - | - | - | - | - |
| Busto and Sellers (1991) | - | B | C | D | - | - | - | - | - | - | - | - | - |
| Talley (1990) | - | - | C | - | - | - | - | H | - | - | - | - | - |
| Talley (1990) | - | - | - | - | - | - | - | - | I | - | - | - | - |
| Tyrer <i>et al</i> (1990) | A | B | C | - | E | - | - | - | - | - | - | - | - |
| Farnsworth (1990) | A | - | - | - | - | - | G | H | - | - | - | - | - |
| Rifkin (1990) | - | - | - | - | - | F | - | - | - | J | K | L | - |
| Roache (1990) | A | B | C | - | - | - | - | - | - | - | - | - | - |
| Rosenbaum <i>et al</i> (1990) | - | - | - | - | - | F | G | - | - | - | - | - | - |
| Miller and Gold (1990) | A | B | - | - | - | - | - | - | - | - | - | - | - |
| DuPont (1990) | A | - | - | - | - | - | G | - | - | - | - | - | - |
| Miller and Gold (1990) | A | B | - | - | - | - | - | - | - | - | - | - | - |
| Miller and Gold (1989) | A | B | - | - | - | - | - | - | - | - | - | - | - |
| Geiselmann <i>et al</i> (1989) | A | - | - | - | - | F | G | - | - | - | - | - | - |
| Kräupl Taylor (1989) | - | - | - | - | - | - | G | - | - | - | - | - | - |
| Kräupl Taylor (1989) | - | - | - | - | - | - | - | - | - | - | - | - | M |
| Noyes <i>et al</i> (1988) | A | B | - | - | - | - | - | - | - | - | - | - | - |
| Total | 10 | 9 | 5 | 1 | 1 | 3 | 6 | 2 | 1 | 1 | 1 | 1 | 1 |

A: specific withdrawal symptoms or syndromes; B: after cessation or discontinuation; C: chronic or repeated use; D: physical & physiological subjective changes; E: stop failure; F: tolerance; G: neuropharmacological adaptation; H: continuing, self-induced need; I: physical dependence doesn't wreck lives; J: abuse; K: compulsive drug seeking; L: social consequences; M: anxious need to avoid the discomfort of drug abstinence.

ion in 40% of the papers. The authors of the three papers that include tolerance as an important criterion do not make clear for what effect in their opinion the users become tolerant: sedation, anxiolysis or euphoria. Looking at combinations of criteria only the criterion of specific withdrawal symptoms and "after cessation or discontinuation" occur fairly often together (27%) albeit in two definitions together with other criteria.

Twenty-seven out of the 250 articles (10.5%) reported that relapse, rebound and withdrawal symptoms frequently overlapped. Only 17 (5 original research papers and 12 reviews) of these gave explicit definitions of at least two of the three concepts.

DISCUSSION

The main finding in our study was that many research reports and review articles on benzodiazepine use for insomnia and anxiety, discussed (aspects of) dependence without giving any definition of these concepts. In addition, the articles which did not provide definitions varied widely in the operationalisations. Most discrepancies were found in the definition of the overall concept of benzodiazepine addiction: no two papers provided the same definition. The highest degree of similar-

ity was found in the description of physical dependence: about one third of the definitions had two criteria in common. It can be concluded that the level of consensus in the reviewed studies is low.

Before discussing the possible implications of these findings, we should take a closer look at the methodology of our study. Anxiety and insomnia were chosen as primary criteria for the selection of studies because they are the main reasons for prescribing benzodiazepines. Clearly, different criteria may have led to the inclusion of other studies.

It is possible that the manual search of the literature published in the second half of 1991 was less effective than the search using Medline and PsychLit. If more articles had been included, the number of different definitions would probably have been larger.

Our results were obtained from journals in English published during a specific four year period, which may have led to distortion. Previous findings were cited in this literature, but probably in a selective way. Our word-by-word content analysis of the definitions, although extensive, was arbitrary and may not have been free from interpretation bias.

In general, explicit definitions of important and basic concepts were scarcely used. It was striking that the use of definitions in the reviews tripled

that in the original research papers. We would like to encourage researchers to communicate their views on dependence beyond adopting certain terminology or the use of particular instruments. This recommendation is supported by the fact that there was considerable disagreement between explicit definitions. There were also considerable differences between the number of definitions given per concept. For instance, euphoria was never explicitly defined, craving only once, but rebound 25 times. This may have been related to the focus of the various studies. The disagreement between explicit definitions per concept is a matter for serious concern.

It was decided not to use the keyword "addiction" as a selection criterion, because both the APA and the WHO have declared this concept obsolete and confusing; reference was instead made to substance dependence. Therefore, the frequently encountered definitions of addiction were surprising. The diversity of definitions reported in table I once again illustrates this point. Apparently the development of the Diagnostic and Statistical Manual for Mental Disorders by the American Psychiatric Association appealed little to the authors of the papers and reviews in our study. In accordance with this conclusion is the distinction many authors made explicitly between physical and psychological dependence. Yet the definitions concerning psychological and physical dependence were less homogeneous than we expected. One might argue that only 50% of the authors defined withdrawal symptoms as being required for physical dependence. Speculating about why this is so, we hypothesized that many authors assume that dependence may well develop in regular users who do not discontinue their use and thus will not develop withdrawal symptoms.

Our results show that there is considerable limitation of the possibility to make a realistic assessment of the prevalence and importance of BZD dependence related phenomena, despite the intense debate in the recent literature. The uncertainty concerning this matter is illustrated by the APA (1990) report on benzodiazepine dependence, toxicity and abuse, which stated that alprazolam and triazolam have become the most frequently prescribed benzodiazepines in the USA. The report cited research which showed that severe withdrawal symptoms have occurred with these compounds. However, the report did not consider anxiety/sedative medications to be a great public health problem. According to the authors, the relationship between the long-term use of BZD and BZD dependence was unclear.

In order to make new headway in the discussion about the risk of BZD dependence, it is imperative to start at a basic level and improve the consensus on criteria concerning aspects of BZD dependence. Explicitly defining the concepts under study will make the results of research which focuses on different aspects of BZD dependence a great deal less confusing. Such developments are necessary to obtain meaningful data on the incidence, prevalence and relevant co-factors of BZD dependence, as well as on its natural history.

It is clear that the literature we reviewed does not provide a clear picture of the criteria for BZD dependence. Nevertheless, studying this literature and discussing the topic with many addiction experts and BZD-users, we would like to suggest a set of criteria for BZD dependence. This set consists of the following components:

- Criteria with respect to acquisition strategies: frequent requests for repeat prescriptions, simulating symptoms to acquire prescriptions, prescriptions by several physicians at the same time, acquisition of BZD *via* relatives, friends, black market.
- Criteria with respect to abuse: higher dosages than usual, extra dosages, wishes or attempts to stop, the need to increase the dose (tolerance), BZD-use to induce euphoria.
- Criteria dealing with rebound and withdrawal: whereas these criteria are mentioned in most of the literature we reviewed here, future research will have to point out the clinical relevance of these criteria.

Note: Tables of all the explicit concept definitions subjected to word-by-word analysis may be obtained from the authors.

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