Dependence potential of antidepressants compared to benzodiazepines

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Abstract

The aim of the present study was to compare the possible dependence potential of antidepressants (ADs) to benzodiazepines (BZDs). The Schedules for Clinical Assessment in Neuropsychiatry (SCAN), the Benzodiazepine Dependence Self-Report Questionnaire (Bendep-SRQ) and the Symptom Checklist-90 (SCL-90) were administered to 70 psychiatric outpatient BZD users and 54 psychiatric outpatient AD users. Significantly more Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised (DSM-III-R) as well as International Classification of Diseases, Tenth Edition (ICD-10) past year (PY) and lifetime (LT) dependence diagnoses were made in the BZD group than in the AD group. Bendep-SRQ scale scores for Problematic Use, Preoccupation and Lack of Compliance were significantly higher in the BZD group than in the AD group. The BZD group also had a higher rating on the Withdrawal scale, but this difference was not statistically significant. According to DSM-III-R and ICD-10 criteria ADs do have some dependence liability in psychiatric outpatients, but clearly to a lesser extent than BZDs. Further research is needed to differentiate the dependence potential among the various classes of ADs. © 2002 Elsevier Science Inc. All rights reserved.

Keywords: Antidepressants; Bendep-SRQ; Benzodiazepines; Dependence; DSM-III-R; ICD-10

1. Introduction

It is well known that dose reduction or discontinuation of antidepressants (ADs) may induce withdrawal symptoms (Rosenbaum et al., 1998; Zajecka et al., 1998). Early studies on benzodiazepines (BZDs) also noted withdrawal symptoms; these were followed later by findings indicating other aspects of dependence (Kan et al., 1997). The concept of substance dependence, originally called the “substance-dependence syndrome,” was introduced as a psycho-physiological-social concept by the World Health Organization (WHO) in 1981 (Edwards et al., 1981) and has been translated into the Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised (DSM-III-R) (American Psychiatric Association, 1987), DSM-IV (American Psychiatric Association, 1994) and International Classification of Diseases, Tenth Edition (ICD-10) (World Health Organization, 1992) substance-dependence criteria. Most studies on AD dependence have not used these uniform criteria for substance dependence (Ginestet et al., 1984; Lejoueux et al., 1992; Nathan and Kinney, 1985; Perez de los Cobos et al., 1990; Bertschy et al., 1990; Pringuey et al., 1989; Edwards et al., 1984; Giraud et al., 1994; Reine et al., 1992; Perera and Lim, 1998). Reports that did use these criteria and stated that ADs are not drugs of dependence (Lichtigfeld and Gillman, 1999, 1998; Haddad, 1999; Haddad and Anderson, 1999; Haddad et al., 1998) were not based upon convincing trials. Only a few cases have been described in which dependence on ADs was shown according to the substance-dependence criteria. A case report on three patients that were dependent on the irreversible monoamine oxidase inhibitor (MAOI) phenelzine was accompanied by a review of case reports on dependence on this and other MAOIs, and it was concluded that the irreversible MAOIs tranylcypromine and phenelzine can lead to dependence according to DSM-III-R criteria for substance dependence (Baumbacher and Hansen, 1992). Another two cases have been described in which patients were dependent on the tricyclic AD amineptine according to DSM-III-R criteria for substance dependence (Biondi et al., 1990). In a study on medication dependence in patients with chronic pain, no

Abbreviations: AD(s), antidepressant(s); Bendep-SRQ, Benzodiazepine Dependence Self-Report Questionnaire; BZD(s), benzodiazepine(s); DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; MAOIs, monoamine oxidase inhibitors; SCAN, Schedules for Clinical Assessment in Neuropsychiatry; SSRI, selective serotonin reuptake inhibitor; SCL-90, Symptom Checklist-90

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PII: S0278-5846(02)00209-9
dependence diagnoses according to DSM-III-R criteria for substance dependence were made in the patients who were using ADs (Kouyanou et al., 1997). Finally, the selective serotonin reuptake inhibitor (SSRI) fluoxetine has been shown as a drug of dependence according to DSM-IV criteria for substance dependence in one case report (Mene-cier et al., 1997). Because we found only these few reports, AD dependence appears to represent a minor problem. However, no prevalence studies on AD dependence have been carried out and, therefore, no definite conclusions can be drawn about the dependence potential of ADs. The present study was conducted to address the question: what is the possible dependence potential of ADs compared to BZDs according to DSM-III-R and ICD-10 criteria?

2. Materials and methods

2.1. Settings and subjects

This study was conducted at the Psychiatric Outpatient Department of the University Medical Center St. Radboud Nijmegen, the Netherlands.

To be eligible to participate in the investigation, the subjects had to fulfil the following inclusion criteria: (1) actual BZD use with an average frequency of at least once a week in the BZD group or actual AD use in the AD group; (2) age between 17 and 70 years; (3) ability to speak and read Dutch.

The patients who visited the Psychiatric Outpatient Department during the study period were screened according to these inclusion criteria. Eligible patients were asked to participate by a representative of the treatment team. Patients willing to participate signed informed consent. The response rates were 64% in the BZD group and 81% in the AD group. The total sample of participants consisted of 124 subjects: 70 BZD users and 54 AD users.

2.2. Study design

This study is part of a larger project being conducted on the diagnosis and detection of BZD dependence. The study population participated in an interview during which sociodemographic data were collected and completed the Benzodiazepine Dependence Self-Report Questionnaire (Bendep-SRQ) (Kan et al., 1999), the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Janca et al., 1994) and the Symptom Checklist-90 (SCL-90) (Arrindell and Ettema, 1975).

2.3. Assessment instruments

2.3.1. The Bendep-SRQ

The Bendep-SRQ was constructed at the Department of Psychiatry of the University Medical Center Nijmegen, the Netherlands, to reflect the severity of BZD dependence. The construction process of the Bendep-SRQ and its composition have been described previously (Kan et al., 1999). The Bendep-SRQ reflects four separate dimensions of dependence: Problematic Use (reflecting the patient’s awareness of his/her problematic BZD use), Preoccupation (reflecting the patient’s preoccupation/obsession with respect to the availability of BZDs), Lack of Compliance (reflecting the degree of lack of compliance with the therapeutic BZD regimen) and Withdrawal (reflecting the degree of unambiguity of experienced BZD withdrawal). In the first section of the Bendep-SRQ, the person who administers the questionnaire notes the sex and age of the respondent, the average BZD dose(s) used and the duration of BZD use. In the second and third sections, 5-point use-related items are rated by the respondent according to the degree to which they apply to him/her.

The Bendep-SQR could be administered to the AD and BZD users, because, in all the Bendep-SRQ items, the general term “medication” is used. The type of medication (AD or BZD) was specified by the interviewer.

2.3.2. The SCAN

The SCAN, in which both the DSM-III-R and ICD-10 criteria are operationalized in a semistructured format, was developed in the WHO/US National Institutes of Health (NIH) Joint Project on Diagnosis and Classification of Mental Disorders and Alcohol- and Drug-Related Problems. It is generally acceptable, appropriate and reliable across cultures and settings (Janca et al., 1994). The section “Use of psychoactive substances other than alcohol” from the SCAN was administered to assess dependence in the AD and BZD users (Giel and Nienhuis, 1992). The DSM-III-R and ICD-10 past year (PY) and lifetime (LT) diagnoses of dependence were computed as described in an earlier report (Kan et al., 1997).

2.3.3. The SCL-90

The SCL-90 is a self-report questionnaire consisting of 90 questions, which mainly measures mental complaints the respondent may have been suffering from the week before and/or on the day of testing. It yields scores on nine subscales and a total score for psychoneuroticism (Arrindell and Ettema, 1975). The SCL-90 was administered in order to compare the two groups regarding the degree of psychopathology.

2.4. Statistical analysis

Two independent sample distributions for nominal (categorized) data were statistically compared by means of the chi-square test for $2 \times k$ tables and for ordinal data (age or scores) by means of the Wilcoxon two-sample test. If a statistical test resulted in a $P$ value < 0.05 the difference between both sample distributions was labeled statistically significant. A (asymptotic) 95% confidence interval (CI) for the difference in two independent percentages was calcu-
lated using the normal approximation to the binomial distribution and for the difference in mean values according to the procedure described by Conover (1980). All calculations were done within SAS (version 6.12).

3. Results

3.1. Sociodemographic characteristics and SCL-90 results

The sociodemographic characteristics of our outpatient samples are shown in Table 1. The male to female ratio was fairly equal in the two groups, with slightly more females than males in each case. The majority was married. Consequently, the greater proportion of the patients were living with a partner. About half of the patients had been educated to primary level. The two groups did not differ significantly on any of these sociodemographic characteristics. Likewise, most SCL-90 subscores did not differ significantly. Only the scores on the subscales Sleeping Problems, Anxiety and Somatic Complaints were significantly higher in the BZD group [means (S.D.) BZD group–means (S.D.) AD group: 8.9 (3.8)–7.1 (3.9); 27 (9.9)–23 (8.7); 29 (9.5)–25 (9.0), respectively].

3.2. SCAN results

SCAN results are given in Table 2. DSM-III-R as well as ICD-10 PY and LT diagnoses were made in significantly more of the BZD users than AD users. The ICD-10 diagnoses outnumbered the DSM-III-R diagnoses in the BZD group, whereas the DSM-III-R diagnoses outnumbered the ICD-10 diagnoses in the AD group. Furthermore, no specific AD yielded significantly more DSM-III-R or ICD-10 dependence diagnoses than other ADs. When the ADs were divided into “SSRIs” and “ADs other than SSRIs,” there was no statistically significant difference.

3.3. Bendep-SRQ results

Wilcoxon analyses of the Bendep-SRQ scales showed that the mean scores in the BZD group for Problematic Use, Preoccupation and Lack of Compliance were statistically significantly higher than those in the AD group. The BZD group also had a higher rating on the Withdrawal

### Table 1

<table>
<thead>
<tr>
<th>Sociodemographic variables</th>
<th>BZD users (n=70)</th>
<th>AD users (n=54)</th>
<th>95% CI</th>
<th>Statistical test for differencea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>47</td>
<td>48</td>
<td>(−19%, 17%)</td>
<td>0.91</td>
</tr>
<tr>
<td>Female</td>
<td>53</td>
<td>52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age ± S.D. (years)</td>
<td>43 ± 11</td>
<td>43 ± 11</td>
<td>(−4, 4)</td>
<td>0.97</td>
</tr>
<tr>
<td>Marital/social status (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single/no relationship</td>
<td>16</td>
<td>13</td>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td>Engaged/steady relationship</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>57</td>
<td>57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Divorcedb</td>
<td>13</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Widowedb</td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living arrangement (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.19</td>
</tr>
<tr>
<td>Alone (own lodging)</td>
<td>21</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With partner</td>
<td>64</td>
<td>78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>14</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level of education (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.74</td>
</tr>
<tr>
<td>Primary</td>
<td>51</td>
<td>44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>26</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced</td>
<td>23</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Financial income (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.28</td>
</tr>
<tr>
<td>Profession/pension</td>
<td>34</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployment benefit</td>
<td>16</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disability benefit</td>
<td>27</td>
<td>43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partner’s income</td>
<td>14</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td>6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a All variables were statistically tested using χ² tests except for age, which was tested by the two-sample Wilcoxon test.
b Categories taken together in statistical test calculations.

### Table 2

<table>
<thead>
<tr>
<th>DSM-III-R and ICD-10 dependence diagnoses according to the SCAN</th>
<th>BZD (n=70)</th>
<th>AD (n=54)</th>
<th>95% CI for difference in percentagesa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DSM</td>
<td>ICD</td>
<td>DSM</td>
</tr>
<tr>
<td>PYb n (%)</td>
<td>33 (47)</td>
<td>41 (59)</td>
<td>8 (15)</td>
</tr>
<tr>
<td>LTc n (%)</td>
<td>38 (54)</td>
<td>46 (66)</td>
<td>10 (19)</td>
</tr>
</tbody>
</table>

a Differences were statistically tested using χ² tests and all four P values were <.001.
b Past year dependence diagnosis.
c Lifetime dependence diagnosis.
We assumed that the Bendep-SRQ questions were formulated in such a general way that they could also be applied to AD users. All the AD users filled in three of the four scales of the Bendep-SRQ; they had significantly lower scores than the BZD group. Only 30% of the AD users filled in the Withdrawal scale versus 81% of the BZD users. The non-significant difference in Withdrawal scores between the AD and BZD groups was probably due to insufficient statistical power owing to this small number of respondents in the AD group. Probably, more BZD users filled in this scale because BZDs are frequently used to suppress acute anxiety, but are not used again until the anxiety reappears. This is in contrast with the usual advice given with ADs to take a steady dose every day at the same time, despite possible unpleasant side effects. Possibly, AD withdrawal could be detected in AD users by the Withdrawal scale of the Bendep-SRQ in the period that the dose was being reduced because the AD effect no longer seemed to be necessary.

Because both samples were recruited from only one outpatient department, generalization of our findings to users of BZDs and ADs in general would be inappropriate. In the BZD group, the use of ADs was not excluded and in the AD group, the use of BZDs was not excluded. In both samples, questionnaires focussed on the drug to be investigated.

### 4. Discussion

BZD and AD users visiting a psychiatric outpatient department were invited to participate in the present study on the dependence liability of ADs based on the evaluation of different test results. The different response rates in the two groups, 64% in the BZD group and 81% in the AD group, possibly reflect public attitude to BZDs as highly addictive agents. BZD users might avoid confrontation with the affirmation of a self-assumed diagnosis of being dependent on BZDs.

Sociodemographic variables and SCL-90 scores did not show any statistically significant differences, besides the significantly higher mean scores in the BZD group on the SCL-90 subscales Sleeping Problems, Anxiety and Somatic Complaints. This indicates that the two groups were fairly comparable.

Based on the literature on this topic, it was postulated that ADs would have lower dependence potential than BZDs. In line with this supposition, the SCAN results showed significantly more dependence diagnoses among the BZD users than among the AD users: 47% in the BZD group versus 15% in the AD group (Table 2). The low prevalence rates of PY and LT dependence diagnoses in the AD group supported the hypothesis that ADs carry a much smaller dependence risk than BZDs. The prevalence rates of AD and BZD dependence depended on the classification used. The DSM-III-R dependence diagnoses outnumbered the ICD-10 diagnoses in the AD group whereas the reverse was true in the BZD group (Table 2). This appears to be caused by one of the systematic differences between the DSM-III-R and the ICD-10 classification (Kan et al., 1997): "social harm or repeated risk-taking behaviour," which is only a DSM-III-R criterion, was more frequently positive in the AD group. Since this criterion is no longer present in the DSM-IV, one can expect that the difference found in the number of dependence diagnoses between both classification systems in this study is reduced.

We thank Drs. W.H. Doesburg and W.A.J.G. Lemmens, Department of Epidemiology and Biostatistics, University of Nijmegen, for their statistical advice.

### 5. Conclusion

This study showed that ADs do have some dependence liability in psychiatric outpatients, but clearly to a lesser extent than BZDs. This was reflected by lower prevalence rates of DSM-III-R and ICD-10 diagnoses and lower Bendep-SRQ scores.

The fact that no specific AD yielded significantly more DSM-III-R or ICD-10 dependence diagnoses than other ADs may be due to the small number of users in the AD subgroups. Further research is needed to differentiate the dependence potential among the various classes of ADs.

This study also showed that the Bendep-SRQ scales Problematic Use, Preoccupation and Lack of Compliance discriminated the effects of BZD use very well from those of AD use. It appears that the use of the Bendep-SRQ can be extended to AD users.

### Acknowledgments

We thank Drs. W.H. Doesburg and W.A.J.G. Lemmens, Department of Epidemiology and Biostatistics, University of Nijmegen, for their statistical advice.

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