PRIMARY AND SECONDARY SUBSTANCE MISUSERS: DO THEY DIFFER IN SUBSTANCE-INDUCED AND SUBSTANCE-INDEPENDENT MENTAL DISORDERS?

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Abstract — Aims: This study evaluated the primary/secondary distinction among substance misusers according to comorbid mental disorders. Methods: A consecutive sample (n = 287) of DSM-IV substance dependents from public treatment facilities in two counties in Norway were assessed by the Composite International Diagnostic Interview. According to the debut of the first independent mental disorder, patients were divided into primary substance use disorder (SUD) (17%), secondary SUD (76%) and SUD in the same year as the first mental disorder (7%). Results: A lifetime substance-independent mental disorder was found in 90%. Forty-two per cent had a combination of substance-independent and substance-induced mental disorders. Five per cent had substance-induced mental disorders only. Primary SUD patients comprised less women, and a lower number of substance-independent mental disorders. Secondary SUD patients had more major depression, phobic disorders and obsessive-compulsive disorder. There were no differences between primary SUD and secondary SUD regarding the number of substance-induced disorders or the pattern of substance misuse. Conclusions: Clinical differences between primary and secondary SUD were small and do not support the distinction.

INTRODUCTION

There is a strong co-occurrence of substance use disorders (SUDs) with other mental disorders in the general population (Regier et al., 1990; Kessler et al., 1997; Merikangas et al., 1998) and an even stronger relationship within clinical groups (Hesselbrock et al., 1985; Helzer and Pryzbeck, 1988; Ross et al., 1988; Tomasson and Vaglum, 1995; Driessen et al., 1996, 1998; Kokkevi et al., 1998; Compton et al., 2000). However, there is far less empirical evidence regarding the actual mechanism of this co-occurrence (Winokur, 1990; Kessler and Price, 1993; Mueser et al., 1998; Kushner et al., 2000). It is of both theoretical and clinical importance to clarify further these possible relationships.

An important approach to the investigation of the association between SUDs and mental disorders has been the classification of mental disorders among SUD patients into substance-independent and substance-induced mental disorders. Substance-induced mental disorders are characterized by their development in close connection with the use of substances, their presence only when the person uses substances, and their supposed improvement during the initial weeks of abstinence, even without specific treatment (Akiskal, 1995; Kadden et al., 1995). The identification of mental disorders that are independent of SUDs is mainly based on the argument that if such a disorder was manifested (lifetime prevalence) before the onset of any SUD, it is likely that the mental disorder is independent of the substance misuse. Consequently, such mental disorders may need to be treated differently from those that have been induced by the use of substances (Brown et al., 1995; Goodwin and Guze, 1996).

Concerning the classification of comorbid mental disorders, it is always difficult to do such classification with a retrospective design. Retrospective information depends on the patient’s capability to recall. The best would be to have a prospective design, but it is difficult to carry out such studies. Axis I mental disorders that started before the establishment of the first SUD are more easy to classify as substance-independent mental disorders, than mental disorders that commenced after establishment of the SUD. Such disorders can be both independent of, and induced by, the SUD. Usually, in this research field, substance-induced mental disorders are classified as those disorders that have occurred after establishment of the SUD. In the present study, we have separated those mental disorders that occurred after the SUD, into substance-induced and substance-independent mental disorders by using the Composite International Diagnostic Interview (CIDI). CIDI allows every section to be followed by probe questions to assess whether the mental disorder was caused directly by using medication, drugs or alcohol (Wittchen, 1994). If the symptoms can be explained exclusively by such causes, they are classified as substance-induced mental disorders. If the mental disorders are not induced by the use of substances, they are classified as substance-independent mental disorders. Consequently, substance-independent mental disorders may commence before or after a SUD is established.

Prevalence rates of mental disorders among SUD patients depend upon how mental disorders are defined. By counting only substance-independent mental disorders (onset of mental disorder before onset of SUD, or occurrence of a mental disorder in a prolonged substance-free period of 3–6 months), the comorbidity rate of SUDs and mental disorders was reduced to 60–75% in several studies (Schuckit et al., 1990, 1997a,b; Kadden et al., 1995). However, some researchers have argued that the criteria for operationalizing substance-independent mental disorders have been too restrictive in these studies (Kushner et al., 2000), and others have not found the distinction between substance-induced and substance-independent mental disorders clinically useful (Penick et al., 1994; Kadden et al., 1995). Other studies do not separate mental disorders into substance-independent and substance-induced disorders. They usually analyse whether the mental disorder came before or after the SUD (Driessen et al., 1996; Compton et al., 2000).

In a recent review, Wittchen et al. (1996) reported that 80–90% of substance misusers possibly developed the other

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mental disorder before SUD onset. A German study that used the CIDI in a sample of 100 alcoholics found that 80% of those with a mental disorder developed the condition before the onset of SUD (Driessen et al., 1996).

Concerning the classification of substance misusers, it has been customary to classify substance misusers as primary misusers (primary SUD) if the first Axis I mental disorder began after the SUD, and as secondary misusers (secondary SUD) if the Axis I mental disorder(s) were manifested before the SUD. The term secondary SUD does not imply that the SUD is caused by the mental disorder, only that it started some time after the mental disorder. One important, but still unsolved, question is whether primary and secondary SUD patients really differ with regard to the prevalence and type of both substance-independent mental disorders and substance-induced mental disorders. Until now, most of the studies have been done in the USA in highly selective clinical samples, and the validity of generalizing these findings is unclear. There is therefore a need for studying this important question outside the USA, where the drug scene is different. Such studies should examine samples representing the heterogeneity of the SUD population, and explore whether there are clinically important differences in comorbid disorders between the primary and secondary SUD groups. In addition, it is also of interest, in clinically representative samples, to examine more specifically the subgroup of patients who have exclusively substance-induced mental disorders, so as to identify the magnitude of the mental disorder as well as other characteristics of this subgroup. Since it may be difficult in retrospective studies to clearly know when the first SUD/Axis I disorder started we excluded those patients who got both disorders in the same year.

With this background, we have conducted a cross-sectional study, completing personal interviews with a consecutive sample of treatment-seeking SUD patients from public treatment facilities for SUD patients in two neighboring counties in Norway (with a total population of approximately 290 000 people aged over 18 years). To our knowledge, this is the first study of its type in Scandinavia. The questions we explored are: (1) what is the prevalence of substance-induced and substance-independent mental disorders in this consecutive sample?; (2) are there any differences in sociodemographic variables or SUDs between patients with substance-induced, and those with substance-independent, mental disorders?; (3) among patients with substance-independent mental disorders, what is the prevalence of primary and secondary SUDs?; (4) are there any differences between primary and secondary SUD patients regarding sociodemographic variables, substance use and the prevalence of Axis I disorders?

SUBJECTS AND METHODS

A consecutive sample (n = 287) of DSM-IV (American Psychiatric Association, 1994) substance dependents from three out-patient (n = 116) and six in-patient public facilities (n = 171) were assessed by the Norwegian National Client Assessment form (sociodemographic and substance use variables) and the structured interview CIDI (Axis I disorders). The response rate was 42%. In spite of this relatively low response rate, the sample appears to be reasonably representative for treatment-seeking SUD patients. Compared with a national sample of treated substance misusers (n = 5000) in Norway, the main difference was only that our sample included rather fewer young drug misusers. In the analyses, we did not distinguish between substance misuse and substance dependence. All patients fulfilled DSM-IV criteria for at least one substance dependence. With regard to the onset of SUD, we chose as age of onset the first time the person fulfilled either a dependence or a misuse diagnosis.

The assessment with the CIDI was conducted at the earliest 4 weeks after discontinuation of substances among in-patients. This was more difficult to carry out among out-patients, and we included such clients if they were sober in the assessment situation.

About one third of the patients received medications because of mental problems during the last month before assessment.

Psychiatric Axis I disorders were evaluated using the Norwegian version of the CIDI, Lifetime version, the computer version of CIDI-M 1.1. CIDI is a structured psychiatric interview based on DSM-IV criteria and the corresponding diagnosis in ICD-10. CIDI focuses on both lifetime symptoms as well as those of the last 12 months, age of onset and recency. In this study, we used the version of the CIDI examining symptoms over the lifespan. The time of onset (and recency) of a disorder are assessed in relation to the year when a sufficient number of criteria of a specific diagnosis was fulfilled for the first and most recent time. For the purpose of this study, we used a non-hierarchical diagnostic system.

The CIDIs were mostly conducted by the two researchers (K.B. and A.S.L.), who had taken part in the training workshops by The National WHO Training Centre (Munich). One third of the interviews were conducted by trained clinicians (psychiatrists, social workers psychiatric nurses). The two researchers in the project trained these interviewers using a standardized 4-day training programme. Structured diagnostic interviews, such as CIDI, usually possess higher test–retest reliability than clinical interviews (Robins et al., 1989). The CIDI has shown good feasibility in general populations, high inter-rater reliability, and has been subjected to tests of reliability and validity with satisfactory results (Janca et al., 1992a;b; Williams et al., 1992; Wittchen, 1994). Further information about sampling, subjects, methods and data analyses is described in another paper (Landheim et al., 2003).

RESULTS

Prevalence of substance-induced and substance-independent mental disorders

In all, 259 patients (90%) fulfilled the criteria for at least one lifetime substance-independent mental disorder, and 15 patients (5%) had exclusively substance-induced mental disorders. Another 13 subjects (5%) were without any additional mental disorder and were excluded from the analyses. In all, 120 patients (42%) had one or more substance-induced mental disorders in addition to one or more substance-independent mental disorders (Table 1).

Differences between substance-induced and substance-independent mental disorders

The subgroup exhibiting only substance-induced mental disorders did not differ significantly from patients with
substance-independent mental disorders with regard to sociodemographic variables (Table 2) and substance use (main substance, mean number of substances, duration of dependency).

Classification in primary and secondary SUD groups

Among those patients with a substance-independent mental disorder, 43 patients (17%) were classified as primary SUD. These individuals had a SUD at least 1 year before the emergence of any other mental disorder. Furthermore, 198 patients (76%) were classified as secondary SUD, as they developed a mental disorder at least 1 year before the first SUD diagnosis. In 18 patients (7%), the SUD and the mental disorder emerged during the same year, thereby making it difficult to decide which was the initial disorder. Subsequently, these patients were excluded from comparisons between the primary and secondary SUD groups.

Differences between primary and secondary SUD patients

The only significant sociodemographic difference between the primary and secondary SUD groups was that of gender (Table 2). More than one third of the secondary SUD group were women, compared with only 9% (n = 4) among those with primary SUD. Because of this large gender difference, we controlled for gender when we compared primary and secondary SUD.

Concerning the length, extent and severity of the substance use, there was only one significant difference as shown in Table 3. As expected, patients with primary SUD more often had an early average onset of SUD, compared with secondary SUD patients (17.8 vs 22.9 years, \( P = 0.003 \)). For each misused substance, the primary SUD group had a higher frequency of use than the secondary SUD group, but the differences were not significant. The mean number of SUD diagnoses was quite similar in the primary and secondary SUD groups (2.8 vs 2.5). To further examine differences between groups, we conducted a series of multivariate analyses using logistic regression, controlling for gender. In the series of analyses, each disorder was treated as a dependent variable, while primary/secondary SUD and gender were independent variables. These analyses did not change any of the differences between primary SUD and secondary SUD, which are shown in Tables 2 and 3.
Axis I disorders were significantly more prevalent in the secondary SUD group (4.4 vs 2.4, \( P = 0.003 \); Table 4). When comparing the primary and secondary SUD groups, the secondary SUD group had a significantly higher incidence of major depression and three anxiety disorders: social phobia, simple phobia and obsessive-compulsive disorder. The primary SUD group had a significantly higher prevalence of substance-induced mental disorders. When controlling for gender, however, this difference became non-significant.

**DISCUSSION**

Approximately 90% of all patients had developed a substance-independent mental disorder at some point in their lives. In addition, nearly 50% of patients had suffered from one or more substance-induced mental disorders. About 40% of patients had both substance-induced and substance-independent mental disorders, thus demonstrating the problem of classifying SUD patients based on this distinction. The treatment system must obviously be able to diagnose and treat both types of disorders, even when they occur in the same person. Only 5% had exclusively substance-induced mental disorders, and this small number makes it difficult to find significant differences between this group and the group with independent mental disorders.

It is important to note that three quarters of the patients with comorbid mental disorders developed their first independent mental disorder before the onset of any SUD (secondary SUD group). Only 17% had a primary SUD, a percentage that may be somewhat underestimated because of the composition of our sample. However, it does accord well with the review by Wittchen et al. (1996), and it shows that regardless of the presence of substance-induced mental disorders, the majority of substance misusers also had independent mental disorders that required specific treatment. For some, early and adequate treatment might possibly have prevented the development of a secondary SUD, or might have made the course of the SUD less serious. Our findings highlight the importance of evaluating and treating psychiatric disorders in substance misusers being treated for their dependence for the first time, and to evaluate substance misuse in general patients with a first-onset psychiatric disorder.

The primary and secondary SUD groups were very similar with regard to sociodemographic variables, except for gender. Accordingly, it is well established that the onset of psychiatric disorders precedes the onset of SUD more often in women than in men (Brady and Randall, 1999).

Also as expected, the primary SUD group had an earlier onset of SUD (mean = 17.8 years) than the secondary SUD group (mean = 22.9 years). However there were small differences with respect to the other substance use variables. Differences in substance use could not explain differences in the prevalence of mental disorders between the groups. Neither was there a difference in substance-induced mental disorders between the groups. The results from other studies vary in this regard. Most studies report an earlier onset of alcoholism and more severe substance misuse among primary alcoholics (Roy et al., 1991; Tsuang et al., 1995; Driessen et al., 1996; Schuckit et al., 1997b); however, Merikangas and Gelmenter (1990) found few clinical differences between primary and secondary alcoholics.

Concerning Axis I disorders, the secondary SUD group had significantly more Axis I disorders than the primary SUD group (4.4 vs 2.4, \( P = 0.003 \)). Major depression, social phobia, simple phobia and obsessive-compulsive disorder were more frequent in the secondary SUD group, with this difference remaining after controlling for gender. These are well defined psychiatric disorders with effective treatment methods, so SUD patients should also receive such treatment. Even if the SUD patients become abstinent, the independent mental disorders may persist. With regard to dysthymia, the differential diagnosis versus substance-induced mood disorder may be difficult. However, the prevalence of dysthymia was the same in the primary SUD and secondary SUD groups (44.2 vs 45.4%).

About one third of the patients received medications when they were assessed. Such medication may have modified the presence of symptoms of psychiatric disorders at the time of evaluation, but have possibly not influenced the age of onset of SUD or the differences in prevalence of psychiatric disorders between the primary and secondary SUD groups.

**Table 4. Lifetime Axis I disorders (ICD-10) in primary and secondary SUD groups**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Primary SUD (n = 43)</th>
<th>Secondary SUD (n = 198)</th>
<th>Significance (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substance-induced disorders</td>
<td>65.1</td>
<td>41.9</td>
<td>0.006</td>
</tr>
<tr>
<td>All affective disorders</td>
<td>53.5</td>
<td>74.9</td>
<td>0.005</td>
</tr>
<tr>
<td>Bipolar</td>
<td>2.3</td>
<td>6.3</td>
<td>NS</td>
</tr>
<tr>
<td>Major depression</td>
<td>21.5</td>
<td>53.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>44.2</td>
<td>45.4</td>
<td>NS</td>
</tr>
<tr>
<td>All anxiety disorders</td>
<td>84.2</td>
<td>92.9</td>
<td>NS</td>
</tr>
<tr>
<td>Agoraphobia with/without panic</td>
<td>47.5</td>
<td>53.8</td>
<td>NS</td>
</tr>
<tr>
<td>Social phobia</td>
<td>34.2</td>
<td>57.6</td>
<td>0.010</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>23.8</td>
<td>20</td>
<td>NS</td>
</tr>
<tr>
<td>Simple phobia</td>
<td>21.4</td>
<td>62.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>0.0</td>
<td>10.6</td>
<td>0.026</td>
</tr>
<tr>
<td>PTSD(a)</td>
<td>16.7</td>
<td>22.3</td>
<td>NS</td>
</tr>
<tr>
<td>Somatoform disorder</td>
<td>21.4</td>
<td>32.3</td>
<td>NS</td>
</tr>
<tr>
<td>Eating disorder</td>
<td>4.9</td>
<td>11.5</td>
<td>NS</td>
</tr>
<tr>
<td>Mean number of Axis I disorders(b) (SD)</td>
<td>2.4 (1.5)</td>
<td>4.4 (2.6)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

NS, not significant.

\(a\)Post-traumatic stress disorder.

\(b\)Only substance-independent disorders.
The majority of the patients had independent mental disorders. The substance-independent/induced distinction did not reduce the number of patients with comorbid mental disorders, as was the case in some American studies (Schuckit et al., 1990, 1997a,b; Kadden et al., 1995). The primary SUD group did not display more severe substance use, and, even if they had fewer mental disorders, they were of the same type as in the secondary SUD group. Therefore, it is difficult to use the primary/secondary distinction to select a group of substance misusers that do not need psychiatric treatment. Our results question the clinical validity of differentiating between primary and secondary SUD patients. Even though it seems to be of clinical interest in some studies, these samples differ in many ways from our sample. Compared with many clinical studies from the USA and Europe our sample was less educated and with a lower proportion employed (Kadden et al., 1995; Tomasson and Vaglum, 1995; Driessen et al., 1996, 1998; Schuckit et al., 1997a,b; Kokkevi et al., 1998). Our sample was drawn from public institutions and not private clinics that may be supposed to have a somewhat less sick clientele.

Nevertheless, the distinction between substance-independent and substance-induced mental disorders should still be used with respect to the actual disorder of the patient. However, because many patients have both types of mental disorders, the terms ‘substance-independent’ and ‘substance-induced’ should be used to classify disorders, but not patients.

The current study has certain limitations. Our methods are retrospective, and recall bias is always an important problem. The accuracy of self-reported age of onset is generally poorer among older adults, and older subjects may tend to report an older age of depression onset (Prusoff et al., 1988). The subjects using illicit substances could easily recollect when they started use/misuse of different substances, whereas pure alcoholics described a more gradual development. The co-occurrence of disorders also introduces complications regarding accurate assessment and diagnosis (Blanchard, 2000). The validity of structured interviews, such as the CIDI, can also be questioned, which is a general problem for all epidemiological research. Our findings are, however, in good accordance with studies from other countries. The strength of the CIDI in substance misuse research is that it has a formal training programme for interviewers. Furthermore, the CIDI has a system which excludes psychiatric symptoms that are clearly elicited by the use of substances.

A further limitation is that only 42% of the patients participated in the study. Our comparisons with dropouts from the sampling process and the clients from the national sample indicate that we have an under-representation of young drug misusers. From several other studies, we know that poly-substance misusers have a higher prevalence of symptom disorders than pure alcoholics (Ross et al., 1988). Furthermore, it is well documented that young substance misusers have a higher prevalence of psychiatric disorders than older substance misusers (Tomasson and Vaglum, 1995; Merikangas et al., 1998). Given a better representation of young drug misusers in the sample, we could expect to find an even higher prevalence of Axis I disorders. The strength of the study, however, is the treatment population-based sample, the heterogeneity of treatment institutions included, and the use of structured interviews with well established reliability.

In conclusion, we found no differences between primary and secondary misusers with regard to substance misuse or substance-induced mental disorders. Secondary SUD patients were more often women, and had a higher prevalence of substance-independent mental disorders, especially anxiety disorders. However, the need for treatment of substance-independent mental disorders was present in both the primary and secondary SUD groups, and the distinction in primary and secondary SUD groups seems to be no longer clinically valid. The distinction between substance-independent and substance-induced mental disorders was useful in this study, but since 40% of the misusers had both, it is not possible to use this distinction to classify substance misusers with regard to the need for psychiatric services.

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