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Zsolt Demetrovics [a]
[a] Addiction Research Unit, Eotvos Lorand University, Budapest, Hungary

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Co-morbidity of drug addiction: An analysis of epidemiological data and possible etiological models

ZSOLT DEMETROVICS

Addiction Research Unit, Eotvos Lorand University, Budapest, Hungary

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Abstract
This review summarizes the literature on psychiatric co-morbidity of substance use. The author overviews general population epidemiological surveys as well as clinical studies, and discusses both DSM axis I and axis II disorders. After presenting epidemiological data the author analyzes the nature of relationship between psychoactive substance use and other mental disorders, and – through examples – four possible models of this relationship are examined. Despite the lack of precisely determined prevalence rates, some definite tendencies could be observed along the consistent results of the studies. Due to methodological problems, however, many questions remain unanswered. Although there are relatively comprehensive studies on psychiatric disorders associated with drug use and drug addiction, the question of causality is relatively unresolved. Theoretically possible relations regarding causality seem to overlap in practice, and in most cases linear type connection is unlikely. It can be concluded that general questions, such as which disorders have a great significance in connection to drug use, can be answered. Additional research is needed, however, to examine the effects of different drug types, race, and gender. Understanding causality also requires further research.

Keywords: *Substance use disorder, co-morbidity, models of co-morbidity, self-medication*

Introduction

A several decades old, influential direction of research on addictions has been trying to reveal the frequency of double and multiple diagnosis and the causality behind such associations (Onken et al. 1997). This increased interest is not accidental, as regarding the question of co-morbidity there is an especially close connection between the claim for

Correspondence: Zsolt Demetrovics, Addiction Research Unit, Eotvos Lorand University, P.O. Box 179, Budapest 1580, Hungary. Tel.: +36 30 97 610 97. Fax: +36 1461 2695. E-mail: demetrovics@t-online.hu

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scientific knowledge and clinical interests. Due to the fundamental recognition that worse therapy prognosis is predicted both for adolescents (Rowe et al. 2004; Tomlinson et al. 2004), and for adults (Rounsaville et al. 1986; Cleary, Hunt, Matheson, Siegfried, & Walter 2008) if the use of psychoactive substances combines with any other mental disorder, it is reasonable that the problem of co-morbidity is often considered as a major issue of addiction.

The presence of psychiatric disorders among substance users, however, rather seems to be general than exception, although it can take various forms. According to different epidemiological and clinical research (Khantzian and Treece 1985; Strain 2002), the frequency of mental and/or personality disorders among adult psychoactive drug addicts is between 50% and 90%. However, at the moment causal relations are not clear. Most hypotheses were formulated for specific cases, thus they are valid only for some combinations of a specific substance and a specific mental disorder. Generally, available data more likely presumes circular than linear causality. The solution of this causality problem however, would be fundamental for its above-mentioned clinical relevance.

In the following section, first epidemiological research – usually on general population data – will be discussed, then research on clinical samples will be mentioned. The former can reveal relationship between drug use in general – especially cannabis use, that is of higher prevalence – and psychiatric disorders, while the latter can give data in connection to opiate and cocaine addictions that are more frequent in clinical settings. In this review, methodological aspects, that certainly make the examination of this issue more difficult, will only be discussed briefly. However, it must be emphasized that differing methods and criterion levels applied in both the diagnosis of drug usage/addiction (Room 1998; Weiss et al. 1998; Strain 2002), and the diagnosis of other psychiatric disorders (Craig 1988a; Torrens et al. 2004; Zimmerman et al. 2004; Corkery and Baldacchino 2006) can contribute to some extent to the diverse results of the examinations. The cause of these dissimilarities often lies not in the research design, but in changes that have occurred to diagnostic criterion systems and to other appliances during the past decades (Room 1998). Another methodological problem during the analysis and interpretation of data could be the incidental sampling in clinical studies, and that data of samples can occasionally be inaccurate and/or differentiation between groups of different substance users is inadequate. On the other hand, it has to be emphasized that there is a relatively high consistence in the raw data received from studies with different methodology and sampling (Craig 2000; Strain 2002) that allows us to formulate a clear picture on the most important trends.

General population epidemiological surveys

Epidemiological studies using nonclinical samples obviously indicate lower co-morbidity prevalence than surveys on clinical samples. In the largest US general population survey aiming to investigate this field with 20,291 participants (NIMH Epidemiological Catchment Area Program; ECA) (Regier et al. 1990), it was found that among those who have tried drugs earlier (6.1% of the sample) (alcohol not included) more than every second person (53%) had some other psychiatric disorder. In the case of the total population this rate was 22%. The highest increase of risk resulting from psychoactive substance usage was found in the case of antisocial personality disorder (OR: 13.4). The frequency of this disorder was 17.8% among those who used drugs in the past. Risk increasing tendency of substance use seemed to be considerable in the case of affective disorders (primarily depression and bipolar

disorder) and schizophrenia. After comparing different substances mental and/or personality disorders were found to be the most frequent among cocaine (76%) and barbiturate (75%) users. The prevalence of disorders was above 60% in the case of hallucinogenic drug (69%), opiate (65%), and amphetamine (63%) users. The lowest prevalence – yet a high absolute number – was experienced in the case of cannabis users (50%). In the National Co-morbidity Survey (Kessler et al. 1994) similar results were found.

The results of some more specific surveys of a smaller scale, focusing on a specific disorder or on a specific type of drug are the same as the above-mentioned ones. Thus data show the co-morbidity of psychoactive drug use, mood, and anxiety disorders (Swendsen and Merikangas 2000; Myrick and Brady 2003), and also a co-morbidity of extensive use of cannabis and these problems (Johns 2001; Rey et al. 2002). However, in case of women there is a stronger connection between cannabis use and depression, than in case of men (Patton et al. 2002). Besides that regular cannabis use is said to be related primarily to schizophrenia (Arseneault et al. 2002; van Os et al. 2002; Zammit et al. 2002), Falck et al. (2004) found a high co-morbidity rate in the case of untreated crack users, however, in the case of small prevalence substances we can rely more on the results of clinical studies.

In the case of adolescents co-morbidity of psychoactive substance use (including alcohol), and other disorders is around 60% (Armstrong and Costello 2002). A typical result of surveys on young population is the frequent occurrence of adolescent attention-deficit hyperactivity disorder (ADHD), conduct disorder and oppositional defiant disorder among substance users. Similarly to adult samples the rate of depression (and suicide) is higher as well (Sullivan and Rudnik-Levin 2001; Kelly et al. 2004). Besides cross-sectional epidemiological surveys, longitudinal studies also support the connection between childhood and adolescent ADHD, adult antisocial behavior and drug use (Moran 1999). Adolescent anxiety disorders are also closely connected to psychoactive substance use of young adults (Regier et al. 1998; Goodwin et al. 2004).

Clinical studies

DSM axis I disorders and drug addiction

The most frequent clinical disorders among opiate addicts are affective disorders, primarily depression (Swendsen and Merikangas 2000; Strain 2002). Compared to general population data the rate of suicide is also higher in certain substance user populations (Kokkevi and Stefanis 1995). The highest prevalence of suicide is among opiate addicts (Engstrom et al. 1991), especially those with bipolar spectrum diagnosis (Maremmani et al. 2007). During the investigation of 133 drug addicts, Khantzian and Treece (1985) found that 93% of them had some kind of mental or personality disorder. Prevalence of DSM III axis I mental disorders was 77% in the sample, but it must be emphasized that almost every second participant (49%) was diagnosed with both axis I and II disorders. The most frequent mental disorder was affective disorder (60%, mainly depressive disorder), while 11% was diagnosed with anxiety disorder. No cases of psychosis were found, and the proportion of other disorders was also low. Other studies also found affective disorders to be the most frequent problem among opiate users. According to Rounsaville et al. (1982a), at the beginning of treatment 17% of 149 opiate addicts had major depression, and an additional 48% reported of an earlier depressive episode, while 9% showed bipolar problems. Regarding the whole life span, 70% of the patients have had some kind of affective disorder.

Reviewing the association between substance use and bipolar disorder, Vornik and Brown (2006) emphasize that bipolar problems are associated more to dependence than to abuse.

In another study of 533 opiate addicts under treatment, Rounsaville et al. (1982b) found similar results. A total of 24% were diagnosed with current major depression, while life-time prevalence of depression was 54%. Life-time prevalence of any kind of affective disorder was 85% for men and 71% for women, while life-time prevalence of the schizophrenia spectrum was under 1%.

A Spanish research group using three different methods found a prevalence of 19–36% for current affective disorders and 32–55% for affective disorders in the last 12 months (Torrens et al. 2004). Similarly to other studies the second most frequent disorder was the group of anxiety disorders, although contrary to other results prevalence of schizophrenia spectrum was found to be relatively high (8–16% for the last 21 months). The latter result could be due to the distorting effect of the small sample, and also to the presence of cocaine addicts in the sample.

In a study conducted in the UK co-morbidity rates of 216 drug addicts and 62 alcohol addicts were compared (Weaver et al. 2003). In the former group prevalence of major depression was 27%, prevalence of mild depression was 40%, while 19% of patients suffered from severe anxiety symptoms. The frequency of schizophrenia and non-specific psychosis was 3% and 5%, respectively.

The relative inconsistence found in relation to schizophrenia spectrum indicates limitedness of results of small sample clinical studies on low prevalence co-morbid disorders. It can be seen easily that in the case of rare disorders (such as schizophrenia) small samples result in a high margin of error. Weaver et al. (2003) also published data on this: margin of error for the 3% prevalence found for schizophrenia is 1–5.9%, while for the 5% prevalence of nonspecific psychosis it is 2.2–8.3%, at 95% CI. Problem of small samples is increased by effect of race and gender differences on the frequency of symptoms (Chander and McCaul 2003). For example, according to Calsyn et al. (1996) 34.4% of Afro-American women, 24.4% of Afro-American men, 14.1% of white women, and 9.3% of white men exhibit psychotic symptoms.

There is significantly less available information about stimulant users (especially cocaine) than about opiate addicts, while about other substance users (e.g. cannabis) we have not got any clinical information. The comparative study of Craig and Olson (1990) found clinical characteristics of opiate (86 people) and cocaine (107 people) users to be rather similar. They found differences only in the higher anxiety level and more frequent somatoform disorders of heroin users, while cocaine users tended to be more antisocial, and their extent of alcohol abuse was higher than that of heroin users. However, these results are special in a way that the sample consisted exclusively of Afro-American men of low socio-economic state. From the review of Roberts (2000), it can be assumed that in the case of different Afro-American drug users living in the USA, etiological factors contributing to the onset of drug addiction are different from such etiological factors of white drug addicts. According to the assumption of Roberts, for the former group social and environmental factors have a greater impact, while for white people psychopathological factors have a more significant role. The above-mentioned study of Calsyn and Saxon (1990), based on a similarly small but more heterogeneous sample (proportion of white people: 61%, proportion of Afro-Americans: 36%, no data on social background), also concludes that heroin and cocaine users seem to be similar in the degree and type of their psychopathological problems. Unfortunately, due to sample size meta-analysis of race and substance abuse was not possible, but the analysis of race showed that Afro-Americans reported more paranoid symptoms than white people, while the latter group scored higher on the MCMI borderline scale. A subsequent study of

the research group produced similar results (Calsyn et al. 1996). Thus, the authors did not find significant differences between the two groups in respect for affective disorders. The only difference found was that the above-mentioned psychotic symptoms had a higher prevalence in the group of cocaine users (58%), than in the group of heroin addicts (41%). Other studies also pinpoint the significance of depression for stimulant addiction (Kosten et al. 1998).

Although most studies do not differentiate between anxiety disorders, some research mentions the relatedness of generalized anxiety disorder, social phobia, panic disorder, and the use of sedatives (alcohol, benzodiazepines, opiates) (Myrick and Brady 2003). In contrast to the weak connection to obsessive-compulsive disorder, the relation of post-traumatic stress disorder and psychoactive substance use has been mentioned in some studies (Jacobsen et al. 2001).

In accordance with epidemiological survey data, results confirm the association between conduct disorder and ADHD and substance use (Grilo et al. 1995; Flory and Lynam 2003).

Personality disorders and addiction

Prevalence of personality disorders is found to be significantly higher in drug-addicted population, than in general population (10–15%) (Torgersen et al. 2001; Verheul 2001). For research with consecutive or randomly selected sample, including more than 100 participants, Verheul (2001) indicates a prevalence interval between 34.8% and 73% for treated substance users.

The above-mentioned study of Khantzian and Treece (1985) on opiate addicts diagnosed two-third of the patients (65%) with some kind of personality disorder. Strain (2002), in five further studies on opiate addicts under treatment found a rate between 31% and 68%. Kosten et al. (1982) mention a similar ratio (68%) for an opiate-addicted population of 384 inpatients, while in Craig's study (1988b) all the 121 treated opiate addicts were found to have some kind of personality disorder. In the former study, the most frequent problems (45%) were cluster B disorders (dramatic, emotional, erratic); the most common disorder was antisocial personality disorder (35%). Craig found similar results (1988b). The most frequent personality disorder was antisocial disorder (22%), but other cluster B disorders were also present at a high frequency: narcissistic (18%), borderline (16%), histrionic (12%), and also dependent personality disorder from cluster C (16%). In the above reported study of Calsyn and Saxon (1990), 90% of opiate addicts and 97% of cocaine addicts were diagnosed with axis II disorders (from this the proportion of severe cases were 23% and 19%, respectively). Based on their clinical experience, the authors created three groups according more or less to the three clusters of DSM and they found the following results: Opiate addicts are more frequent in the narcissistic/antisocial group (equivalent of cluster B; 36% and 28%) and in the dependent group (equivalent of cluster C; 19% and 11%), while cocaine addiction is more frequent in the reserved and negative group (equivalent of cluster A) (42% and 20%).

Results of later studies are consistent with the above-mentioned results (Brooner et al. 1997; Craig 2000; Verheul 2001), however, their value is greater as they often use greater – some hundreds subjects – or more specific (precisely defined) samples, occasionally allowing an analysis of race and sex differences. For example the results of Calsyn et al. (1996) specify the above-mentioned findings: narcissistic/antisocial type is more frequently found among Afro-Americans (men: 59%, women:31.4%), (28.8 and 26.9%, respectively), although this is the most frequent personality disorder in both groups. However, in the case of dependent

personality disorder the effect is opposite: there is a higher prevalence in the group of white people, both in the case of women and men. In contrast, in the study of Craig et al. (1997) conducted on an Afro-American mixed sample consisting of 441 cocaine and heroin addicts the frequency of narcissistic personality disorder was not found to be higher. This different result might have occurred due to the method, which combines narcissistic and antisocial symptoms, used by Calsyn and co-workers (Calsyn and Saxon 1990; Calsyn et al. 1996). High prevalence of antisocial symptoms was proved in the studies of Craig (2000).

There are some additional studies comparing the profile of heroin and cocaine addicts, similarly to the research done by Calsyn and Saxon (1990). These researches are not consistent in all aspects, for example, as it was already mentioned Craig and Olson (1990), – contrary to Calsyn and Saxon (1990) – found cocaine users more antisocial (the results could come from the combined narcissistic/antisocial category). Though, in a subsequent research (Craig 2000) no difference was found between the two groups. Research on other personality disorders so far is characterized by similarities, or at least by the absence of consistent differences. Cluster A disorders and avoidant personality disorders are exceptional. Some research on small samples ($n < 100$) found a higher prevalence of paranoid (Weiss and Mirin 1986; Kranzler et al. 1994), schizoid and schizotypal (Yates et al. 1989) personality disorders in the group of cocaine addicts. These disorders are not usual among opiate addicts. Three studies have found a higher prevalence of avoidant personality disorder (cluster C) among cocaine addicts (Weiss et al. 1993; Kranzler et al. 1994; Barber et al. 1996).

Besides the above-mentioned personality disorders the prevalence of borderline personality disorder and passive-aggressive personality disorder is relatively high in both cocaine and heroin using groups (Craig 2000; Verheul 2001; Weiss and Mirin 1986). Based on a review of 26 studies (Trull et al. 2000), 18.5% prevalence of borderline personality disorder was found among opiate addicts and 16.8% among cocaine addicts (in drug using population not specified for substance type this rate was 27.4%, and 14.3% among alcohol dependent patients). According to Craig's (2000) review the prevalence of passive-aggressive (negativistic) personality disorder is between 0% and 34% among opiate addicts, and between 3% and 33% among cocaine addicts. Prevalence of narcissistic personality disorder is between 1% and 18% among opiate addicts and between 2% and 32% among cocaine addicts.

The question of causality

Most of the studies presented above consider the question of causality in a superficial way. There is relative concordance on assuming complex mechanisms and not simple linear functions (Swendsen and Merikangas 2000), however, at present these are not discovered in depth. At the current phase of the studies often even the question of time sequence is debated. Four potential hypotheses can be considered: (1) substance use can be interpreted as a symptom of another psychiatric disorder; (2) substance use is developed to cope with the psychiatric disorders (self-medication); (3) psychiatric disorder develops as a consequence of substance use, and (4) both substance use and psychiatric disorder result from a common etiological factor, as parallel processes (see e.g., Strakowski and DelBello 2000; Verheul 2001; Sher and Trull 2002). Yet, it must be emphasized that these four cause and effect relations are not exclusive. Thus it is also possible that, besides a joint risk resulting from a neurobiological or family factor, any of the disorders can evolve first, that

can intensify the original risk factor and contribute to the development of the other disorder. It can certainly be concluded that no model is able to explain the phenomenon of co-morbidity alone. In some specific substance and mental disorder pairs one model could have a better explanation than the other, while in the case of a different pair of disorders the situation could be the reverse. In the following section some examples will be discussed.

Substance use as a symptom of psychiatric disorders

In attempts to classify drug users usually one group is identified as ''antisocial cluster'' or ''psychopaths''. Members of this group can be described as having a high degree of deviant conduct and no other psychological disorder (Cohen 1982; Calsyn et al. 1989). On the basis of these observations we can assume that in these cases substance use may be interpreted as part of the antisocial character. It should be noted that the reverse of the phenomenon is also possible. Diagnostic symptoms of some psychiatric disorders, and accompanied behavioral features of drug problem may significantly overlap. Thus regarding antisocial personality disorder behavioral symptoms are given for compulsive drug users. The situation is similar for borderline personality disorder where impulsivity and uninhibited behavior are symptoms of both the disorder and the drug problem (Trull et al. 2000). As a consequence, diagnosis is basically given even if, for example in the case of antisocial personality disorder, there is no ''genuine'' psychopathy, but the deviant behavior linked to drug use serves as a basis for the diagnosis.

Substance use as a consequence of psychiatric symptoms

The most elaborated model out of the four assumes that substance use compensates for a psychological disorder, it complements missing coping abilities, actually appearing as an attempt for self-medication (Khantzian et al. 1974; Wurmser 1974). According to Khantzian's hypothesis, opiates can counterbalance fear from inner psychological disorganization, and even disorganization itself. Thus, heroin use will serve as an attempt to cope for those who are not able to cope with stressful situations in any adequate way (Khantzian et al. 1974). The approach of self-medication considers drug use always to be secondary, aiming to compensate for the primary psychiatric symptoms. Thus it is an actual coping mechanism, which resulting from its nature is maladaptive, but in some situations it can take, or at least it can attempt to take the role of the defense mechanism that is not available for the person due to some defects in personality development (Demetrovics 2000).

In regard of opiate addiction this theory is especially convincing, as some neurobiological results correspond to psychological observations. Though heroin addicts show a hyporesponsivity to metyrapone induced chemical stress, Kreek (2000) found that long acting opiates, such as methadone may restore and normalize the functioning of this system.

Some further studies on the association between substance use and bipolar affective disorder also strengthen the self-medication theory, emphasizing that substance use often contributes to the improvement of the mood (Sonne et al. 1994; Weiss et al. 2004). In a more recent study, Bizzarri et al. (2007) examined the reasons for alcohol and other substance use among patients with bipolar disorder and healthy controls. Result showed that substance users both with or without bipolar disorder frequently used substances with self-medication purposes such as to alleviate mood or anxiety symptoms, to achieve or maintain euphoria, or to increase energy.

Psychiatric disorder as a consequence of substance use

In the previous section, the self-medication explanation of substance use was reviewed, however, an opposite mechanism, in which repeating substance use could cause or intensify psychiatric disorders, can also be mentioned. The popular dance drug MDMA not only takes its effect primarily via the serotonin system, but chronic MDMA use is also associated with serotonergic neurotoxicity (Gouzoulis-Mayfrank and Daumann 2006). This association provides a realistic explanation for the symptoms of depression often experienced among MDMA users, though this link might be less strong and deterministic than it was presumed earlier (Parrott 2001; de Win et al. 2004). However, mood problems often seem to precede substance use raising the possibility of a circular causality.

The possible role of substance use in provoking mental disorders, however, has also been studied in relation with other psychiatric problems; for example panic disorder (Kecskes et al. 2002), manic symptoms and bipolar disorder (Henquet et al. 2006), or psychosis. Though this relationship seems to be complicated as well, cannabis use has to be considered as a risk factor of schizophrenia (van Os et al. 2002; Zammit et al. 2002).

Shared etiological factor of substance use and psychiatric disorder

Drug use as a cause of the development of psychiatric disorders is especially problematic in case of personality disorders. The latter is more like a permanent, general characteristic of personality, than a state that has evolved as a consequence of an event (such as drug use) during adolescence or later. Although personality disorders – as it has been mentioned earlier – can include substance use as a symptom, and in theory their presence can precede substance use, we cannot reject the possibility of parallel processes. For example, Sher and Trull (2002) believes that this possibility is the most likely in case of antisocial personality disorder and borderline personality disorder.

Discussion

Although there is a relatively comprehensive picture – based on general population and clinical studies – available on the co-morbidity of psychoactive substance use and addiction, the question of causality is relatively unresolved. The theoretically possible relations seem to overlap in practice, and in most cases linear causality can be excluded. Clarification of this causality would be urgent to fulfill clinical needs and to increase the efficacy of treatment. Precise diagnosis of co-morbid disorders must be a precondition of efficient therapy, but in most cases identification of causality might not be such a strong precondition. Thus it is important to emphasize that efficient clinical work does not require clear cause and effect relations, on the contrary, it can deal well with the overlap or coexistence of the above-described possible models.

However, clinicians working with addicted people in any case need to pay special attention to their patients' possible co-morbid disorders. Even if there is no causal relationship between the two problems one might worsen the symptoms of the other (Corkery and Baldacchino 2006). In general, it can be said that those who suffer from both substance use and mental disorders have a worse prognosis than those with only one disorder. However, it also has to be mentioned that in some cases the treatment of one disorder might alleviate the symptoms of the other as well. Yet to understand the above phenomena better, further

research should focus more on distinguishing between different types of substance use problems and mental disorders. If we intend to have a clearer picture on causality and especially if we want more effective contribution to the treatment of addicted patients with co-morbid disorders, we should rather study the link between the use of one specific substance and one specific mental disorder.

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