



Understanding comorbidity between substance use, anxiety and affective disorders: Broadening the research base

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ABSTRACT

In this paper, we argue that the research base for understanding comorbidity between substance use and other mental disorders needs to be broadened. We specifically advocate for: 1) more prospective epidemiological studies of relationships between alcohol and other drug use disorders and anxiety and mood disorders; 2) greater use of twin study designs to disentangle shared genetic and environmental contributions to comorbidity; 3) prospective neuroimaging studies of the effects of early and sustained alcohol and drug use on the developing adolescent brain; 4) a greater focus on the effects on comorbidity of primary and secondary prevention interventions for substance use, anxiety, affective and conduct disorders among children and adolescents; and 5) better evaluations of the impact of treatment upon persons with comorbid substance use and other mental disorders.

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In the addictions field, psychiatric comorbidity has come to mean the co-occurrence of one or more mental disorders with one or more substance use disorders during some period of time, such as, a year or a lifetime. In specialist mental health services, comorbidity is often construed more narrowly as “dual diagnosis”: the co-occurrence of a substance use disorder with schizophrenia or another psychotic disorder. Comorbid mental and substance use disorders may occur *concurrently* and *successively*. Concurrent comorbidity occurs when two or more disorders are present at the same time, such as, schizophrenia and alcohol dependence. Successive comorbidity occurs when disorders occur at different times in a person's life, in ways that may or may not be causally related to each other. The complexity of comorbidity between substance use disorders and mental disorders remains a significant challenge to clinicians and researchers.

1. Comorbidity: beyond specialist health services

Schizophrenia and bipolar disorder have been given an understandably high priority by those in the specialist mental health system who have to treat the distress and disability that these disorders cause. People with dual diagnoses are less likely than persons with psychosis alone to comply with medication, and more likely to

experience psychosocial problems, depression, suicidal behaviour, rehospitalisation, homelessness, and higher family burden (Bartels, Drake & McHugo, 1992; Drake, Mueser, Clark & Wallach, 1996).

There are, however, different types of comorbidity seen in patients treated by specialist mental health and addiction services (Hall & Farrell, 1997). Addiction services see fewer patients with psychoses; most have anxiety, affective and personality disorders that often go undiagnosed and untreated and affect outcomes of addiction treatment (Chan, Dennis & Funk, 2008). For example, in a recent longitudinal study of heroin dependence, major depression was the diagnosis most consistently associated with poor outcomes over 3 years of follow-up. Those who were depressed in the preceding month were more likely to use heroin and other drugs, share needles, experience injection-related problems, engage in crime, and experience poorer physical and mental health (Teesson et al., 2008). Studies of specialist treatment samples in either type of specialist setting do not provide an accurate picture of comorbidity in the population because persons with comorbid disorders are more likely to seek and be treated by such services (Berkson, 1946; Galbaud du Fort, Newman & Bland, 1993). Epidemiological surveys of representative samples of the population are needed to obtain a more accurate picture of comorbidity that is unaffected by treatment seeking.

2. What have population studies shown?

The richest epidemiological data on patterns of comorbidity comes from surveys in the USA such as the National Comorbidity Survey (NCS) in the early 1990s (Kessler et al., 1994), its replication (NCS-R) in 2001–2002 (Kessler, Chiu, Demler, Merikangas & Walters, 2005) and the National Epidemiological Survey on Alcohol and Related

Abbreviations: NCS, National Comorbidity Survey; NCS-R, National Comorbidity Survey Replication; NESARC, National Epidemiological Survey on Alcohol and Related Conditions; NSMHWB, The National Survey of Mental Health and Well-being, Australia; SUD, substance use disorder.

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Conditions (NESARC) (Compton, Thomas, Stinson & Grant, 2007; Hasin, Stinson, Ogburn & Grant, 2007). Similar studies have also been conducted in other developed countries including Australia (The National Survey of Mental Health and Well-being; NSMHWB) (Andrews, Hall & Henderson, 2001; Andrews, Hall, Teesson & Henderson, 1999), Canada (Gratzer et al., 2004); Germany (John, Meyer, Rumpf & Hapke, 2004), The Netherlands (de Graaf, Bijl, Smit, Vollebergh & Spijker, 2002); and the United Kingdom (Farrell et al., 2001); see Jane-Llopis & Matytsina, 2006 for a review.

These epidemiological studies have revealed important facts about psychiatric comorbidity in the population (Kessler & Wang, 2008). First, comorbidity between anxiety, depressive and substance use disorders is very common, with a third to a half of persons with any mental disorder meeting criteria for another mental or substance use disorder at some point in their lives (Kessler & Wang, 2008; Merikangas & Kalaydjian, 2007). Second, the highest rates of comorbidity are between: (i) anxiety and mood disorders (Jorm, 2006; Merikangas & Kalaydjian, 2007) and (ii) between alcohol and other substance use disorders (SUDs) (Degenhardt, Hall & Lynskey, 2001). Third, there are also high rates of comorbidity between SUDs and depression and anxiety and between conduct disorders and antisocial personality disorder and SUDs (Burns & Teesson, 2002; Teesson & Burns, 2001). Fourth, all of these disorders typically have their onset in late adolescence and early adulthood, making it challenging to sort out cause and effect (Kessler & Wang, 2008). Fifth, there are low rates of treatment seeking for SUDs despite the considerable disability that they cause (Kessler & Wang, 2008; Teesson & Burns, 2001). Treatment seeking increases with the severity of personal problems related to drug use, being highest among those with anxiety and depression (Teesson & Burns, 2001). Even so, only a minority of those with severe substance use disorders receive treatment (Compton et al., 2007). Sixth, the treatment provided to those with SUDs is often inadequate (Kessler & Wang, 2008). Much of this treatment is provided by primary care practitioners who may not be well-trained to diagnose, treat or refer patients for specialist treatment (Teesson & Burns, 2001).

3. Why does comorbidity matter?

Comorbidity matters for several important reasons. First, it is the rule rather than the exception with mental disorders; if we ignore comorbid disorders when studying one type of mental disorder, we may mistake characteristics of the disorder under study for those of comorbid conditions (Kessler, 1995; Kessler & Wang, 2008).

Second, persons with comorbid mental disorders often have a poorer treatment response and a worse course of illness over time (Kessler, 1995; Kavanagh, Mueser & Baker, 2003), suffering more impairment, greater social disability and generating larger social costs. This is probably in part because comorbid disorders are not diagnosed and treated and in part because persons with more than one mental disorder are more difficult to treat. Comorbidity may therefore have important implications for treatment. For example, in persons for whom alcohol dependence is a cause of depression, treatment of alcohol dependence may alleviate depressive symptoms (Schuckit et al., 1997a,b). If, however, a person's alcohol dependence is the result of self-medicating depression, then treatment of depression is required for a good outcome.

Third, understanding why different disorders co-occur may also provide important opportunities for prevention. For example, if we can identify persons with symptoms of anxiety and affective disorders we can potentially intervene to reduce their use of alcohol and other drugs before abuse and dependence develop.

4. Understanding comorbidity

There are a number of hypotheses that may explain the comorbidity between substance use and anxiety and affective disorders (Cerde,

Sagdeo & Galea, 2008; Kessler & Wang, 2008). These have very different implications for treatment and prevention of psychiatric comorbidity.

First, one mental disorder may directly produce another e.g. sustained heavy alcohol abuse can produce depression in persons who are alcohol dependent (Raimo & Schuckit, 1998).

A second possibility is that some mental disorders may indirectly increase the risk of a substance use disorder. For example, persons with anxiety and affective disorders may begin to use alcohol and other drugs in an effort to medicate their distress (Kessler, 1995). Although it improves mood in the short term, alcohol as a form of self-medication often miscarries over the longer term, producing alcohol dependence. Similarly, children with conduct disorder are more likely start using alcohol and other drugs earlier than their peers because of their greater propensity to take risks. Earlier initiation and affiliation with drug-using peers produces a longer history of heavier alcohol and other drug use, increasing the risks of developing alcohol and drug dependence at an early age (Cerde et al., 2008; Fergusson & Horwood, 1997).

A third possibility is that comorbidity between substance use and other mental disorders may arise from common causes. The syndrome of delinquency, alcohol and drug abuse, precocious sexual activity, and poor school performance may, for example, be manifestations of a shared genetic predisposition, family circumstances, poverty and abusive environments that increase the chances of developing alcohol and drug dependence disorders and antisocial personality disorder (Jessor & Jessor, 1977; Reinherz et al., 2000).

5. What additional research is needed?

5.1. Prospective epidemiological studies

Hypotheses about the nature of the relationships between comorbid disorders cannot be clearly distinguished in cross-sectional epidemiological studies that use retrospective life histories to assess temporal and causal relationships between disorders. More direct tests are needed using longitudinal studies of mental disorders (e.g. Fergusson & Horwood, 1997) in representative population samples to minimise the selection bias that affects treatment samples. To date a limited number of such studies have been done (see Cerde et al., 2008 for a recent review). Their results suggest that causal relationships can operate in both directions between mental and substance use disorders, e.g. conduct disorder and depression both increase the likelihood of developing substance use disorders; the development of substance use disorders among those with depressive and conduct disorders worsens their course; and persons who develop substance use disorders can develop depressive and anxiety disorders.

For example, Reinherz et al. (2000) followed 360 adolescents over a 17 year period to examine predictors of drug use disorders in early adulthood. Hyperactivity, poor concentration, aggression, and hostility at age 6 predicted substance use disorders in males and females at age 21. Patton et al. (2002) studied the association between cannabis use and symptoms of depression and anxiety in 2,000 young Australians from the age of 14–21 years. Young adult females who used cannabis daily had five-fold higher rates of depressive and anxiety symptoms, after controlling for the effects of other substance use. Weekly cannabis use as a teenager predicted a two-fold higher rate of depression and anxiety in females in young adulthood after controlling for baseline mental health and other potential confounders. By contrast, depression and anxiety symptoms in adolescence did not significantly predict later cannabis use (Patton et al., 2002).

We need large scale follow up studies of epidemiologically defined cohorts of adults to examine relationships between comorbid disorders. The recent 3 year follow up of incident disorders in the NESARC cohort and their relationship to baseline disorders provides a good illustration of the potential value of this approach (Grant et al., 2008). In this study, 34,653 persons who were interviewed in the first

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