The Epidemiology of Dual Diagnosis

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The English language literature on the epidemiology of dual diagnosis is reviewed. The literature shows mental disorders to be significantly related to alcohol and drug use disorders. The strongest associations involve externalizing mental disorders and alcohol-drug dependence. Mental disorders are associated with alcohol-drug use, problems among users, dependence among problem users, and persistence among people with lifetime dependence. These dual diagnoses are associated with severity and persistence of both mental and alcohol-drug disorders. A wider range of mental disorders is associated with nicotine dependence. Most people with dual diagnosis report their first mental disorder occurred at an earlier age than their first substance disorder. Prospective studies confirm this temporal order, although significant predictive associations are reciprocal. Analyses comparing active and remitted mental disorders suggest that some primary mental disorders are markers and others are causal risk factors for secondary substance disorders. The article closes with a discussion of ways epidemiologic research can be used to help target and evaluate interventions aimed at preventing secondary substance use disorders by treating early-onset primary mental disorders.

Key Words: Comorbidity, dual diagnosis, epidemiology, mental disorders, self-medication, substance-related disorders

The current article presents the results of a literature review on the epidemiology of mental-substance comorbidity ("dual diagnosis") based on Medline and Psychinfo searches (keywords: mental comorbidity, alcohol-drug comorbidity, self-medication, dual diagnosis) over the years 1995 to 2004. Scientific interest in dual diagnosis is based on observations in clinical samples that patients with both mental and substance disorders are more persistent, severe, and treatment-resistant than patients with pure disorders (Margolese et al 2004; Brady et al 2004). Less is known, though, about patterns and correlates of dual diagnosis in the general population.

Studies of diagnostic patterns in general population samples carried out in recent years both in the United States (Grant and Harford 1995; Kessler et al 1996, 1997; Regier et al 1990; Warner et al 1995) and elsewhere in the world (Kessler et al 2001; Merikangas and Stevens 1998; Wittchen et al 1998) consistently find that mental disorders and substance use disorders co-occur at much higher than chance levels. Although these associations are stronger in treatment samples than in community samples (Weaver et al 2003), there are advantages to community samples, because treatment samples are biased by the fact that comorbidity is associated with professional help seeking (Regier et al 1990; Rounsaville et al 1987). To give a rough idea of the magnitude of mental-substance comorbidity in general population samples, the US National Comorbidity Survey (NCS) found an odds ratio (OR) of 2.4 for comorbidity between any of the lifetime DSM-III-R mental disorders assessed in that survey and any lifetime alcohol or drug use disorder (Kessler et al 1996). Approximately half (51.4%) of the NCS respondents with a lifetime alcohol or drug use disorder also met criteria for at least one lifetime mental disorder, while 50.9% of the NCS respondents with a lifetime mental disorder also had a history of alcohol or drug abuse or dependence. Comparable results for 12-month comorbidity in the NCS were 42.7% of respondents with an alcohol-drug disorder also having a mental disorder and 14.7% of respondents with a mental disorder also having an alcohol or drug disorder (OR = 2.6).

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Cross-Sectional Disorder Specific Associations

Analysis of cross-sectional associations among disorders in community surveys typically shows much stronger ORs within than between two broad classes of mental disorders (Kessler 1995; Merikangas and Stevens 1998), usually referred to as internalizing disorders (anxiety and mood disorders) and externalizing disorders (oppositional-defiant disorder, conduct disorder, attention-deficit/hyperactivity disorder). Factor analysis finds two major factors that correspond to these two classes (Krueger 1999; Krueger et al 2003). Substance use disorders are much more strongly associated with the externalizing than the internalizing mental disorders (Kessler et al 2003; Kessler et al 2001). Consistent with this general pattern, the anxiety-mood disorder most strongly associated with substance use disorder is bipolar depression. An internalizing-externalizing distinction has also been found in behavior genetic studies. Kendler et al (2003) carried out an analysis of comorbidity in the Virginia Twin Sample, a population-based probability sample of twin pairs, in which the best-fitting model specified separate internalizing (major depression, generalized anxiety disorder, phobia) and externalizing (conduct disorder, antisocial personality disorder, alcohol dependence, drug abuse and dependence) genetic factors that explained most of the observed comorbidity among pairs of individual disorders. This model fit the data equally well for men and women.

It is tempting to conclude from the behavior genetic results that genetic influences account for most comorbidity among mental disorders, including mental-substance comorbidity; however, this conclusion would be premature, as the models on which these results are based assume that the associations among mental and substance disorders are additive. It is possible to evaluate this assumption by determining whether the distribution of cases in the cells of the 2^d cross-tabulation among d comorbid disorders can adequately be reproduced from the two-way marginal associations among all (d)(d-1)/2 logically possible pairs of conditions. Although we are aware of no published reports that have attempted to evaluate this hypothesis, our own preliminary attempts have consistently found that two-way marginals cannot reproduce the distribution in the 2^d cross-tabulation. Multivariate profile analysis methods, such as

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latent class analysis, grade-of-membership analysis, or more general mixture models, are needed to describe this structure. We are only beginning to investigate the extent to which such methods can help us find interpretable structure in the complex multivariate profiles that exist among comorbid mental and substance disorders.

One element of this complexity can be seen in an implicit progression of the ORs relating mental disorders to substance use disorders in conventional bivariate analyses of mental-substance comorbidity. Merikangas et al (1998) uncovered this structure in their analysis of the World Health Organization International Consortium in Psychiatric Epidemiology (ICPE) database, a series of community epidemiologic surveys in six countries, where the ORs of lifetime mental and substance disorders were weakest (unweighted average ORs) for substance use (3.2 for alcohol, 1.8 for drugs), intermediate for substance abuse (4.1 for alcohol, 5.1 for drugs), and highest for substance dependence (4.7 for alcohol, 6.3 for drugs). This suggests that mental disorders are associated with progression of substance use disorders, although cross-sectional associations cannot determine temporal priority in this progression.

More refined distinctions can also be made for comorbidities involving particular kinds of mental disorders with particular kinds of substances, such as anxiety disorders with substances that have anxiolytic effects and mood disorders with substances that have antidepressant effects. Although little epidemiologic data have been published about this level of matching, evidence from treatment samples suggest that such specificities might exist (e.g., Gandhi et al 2003), possibly representing attempts to self-medicate mental disorders (Khantzian 1997); however, despite a number of studies of single substances that argue indirectly for such specificity being at work (e.g., Tournier et al 2003; Ogborne et al 2000), detailed comparison across a range of mental disorders and substances fails to find a strong match between type of mental disorder and type of drug (Aharonovich et al 2001). A possible limiting factor here is that such a high proportion of drug abuse in the community involves polysubstance abuse, in which the particular types of drugs used are responsive to availability and street price.

Temporal Priority and Age of Onset

A number of community epidemiologic surveys have collected retrospective information about age of onset (AOO) of mental and substance disorders, which consistently suggest that mental disorders typically start at an earlier age than substance use disorders (Kessler et al 2003; Merikangas and Stevens 1998; Sareen et al 2001; Swendsen et al 1998; Wittchen et al 1996). Consistent with parallel research in clinical samples (Hahesy et al 2002), this pattern is somewhat stronger among women than men, strongest for comorbidities involving conduct disorder, next strongest for those involving anxiety disorders, and least strong (and, among men, sometimes even reversed) for those involving mood disorders.

Kaplan-Meier AOO curves confirm this general pattern, with anxiety and externalizing disorders having a median reported AOO between middle childhood and early adolescence versus alcohol and drug use disorders having a median AOO between late adolescence and early adulthood (WHO International Consortium in Psychiatric Epidemiology 2000). The typical number of years in the AOO interquartile range (the number of years between the time 25% and 75% of all eventual lifetime cases have onsets) is less than a decade for anxiety disorders, externalizing

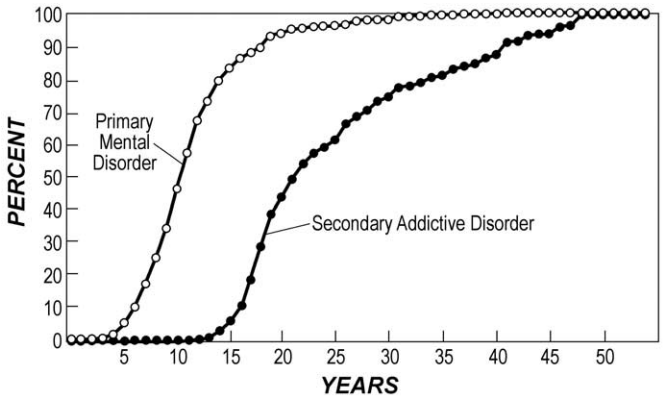

Figure 1. Cumulative age of onset distributions of first lifetime mental disorder and first lifetime addictive disorder in respondents with lifetime co-occurrences of a primary mental disorder with a secondary addictive disorder.

mental disorders, and substance use disorders in most community surveys. The situation is different for mood disorders, though, where median age of onset is later (early adulthood) and the interquartile range is much wider (typically more than 2 decades).

It is instructive to examine visual AOO distributions for temporally primary mental disorders and temporally secondary substance use disorders among people with lifetime mental-substance comorbidity who reported an earlier AOO of their mental than substance disorders. Figure 1 presents such a representation based on data from the NCS. The median AOO of mental disorders is 11 compared with 21 for substance disorders. This summary figure fails to account for cohort effects (Kessler et al 1994) or for differences in the distributions of disorders depending on gender of respondents or on particular mental-substance pairs. Disaggregated analyses of these specifications find two consistent patterns: the vast majority of temporally primary mental disorders begin in adolescence and the median difference between the AOO of these mental disorders and subsequent substance disorders is in the range of 5 to 10 years (Kessler et al 1996).

Predictive Associations Based on Retrospective Reports in Cross-Sectional Surveys

Simple comparisons of temporal priorities are inadequate to document predictive associations (Kessler and Price 1993). This documentation requires analysis of reciprocal series of survival analyses in which each of the two sets of disorders is treated as a series of time-varying covariates that predict first onset of the disorders in the other set. The most comprehensive analyses of this sort were carried out in the ICPE surveys (Kessler et al 2001, 2003). These analyses used a discrete-time survival framework with person-years as the unit of analysis to examine predictive associations between temporally primary mental disorders and the subsequent first onset of substance (alcohol and drugs) use, problems among users, and dependence among problem users. Virtually all ORs linking active mental disorders with the later substance outcomes were greater than 1.0 and 87% statistically significant at the .05 level. Remitted mental disorders had much less consistent effects, indirectly suggesting a causal interpretation. Mental disorders were stronger predictors of substance use (ORs in the range 1.6–7.5) than of the transition from use to

problems (1.4–5.2) or the transition from problems to dependence (.9–7.8).

Interestingly, the effects in the ICPE survival analyses were not dramatically higher for externalizing disorders (conduct disorder, adult antisocial behavior) than for most internalizing disorders in any of the six countries in which these associations were examined. This suggests that the higher cross-sectional ORs of substance use disorders with externalizing than internalizing disorders might be due to stronger effects of substance use disorders or common causes of mental and substance disorders on secondary externalizing disorders than on secondary internalizing disorders. Within the internalizing disorders, phobias had substantially weaker effects than other anxiety disorders and bipolar disorder had dramatically higher effects than other mood disorders. Most ORs were somewhat larger among women than men.

Predictive Associations Based on Prospective Data

As recall bias could be involved in retrospective AOO reports, it is important to turn to longitudinal studies for confirmation. The evidence is most clear and consistent for conduct disorder. McCord and McCord (1960), for example, found in a long-term prospective study that childhood aggressiveness preceded alcohol use and predicted later development of alcoholism. Jones (1975) found much the same results in a long-term follow-up of respondents from the Oakland Growth Study. Similar associations have been consistently found in other long-term longitudinal studies (e.g., Robins 1966; Kellam et al 1983).

The results are more mixed in prospective studies of the temporal priority between internalizing disorders and substance use disorders (Hagnell and Tunving 1972; Johnston and O'Malley 1986; Schuckit and Hesselbrock 1994; Vaillant 1983), most of which used dimensional scales of trait anxiety or depression as the baseline measures (Caspi et al 1996; Hagnell et al 1986; Holahan et al 2001; Kaplow et al 2001; Poikolainen et al 2001; Vaillant 1996; Wennberg et al 2002). While most found baseline anxiety and depression to predict subsequent onset of substance problems, others did not. This could be due to differences in focus of measures in the case of anxiety. For example, Kaplow et al (2001) found that a dimensional measure of generalized anxiety was a significantly positive predictor of alcohol initiation, while a dimensional measure of separation anxiety was a significantly negative predictor of the same outcome in a 4-year prospective study of adolescents.

We are aware of five prospective studies that assessed baseline mental disorders in a diagnostic interview. Crum and Pratt (2001) evaluated the effects of baseline social phobia in predicting subsequent onset of alcohol use disorders in a 13-year follow-up of the Baltimore Epidemiologic Catchment Area sample. No significant effects were found; however, the vast majority of respondents were past the typical age of onset of substance use disorders at baseline. Weissman et al (1999) carried out a small prospective study in a more age-appropriate sample: prepubertal children who either had a DSM-III anxiety disorder, major depressive disorder, or no DSM-III disorder were followed 10 to 15 years. Prepubertal anxiety and depression were both found to have significantly elevated rates of substance use disorders at follow-up. Zimmerman et al (2003) followed a much larger general population sample of adolescents and young adults over 4 years to assess the effects of baseline anxiety disorders on later onset of alcohol disorders. Baseline social phobia and panic disorder predicted alcohol disorders, while the other anxiety disorders (panic attack, agoraphobia, specific phobia, generalized anxiety disorder) did not. Costello et al (2003) followed a large general population sample of children who were aged 9 to 13 at baseline to age 16 and found that both anxiety disorders and conduct disorder predicted onset of substance abuse, while major depression, attention-deficit/hyperactivity disorder (ADHD), and oppositional-defiant disorder did not. Kushner et al (1999), finally, followed a sample of college students 3 to 6 years to evaluate associations between anxiety disorders and substance use disorders. Baseline anxiety disorders assessed globally significantly predicted subsequent onset of alcohol disorders. Costello et al (2003) and Kushner et al (1999) were the only two of these studies to examine reciprocal associations of substance abuse predicting later onset of mental disorders. Costello et al (2003) failed to find any significant associations of this type, while Kushner et al (1999) found significant effects of alcohol use disorders predicting subsequent anxiety disorders.

Two limitations in the specifications of these analyses are noteworthy. First, they all fail to include detailed controls for risk factors that might be common causes of primary mental and secondary substance disorders. The same criticism holds for the retrospective analyses reviewed in the last section. Because of this limitation, there is a considerably greater likelihood than would otherwise be the case that the temporally primary mental disorders are markers rather than causal risk factors. Second, even if one is willing to entertain the possibility that mental disorders are risk factors for subsequent substance use disorders, very little attention was given in either the retrospective or prospective analyses to comorbidities among temporally primary mental disorders. As a result, intervention targeting could be compromised. Replicated large-scale epidemiologic data analyses would be needed to obtain refined results about such specifications. Fortunately, datasets exist that could be used for this purpose. Coordinated parallel secondary analyses of these data are needed to refine our understanding of these predictive associations.

Comorbidity and Course of Illness

Long-term prospective epidemiologic surveys have also been used to study associations of comorbidity with course of illness (Hagnell and Grasbeck 1990; Murphy 1990). These studies show consistently that comorbid disorders are more chronic than pure disorders. Indirect evidence based on cross-sectional epidemiologic surveys is also consistent with these prospective findings in showing that respondents with a retrospectively reported lifetime history of mental or substance use disorder report a significantly more persistent and severe course if they also report lifetime comorbidity (Kessler 1995). A complication in making sense of these results, though, is that comorbidity might merely be indicative of a more serious primary condition (Kovacs 1990; Merikangas et al 1988) or more adverse life situations (Farris et al 2003; Riggs et al 2003). No systematic research has been done to explore this issue, although several large long-term prospective datasets are available to do so (Angst et al 1990; Hagnell and Grasbeck 1990; Murphy 1990). A result that is inconsistent with this notion is that some types of comorbidity are more important predictors of course than others. For example, primary conduct disorder and antisocial adult behavior are more important than other primary mental disorders in predicting the subsequent course of secondary alcohol dependence (Menuck 1983; Tardiff et al 1981). This might be due to special effects of specific risk

factors (e.g., impulse dysregulation) on these particular mental disorders more than others as well as on substance disorders, to an effect of these particular mental disorders on exposure to drug use opportunities, or to some other specifying influences.

One possible reason for the association between comorbidity and illness course is that treatment is less effective among patients with dual diagnosis than pure diagnoses. This is a rapidly evolving area of research (Le Fauve et al 2004) that is beyond the scope of the current report to evaluate, because it involves the assessment of controlled clinical studies rather epidemiologic studies. It is worth noting, though, that the association of comorbidity with environmental adversity complicates efforts to evaluate whether comorbidity itself influences treatment response rather than environmental adversity influencing treatment response. We know, as a simple descriptive matter, that special challenges exist in treating patients with dual diagnosis because of their typically greater clinical severity, greater exposure to environmental risk factors, and the restricted set of pharmacological agents available for treatment because of heightened concerns about abuse potential (Kranzler and Rosenthal 2003). These complexities lead to a significant association existing between comorbidity and poor treatment response. We also know that patients with dual diagnosis can be treated effectively when the intensity of the treatment is commensurate with the complexity of the disorder (Timko and Sempel 2004) and that substance treatment patient-program matching based on information about comorbid mental disorders can sometimes improve treatment response (Gonzales et al 2003); however, formidable challenges exist in realizing the potential of the observations in the last sentence due to a continued lack of knowledge about effective treatments for complex comorbid cases, a shortage of adequately trained professionals to deliver these treatments (e.g., a shortage in child-adolescent psychiatrists), and a shortage of treatment settings that provide integrated treatment of dual diagnosis.

Making Sense of the Associations

Based on the results reviewed above, at least some evidence exists for each of four broad possibilities to explain observed patterns of mental-substance comorbidity. The first is that mental disorders lead to the onset and/or persistence of substance use disorders, most plausibly through processes that involve increased exposure to drug use (associated largely with conduct disorder), disinhibition to experiment with drugs (associated with impulse-control disorders), and self-medication of dysphoric mood. The second is that substance use disorders lead to the onset and/or persistence of mental disorders, most plausibly through a combination of biological mechanisms, such as heavy cocaine use having brain-kindling effects that cause panic attacks, and environmental mechanisms whereby substance disorders cause increased exposure to stress and decreased access to stress-buffering coping resources. The third is that there are common causes, either genetic or environmental, that lead to the onset and/or persistence of both types of disorder. Finally, methodological factors involving either sampling, reporting, or measurement might lead to overestimation of comorbidity.

The evidence reviewed up to now provides little help in reducing the complexity of these various possibilities. Significant associations have been found both for a wide range of mental disorders predicting later substance disorders and for substance use disorders predicting later onset of mental disorders. These associations have all been linked to environmental and genetic common causes. Existing epidemiologic data could be used to refine this understanding, but analyses would have to be more fine-grained than in the past. For example, self-medication is thought to help mediate the effects of internalizing mental disorders on the onset and course of substance use disorders (Degenhardt et al 2003). If so, though, we would expect substance use to peak on days of high stress among people with internalizing disorders. We know of only one evaluation of this prediction in an epidemiologic sample (Tournier et al 2003). This study used the daily diary experience sampling method to study day-to-day covariation between stress and substance use among respondents with and without anxiety disorder. No evidence for significant covariation of this sort was found in that study. Evidence consistent with the self-medication hypothesis, however, has been found repeatedly in less fine-grained studies that show anxious people to be more likely than others to report using alcohol as a means of coping with social stress (Carrigan and Randall 2003). Prospective epidemiologic studies are needed to evaluate the effects of such self-medication in the context of anxiety disorders on the onset of secondary substance use disorders.

The ideal way of sorting out inconsistent results of this sort is to carry out an experimental treatment study. Given that a great many such studies exist, one might think that this literature would be fertile ground for information about reciprocal causal effects between mental and substance disorders. As it turns out, though, this is not the case due to the fact that treatment trials seldom follow respondents over a long enough period of time to assess indirect treatment effects on the prevention of secondary disorders; however, uncontrolled treatment studies can sometimes be used to provide rough approximations. For example, a number of uncontrolled ADHD treatment studies have followed patients over 4 years or longer to evaluate concerns that treatment with stimulants is associated with increased risk of later substance use disorder. A meta-analysis of these studies showed that stimulant treatment was actually associated with a significant decrease in risk of later substance use disorder (Wilens et al 2003). This result indirectly suggests that at least some part of the widely documented association between ADHD and elevated risk of substance use disorders is due to ADHD causing substance abuse.

Epidemiologic studies can sometimes be used to approximate the results of uncontrolled treatment studies. This is especially true when epidemiologic data show that treatment of a given mental disorder is related to low risk of developing a secondary disorder after controlling for possible confounding variables (Goodwin and Olfson 2001). Given that selection bias is normally in the direction of more severe cases having a higher probability of receiving treatment, such a result strongly suggests that the primary disorder is a cause of the secondary disorder. In the more typical case, treatment of the primary disorder is positively associated with the subsequent onset of secondary disorders, presumably because of treatment selection bias (Regier et al 1990). Even here, though, statistical methods based either on instrumental variables models (McClellan et al 1994) or propensity score models (Foster 2003) can sometimes be used to make plausible inferences about treatment effects from epidemiologic data. These methods are currently underutilized in the analysis of epidemiologic data on mental-substance comorbidity.

Comorbidity Between Mental Disorders and Nicotine Dependence

Although the review has thus far focused on comorbidities of mental disorders with alcohol and drug use disorders, there is a separate, but related, epidemiologic literature on comorbidities between mental disorders and nicotine dependence. Significant positive associations of smoking with both mental disorders and alcohol-drug use disorders have been documented in a number of epidemiologic studies (Breslau et al 2001; Covey et al 1994; Glassman et al 1990; Lasser et al 2000). The literature on comorbidities between smoking and alcohol-drug use disorders conceptualizes smoking as an early stage, or "gateway," to the use of marihuana and other illegal drugs (Kandel et al 1992), although the mechanisms appear not to be causal (Golub and Johnson 2001). The literature on comorbidities between smoking and mental disorders, in comparison, has documented reciprocal predictions. There is an elevated risk of first onset of major depression, panic disorder, and generalized anxiety disorder among smokers (Breslau and Klein 1999; Breslau et al 1998; Brown et al 1996; Johnson et al 2000; Kendler et al 1993). Reciprocally, dimensional scales of trait anxiety and depression assessed in samples of adolescents have been found to predict the subsequent initiation of smoking (Patton et al 1998), although other studies failed to replicate this association (Goodman and Capitman 2000; Wu and Anthony 1999).

Breslau (2004) and Breslau et al (2004) have carried out the most extensive epidemiologic analyses of comorbidity between mental disorders and nicotine dependence based on cross-sectional data collected in the Tobacco Supplement of the US National Comorbidity Survey. With regard to mental disorders predicting smoking, they found that a wide range of DSM-III-R anxiety and mood disorders predict both the subsequent first onset of regular smoking and the progression from regular smoking to dependence (Breslau et al 2004). Importantly, though, these associations were largely confined to active mental disorders. That is, respondents with a history of anxiety or mood disorders did not have elevated risk of either initiating regular tobacco use or, among users, of progressing from regular use to dependence. This specification raises the possibility that prevention of nicotine dependence might be an indirect consequence of the effective treatment of anxiety or mood disorders; however, no long-term experimental research has been carried out to evaluate this prediction directly. As noted in an earlier section, it might also be possible to use instrumental variables or propensity score models in epidemiologic studies to carry out an indirect test of this prediction, although no study of this sort has as yet been reported in the literature.

With regard to smoking predicting mental disorders, Breslau et al (2004) found much more variation in effects. A lifetime history of daily smoking was found to predict the subsequent first onset of mood disorders, but the strength of this association was unrelated to whether the respondent was currently smoking versus no longer smoking at the time of the onset of mood disorder. Among remitted smokers, onset of mood disorder was unrelated to the number of years it had been since the respondent last smoked. Among active smokers, furthermore, onset of mood disorder was unrelated to intensity of smoking (either nicotine dependence or pack-years of cigarettes smoked). Virtually identical results were found for smoking predicting the onset of alcohol or drug abuse or dependence. These results are most consistent with smoking being a marker of risk rather than a causal risk factor of mood and alcohol-drug use disorders and strongly suggest that neither prevention of smoking nor successful smoking cessation would have led to a reduction in the subsequent onset of these later disorders. Again, though, we are aware of no experimental evidence to confirm this prediction directly.

The situation was different for associations between smoking and the subsequent onset of panic disorder, agoraphobia, and posttraumatic stress disorder (PTSD) in the Breslau et al (2004) analyses, where current smoking was a more powerful predictor of onset than was past smoking. In the case of PTSD, furthermore, nicotine dependence among active smokers was a significant predictor of onset. It is not clear whether the association between current, but not past, nicotine dependence and PTSD is due to nicotine dependence being a marker of lifestyle factors related to trauma exposure, to psychological vulnerability that predicts PTSD once exposed to trauma, or to some combination of these processes. In either case, though, it seems implausible to think that a smoking cessation program would be effective in preventing PTSD. A more likely scenario is that current nicotine dependence can be seen as a marker or risk that could be used to target individuals for more intensive study aimed at providing insights into the neurobiology of PTSD.

Primary Prevention of Secondary Substance Disorders

The most obvious area where the epidemiologic evidence has potential clinical relevance is in regard to the finding that primary mental disorders strongly predict later substance use disorders. This raises the question of whether early successful treatment of primary mental disorders would be effective in reducing subsequent substance disorders. The effect sizes in epidemiologic surveys are such that the question is of more than passing interest. Simulations in the ICPE surveys, for example, suggest that as much as 50% of all substance dependence would be prevented by successful treatment of temporal primary mental disorders if the associations found in survival analyses were causal (Kessler et al 2003). Although there are probably some types of mental-substance comorbidity that would be exceedingly difficult to prevent (e.g., comorbid panic and cocaine abuse due to brain kindling), there are others for which successful prevention is a plausible possibility. Substance use disorders that occur secondary to primary phobias are a good case in point. Comorbidity between phobias and substance use disorders has been found in a number of clinical studies (Chambless et al 1987; Roy et al 1991) with phobias almost always preceding substance abuse in age of onset by as much as a decade (Christie et al 1988; Hesselbrock et al 1985). Substance abuse secondary to phobia is particularly common among women, with close to a third of all female alcoholics reporting an earlier phobia (Helzer and Pryzbeck 1988). This comorbidity is traditionally attributed to anxiety promoting the use of alcohol and drugs as a form of self-medication (Klein 1980), an interpretation supported by reports that the vast majority of patients with phobias self-consciously use alcohol or drugs to manage their fears (Bibb and Chambless 1986). Based on this thinking, interventions might be aimed either at curing the phobia before secondary substance abuse begins or at teaching treatment-resistant phobics alternative strategies for managing their fears. There is good reason to believe that these strategies could be quite effective. If so, they would reduce a substantial percent of lifetime substance use disorders and an even greater percent of current disorders. This is because alcoholics and substance abusers with primary pho-

bias are more chronic than primary alcoholics and substance abusers, presumably because continued fears precipitate further drinking (Marlatt and Gordon 1980).

The challenge for psychiatric epidemiologists concerned with intervention opportunities such as this is to enhance understanding of the causal processes sufficiently to guide intervention targeting. There are formidable methodological problems involved in doing this, but a number of compensating practical advantages also exist of conducting preventive trials in populations at risk for comorbid disorders (Kendall and Kessler 2002; Kessler and Price 1993). First, the ease of identifying persons at risk for a secondary disorder is greater when they already meet criteria for a primary disorder. Second, already diagnosed groups are at high risk of secondary disorders, increasing the efficiency and power of preventive trials. Third, primary prevention of secondary disorders may allow experimental epidemiologists to use already developed treatment technologies as part of the available technology of preventive intervention strategies. Fourth, conducting preventive trials with diagnosed clinical populations at risk for the development of secondary disorders may increase the social warrant for preventive intervention. Fifth, the prevention of secondary disorders would eliminate the exacerbation of primary disorders that are known to accompany the onset of secondary disorders. In this way, such interventions would lead to secondary prevention of primary disorders in addition to primary prevention of secondary disorders.

It is important to appreciate, in working with these complex models, that there may be differences in the effects of risk factors depending on the gender and age of respondents. These specifications have largely been ignored in previous studies of comorbidity. This is a serious limitation, as patterns of comorbidity differ dramatically by these specifiers. For example, comorbid alcoholism is much more often found to be primary and associated with antisocial personality disorder among men and secondary and associated with affective disorders and anxiety disorders among women (Hesselbrock et al 1986; Roy et al 1991). Furthermore, strong and consistent evidence has been found that depressed patients with an early onset have a stronger family history of both depression and alcoholism than those with a late onset (e.g., Mendlewicz and Baron 1981).

Social context can also have a powerful effect on comorbidity. The most dramatic illustration of this fact concerns changes in patterns of substance use, which affect the base rates on which to evaluate the sensitivity of substance use disorders as predictors of mental disorders. This is illustrated in the work of Weiss et al (1988), who studied a sample of hospitalized cocaine abusers in 1980 to 1982 and found very high rates of primary affective disorder. In a replication between 1982 and 1988, however, much weaker evidence of primary affective disorder was found. The authors concluded that this change reflects the fact that cocaine use is more widespread and, at least in some segments of society, becoming normative. Secular changes of this sort can complicate analysis of the impact of mental disorders on substance use and vice versa; however, they also present special opportunities. For example, Weiss et al (1988) found that the impact of cocaine abuse on course of primary depression decreased as the prevalence of cocaine use increased in the population. This finding suggests that the strong initial effect of cocaine in the early 1980s was due more to the social meanings of cocaine use during that time and to early adopters having higher rates of prior depression than late adopters rather than to any direct effects of the substance itself. Analyses of comorbidity that use short-term historic changes of this sort in creative ways could provide important insights that have been overlooked in prior investigations. The fact that patterns of drug use in America have been changing rapidly in recent years suggests that this strategy could be feasible for many applications.

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