Chapter 1
Epidemiological Perspectives on Co-Occurring Anxiety Disorder and Substance Use Disorder

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Introduction

The purpose of this chapter is to review the issue of anxiety disorders co-occurring with substance use disorders (SUDs) ("co-morbidity") from an epidemiological perspective. Generally speaking, epidemiology pertains to the study of the various factors influencing the occurrence, distribution, prevention and control of disease, injury and other health-related events in defined human populations. The quasi-experimental methodology of the typical epidemiological study – contrasting the rates of an outcome between naturally occurring groups – is well suited to the problem of co-morbidity.

For instance, epidemiological data collected in representative community-based samples avoid many of the biases built into studies of co-morbidity in institutional/clinical samples. Such data are also more flexible than are clinical data in assigning the status of outcome between co-morbid disorders. From the epidemiological perspective, for example, which co-morbid disorder is designated as the outcome and which as a putative risk factor is analytically arbitrary. By contrast, outcome status in clinical samples is typically fixed (i.e., all SUD treatment patients have an SUD).

The most basic epidemiological question asks to what extent having either an anxiety disorder or SUD (again, the predictor-outcome arrangement is analytically arbitrary) modulates one's risk for the other disorder. Epidemiological studies can also document changes in risk for the later development of a co-morbid disorder (e.g., SUD) conferred by the earlier presence of an index disorder (e.g., anxiety disorder). Beyond the useful service of quantifying the

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extent of co-morbidity under various conditions, such data also have the capacity to both generate and, in a limited sense, test some critical hypotheses concerning the nature of co-morbidity. We explore each of these issues, in this chapter.

First we highlight methodological and theoretical issues related to epidemiological studies concerning co-morbidity. Next we review data from major community-based epidemiological studies related to co-morbidity separated by several variables of interest (e.g., specific anxiety disorder type, specific SUD type). For each variable of interest, we attempt to highlight and interpret findings based on a broad survey of the co-morbidity literature. Finally, we provide a discussion of what we consider to be the primary conclusions that can be drawn from the review and the primary challenges that remain to be resolved in the epidemiological study of co-morbidity.

Methodological Issues

Chance overlap vs. covariation. Epidemiological studies typically quantify the magnitude of co-variation between co-morbid disorders in terms of the odds ratio (OR); i.e., the ratio of the odds of having an index condition (e.g., an SUD) when the co-morbid condition (e.g., anxiety disorder) is present (numerator) vs. absent (denominator). An OR of 1, therefore, indicates that the odds of the outcome occurring (the index disorder) are the same whether or not the putative risk factor (the co-morbid disorder) is present or absent. This would occur when chance alone is dictating the co-occurrence of the two disorders. ORs departing from 1 indicate that the co-morbid disorder increases the risk for the outcome (i.e., for ORs > 1) or decreases the risk for the outcome (i.e., for ORs < 1). Greater departures from 1 indicate proportionally greater co-variation between the co-morbid disorders.

Cross-sectional vs. longitudinal and prospective designs. Cross-sectional epidemiological designs index the degree of co-variation between co-morbid disorders for a specified time span (e.g., "current," "lifetime") as reported at a single data collection point. Therefore, the co-morbid disorders identified in a cross-sectional design may or may not have been active at the same time. In our view (e.g., see Kushner, Abrams, and Borchardt 2000), establishing that such cross-sectional associations exist with a non-trivial magnitude is an important first step in judging the clinical and theoretical importance of co-morbidity.

Once such co-variation is established, additional information about the nature of the association between co-morbid disorders can be gleaned by knowing the temporal relationship of their onsets and remissions. Longitudinal data provide information about change over multiple time points in one or more variables of interest. Retrospective methods can provide longitudinal data by asking individuals at a single time point to recall and report how their status on variables of interest (e.g., symptoms) have changed over a specified time period. For example, individuals can be asked to recall which of two co-morbid

disorders began first. Prospective methods also provide longitudinal information but have the additional advantage of collecting real-time data (i.e., status at the time data are collected) over multiple time points extending into the future. Time effects (e.g., faulty memory) and cohort effects (e.g., changes in cultural and clinical norms over time) are more likely to distort retrospective data than those that are collected prospectively.

Community-based vs. clinic-based samples. Berkson (1949) noted that individuals with multiple disorders are more likely to be referred (by self or others) to treatment than are those with a single disorder. This would serve to inflate the prevalence of co-morbidity in treatment settings relative to the rates that exist in the community. Therefore, large representative community databases yield the most informative (i.e., least biased) epidemiological data regarding psychiatric co-morbidity. These include the Epidemiological Catchment Area (ECA) survey (e.g., Helzer & Pryzbeck, 1988; Regier et al., 1990), the National Co-morbidity Survey (NCS) (e.g., Kessler et al., 1997, 2005) and the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (e.g., Grant et al., 2004). The International Consortium in Psychiatric Epidemiology (ICPE) also provides relevant data that is based on studies both in the U.S. and elsewhere (Mexico, Canada and Europe) (Merikangas et al., 1998). Each of these surveys includes sample sizes that range into the thousands and form the core of the data we review below.

Diagnostic specificity and co-morbid associations. Because various drugs of abuse (including alcohol) have profoundly differing pharmacokinetics, psychoactive, legal and cultural characteristics, it would be very surprising indeed to find that the effects of each establishes the same operant dynamic and psycho-physiological effects among individuals with anxiety disorder. Similarly, specific anxiety disorders (e.g., panic disorder, generalized anxiety disorder, social phobia) may vary considerably in terms of their subjective and behavioral manifestations and may well involve unique neuro-anatomical and neuro-chemical substrates that are differentially affected by drugs and alcohol (Kushner, Sher, & Beitman, 1990). Specific anxiety disorders might also vary in terms of the availability of alcohol and the permissibility of drinking found in the circumstances in which symptoms typically manifest (e.g., work vs. parties vs. driving). These issues suggest that more diagnostic specificity will provide more accurate information regarding co-morbidity. However, this issue is ultimately informed by the data and practical constraints on how data are collected and analyzed. We consider each of these issues in this chapter.

Theoretical Issues

Epidemiological data are best interpreted with an understanding of the various possible links between co-morbid conditions. In this regard, the co-occurrence between two disorders could indicate that: (a) distinct underlying liabilities to the

disorders are correlated (i.e., related but not causally so), (b) the same underlying liability is manifested as putatively distinct disorders (i.e., spectrum disorders), (c) either disorder causes each other directly, (d) the "co-morbid" disorder is really a third type of disorder that is distinct from either condition alone, or (e) the co-morbidity emerged for artifactual reasons (e.g., sampling from a segment of the population where co-morbidity is more concentrated than it is in the population at-large) (e.g., Klein & Riso, 1993; Krueger & Markon, 2006; Kushner, Abrams, and Borchardt 2000; Neale & Kendler, 1995).

Within many of these possible associations (models) a variety of theories and mechanisms might apply. For example, SUD might promote the onset of anxiety disorder (model) via psychophysiological perturbations (theory 1) or via environmental perturbations (theory 2). Theory 1 would fit with a "neuro-kindling" process (mechanism 1) resulting from multiple withdrawals (e.g., Kushner et al., 1990) or with a process related to substance-induced disruption in the stress-response system (see chapter 2 mechanism 2). Similarly, the idea that anxiety disorder promotes the onset of SUD (model) could occur via attempts at "self-medication" of anxiety symptoms (theory) via the neuro-depressant effects of some drugs like alcohol (mechanism 1) or via the boost to psychological well-being that can result from some drugs such as cocaine and hallucinogens like ecstasy (mechanism 2). Using epidemiological data, we have limited but important possibilities of considering the "fit" of these various possibilities.

Cross-Sectional Co-morbid Associations

Abuse vs. dependence and alcohol vs. other drugs. The various studies shown in Table 1.1 converge on the conclusion that anxiety disorders demonstrate a greater association in the case of dependence vs. abuse and in SUDs involving drugs vs. alcohol. In absolute terms, knowing whether the SUD is related to drugs vs. alcohol accounts for slightly more predictive variance than does knowing whether the SUD is related to abuse vs. dependence. The bottom row in Table 1.1 shows that alcohol abuse is the weakest predictor of all with average OR of only 1.5. It is also notable that the association with anxiety disorder is slightly stronger for drug abuse (OR = 2.6) then it is for alcohol dependence (OR = 2.4). This is suggestive of an interaction between abuse vs. dependence with drug vs. alcohol in predicting co-morbidity with anxiety disorder.

It is possible that abuse is more associated with externalizing disorders such as anti-social personality while dependence is more associated with internalizing disorders such as anxiety disorders. This is roughly consistent with the viewpoint put forward by Cloninger (1987) who distinguished two alcoholism subtypes along these lines. According to this view, trait anxiety ("harm avoidance") promotes a style of drinking that is more likely to result in dependence while anti-social traits ("novelty seeking") promotes a style of drinking that is

Table 1.1 Drug and alcohol abuse vs. dependence in Co-morbidity

	Drug disorder		Alcohol disorder	
	Abuse	Dependence	Abuse	Dependence
ECA	2.3	2.4	1.0	1.8
NCS	1.4	3.3	1.2	2.1
NESARC	1.7	6.2	1.1	2.6
ICPE-US-Fresno(MAPPS)	3.1	4.0	1.8	2.7
ICPE-Germany(EDSP)	4.4	5.2	1.9	3.2
ICPE-Mexico(EPCP)	2.8	4.6	1.7	2.7
ICPE-Netherlands(NEMESIS)	2.0	5.2	1.0	1.8
ICPE-Ontario(OMHSS)	2.9	3.4	2.2	2.5
Means (any drug vs. alcohol)	**3.5 (Any Drug)**		**2.0 (Any Alcohol)**	
Means (any dependence vs. any abuse)	**3.0 (Any Dependence)**		**2.1 (Any Abuse)**	
Means (abuse vs. dependence by drug vs. alcohol)	**2.6**	**4.3**	**1.5**	**2.4**

ICPE = International Consortium in Psychiatric Epidemiology.
MAPPS = Mexican American Prevalence Services Survey (n = 3,012, Fresno)
EDSP = Early Developmental Stages of Psychopathology Study (n = 3,021, Munich)
EPCP = Epidemiology of Psychiatric Co-morbidity (n = 1,932, Mexico City)
NEMESIS = Netherlands Mental Health Survey and Incidence Study (N = 7,076, 90 municipalities in Netherlands)
OMHSS = Ontario Mental Health Supplemental Survey (n = 6,902)
ECA = Epidemiologic Catchment Area Survey (U.S., n = 20,000)
NCS = National Co-morbidity Survey (U.S., n = 8,098)
NESARC = National Epidemiologic Survey on Alcohol and Related Conditions (U.S., n = 43,093)

more likely to result in abuse. However, some studies have failed to find such distinctions (e.g., Sannibale & Hall, 1998). Another possibility is that much of the anxiety disorder in co-morbidity is a result of physiological and psychological processes associated with dependence-based withdrawal (e.g., Schuckit & Hesselbrock, 1994).

It is interesting that drug-related SUDs are in general more strongly associated with anxiety disorders than are alcohol-related SUDs; especially since the bulk of clinical studies in this area relate to alcohol use disorders (c.f., Kushner et al., 1990, 2000). This is difficult to interpret for two primary reasons. First, there may well be considerable overlap (i.e., co-morbidity) between drug and alcohol disorders. For example, Helzer and Pryzbeck (1988) reported that the odds of having either a drug disorder or alcohol use disorder was increased more than seven fold among individuals with the other. Therefore, data sets examining co-morbidity with anxiety disorder would more optimally be split into those with only a drug use disorder, only an alcohol use disorder and those with both. Unfortunately, none of the studies we reviewed included these subgroups. A second problem with interpreting this effect is that combining all types of drug use disorder (e.g., cocaine, marijuana, hallucinogens) into one category could add noise to that category. However, this potential "noise"

might be expected to reduce rather than elevate the association of anxiety disorder to drug use disorder relative to alcohol use disorder.

Co-morbidity in specific drugs of abuse. The ECA (i.e., Regier et al., 1990) is the only large epidemiological database to publish anxiety disorder co-morbidity rates with SUDs involving specific drug types. Notably, these ORs range from a low of 2.3 (marijuana) to a high of 5.0 (hallucinogens). Others in descending order are 4.5 (barbiturates), 2.9 (both cocaine and amphetamines) and 2.8 (opiates). Again, these categories are not mutually exclusive and they also combine abuse and dependence (a distinction shown in Table 1.1 to be important). Nonetheless, these data would appear to defy a simplistic self-medication view. Apparently, not all individuals (or perhaps not even a majority) with an anxiety disorder prefer the depressant-type drugs (including alcohol) that might reasonably be expected to reduce the physiological manifestations of anxiety. Rather, Regier et al. (1990) find that SUDs involving hallucinogens – a family of drugs not known to have a calming effect on users – demonstrate the strongest association with anxiety disorders.

One possible explanation for these findings is that self medication dynamics may account for more cases of co-morbidity involving drugs with depressing or tranquilizing effects while drugs with stimulating effects are more likely to trigger, aggravate or maintain anxiety disorders (e.g., Kushner, Abrams, and Borchardt 2000). Again, this suggests multiple initiation trajectories into co-morbidity where either condition might cause the other via different mechanisms. On the other hand, even physiological stimulants (e.g., cocaine, nicotine, ecstasy) might include psychological effects related to enhancing generalized self-efficacy, or a personal sense of well-being that could, conceivably, be especially reinforcing among anxiety disordered individuals as per the classical self-medication view.

Co-morbidity in specific anxiety disorders. More than 15 years ago, we noted that the clinical literature revealed variable levels of base rate-adjusted SUD comorbidity among the various anxiety disorder subtypes (Kushner et al., 1990). As noted earlier, however, clinical samples are potentially biased in a number of ways. In fact, Table 1.2 summarizes data from various surveys showing only modest variability between the various anxiety disorders in terms of co-morbidity risk. For alcohol dependence, ORs range from an average low of 2.0 for simple phobia to a high of 3.1 for panic disorder (OR = 3.0 for GAD). This same basic pattern holds up in drug dependence; albeit, with overall higher ORs (as expected from Table 1.1). Considering data from drug and alcohol dependence together (bottom row of Table 1.2), GAD shows the greatest absolute co-morbidity (OR = 5.1), with agoraphobia showing the next greatest associations (OR = 4.7). Simple phobia remains the anxiety disorder with the weakest association to co-morbid SUD (OR = 2.6).

While type of drug seems to affect co-morbidity rates (see above), it was surprising based on our earlier review of clinical studies (Kushner et al., 1990) that the epidemiological data reviewed here did not find greater variability for

Table 1.2 Association of alcohol and drug dependence with specific anxiety disorders

	Any anxiety	GAD	Panic disorder/no Ag ("Panic")	Panic/ with Ag ("Agoraphobia")	Social phobia	Specific phobia
Alcohol dependence						
ECA	2.1		3.8	2.6	2.1	1.6
NCS	2.1	2.8	2.0	1.7	2.2	2.1
NESARC	2.6	3.1	3.4	3.6	2.5	2.2
Means	**2.3**	**3.0**	**3.1**	**2.6**	**2.3**	**2.0**
Drug dependence						
NCS	3.3	3.8	3.8	2.8	2.6	2.5
NESARC	6.2	10.4	7.6	10.5	5.4	3.8
Means	**4.8**	**7.1**	**5.7**	**6.7**	**4.0**	**3.2**
Drug and alcohol dependence combined						
Means	**3.6**	**5.1**	**4.4**	**4.7**	**3.2**	**2.6**

See notes from Table 1.1 for definition of abbreviations.

type of anxiety disorder. It is possible that the apparent disjunction between clinical and community data is the result of referral patterns. For example, the more common anxiety disorders found in alcoholism treatment patients (e.g., social phobia and agoraphobia) might associate with a more severe form of SUD that is, therefore, more likely to lead to treatment. Consistent with this viewpoint, Kushner et al. (2005) found that social phobia and panic with agoraphobia predicted relapse in treated alcoholics better than did other anxiety disorders. That same study also found that GAD was more likely to resolve following SUD treatment than were anxiety disorders such as social phobia and PTSD. These finding suggest that while the epidemiological data may capture the most unbiased associational quantities in co-morbidity, they may also obscure qualitative distinctions in the way specific anxiety disorders come to be associated with and act upon SUDs.

Number of anxiety disorders. It must be considered that over half of individuals with a specific anxiety disorder subtype also have at least one additional anxiety disorder subtype (e.g., Goodwin et al., 2004; Himle & Hill, 1991). Therefore, the number of anxiety disorders (or "psychiatric load") might be another parameter relevant to co-morbidity involving an SUD. Merikangas et al. (1998) examined this issue in a community sample using the ICPE data set showing that more diagnoses, including (but not limited to) various anxiety disorders and depression, increases the SUD co-morbidity risk. For example, the risk (ORs) for alcohol and drug dependence among those with a single psychiatric disorder was 2.2 and 2.4 (respectively) while these risks (ORs) were 5.0 and 7.8 (respectively) for those with more than two psychiatric disorders. These data mesh with clinical studies showing that the number of anxiety disorders is a significant predictor of a worse psychiatric course for co-morbid patients following alcoholism treatment (Kushner et al., 2005).

Gender and co-morbidity rates. Anxiety disorders are more common in women and SUDs are more common in men (e.g., Lewis, Bucholz, Spitznagel, & Shayka, 1996). However, it would be a logical error to conclude that differing base rates of disorder for men and women indicate differing magnitudes of co-morbidity based on gender. Data from the NCS (Kessler et al., 1997) (Table 1.3) shows base rate adjusted co-morbidity rates (i.e., ORs) for men and women across the various anxiety disorders. One thing that stands out in Table 1.3 is that for men, there are no positive associations between alcohol abuse and anxiety disorders while PTSD and GAD both actually have negative associations with alcohol abuse. Men with PTSD are only about half as likely to have alcohol abuse as compared to men without PTSD. Considering all anxiety disorders and alcohol disorders together (right most column in the last two rows of Table 1.3), women with either disorder are approximately one-third more likely to have the co-morbid disorder as compared to men.

The reason for this moderate gender effect is not clear. Perhaps women and men are prone to different subtypes of alcohol disorder (i.e., even within the broader DSM diagnostic categories of dependence and abuse) that are differentially prone to association with anxiety disorder. Cloninger (1987) distinguishes two types of alcoholism, only one of which ("type 1") he believes is related to the "escape" oriented drinking associated with the "self-medication" of anxiety symptoms. In fact, more women than men can be classified as having type 1 alcoholism (e.g., Sannibale & Hall, 1998); however, these researchers and others have found that individuals with alcohol use disorders often do not fall cleanly into one vs. the other of Cloninger's subtypes.

Table 1.3 Comorbidity across specific anxiety disorder by gender

	GAD	Panic (w/o ag)	Agoraphobia	Social phobia	Simple phobia	PTSD	**Any Anxiety**
Men (AlcDep)	3.9	2.3	1.8	2.4	3.1	3.2	**2.2**
Women (AlcDep)	3.0	3.0	2.5	2.6	2.6	3.6	**3.1**
Men (AlcAb)	0.7	0.8	1.3	1.0	0.9	0.5	**1.0**
Women (AlcAb)	1.31	1.6	1.0	1.8	2.2	1.0	**1.8**
Men (any alcohol disorder)	**2.3**	**1.6**	**1.6**	**1.7**	**2.0**	**1.9**	**1.6**
Woman (any alcohol disorder)	**2.2**	**2.3**	**1.8**	**2.2**	**2.4**	**2.3**	**2.5**

From the NCS data set reported by Kessler et al. (1997).

Longitudinal Co-morbid Associations

Order of disorder onset. Among the most common approaches used to assay causal influence in co-morbidity is the retrospective assessment of the order in which disorders first onset. It might or might not be the case that a condition caused an outcome that it predated, but it is certainly the case that a condition did not cause an outcome that it antedated. This logical fact highlights a Popperian opportunity to potentially eliminate incorrect causal theories concerning co-morbidity. That is, causal theories asserting that either SUD or anxiety disorder causes the other in co-morbidity must conform to the implied order of onset to survive (i.e., to remain viable).

Table 1.4 shows that anxiety began first in about three-fourths of the cases in which it was co-morbid with alcohol dependence and in about four-fifths of the cases in which it was co-morbid with drug dependence. What this suggests is that in at least three of four co-morbid cases (involving dependence), we could expect to be able to rule out the possibility that the SUD caused the co-morbid anxiety disorder. However, as noted above, this neither demonstrates that the anxiety problem caused the co-morbid SUD in these 75% nor that the SUD caused the anxiety disorder in the remaining 25%.

Independent vs. induced co-morbid disorders. DSM IV was the first edition of the American Psychiatric Association's diagnostic nomenclature to place importance on and provide a crisp distinction between independent and substance-induced anxiety disorders. To be "independent" by these criteria, an anxiety disorder must: (a) clearly have begun prior to the onset of the SUD; *or* (b) must be found to persist for more than four weeks following the cessation of substance use and withdrawal. We would draw special attention to criterion "b" which goes beyond the simple order of onset criterion (above) by also examining the question of whether a co-morbid anxiety disorder appears to be capable of persisting once active substance abuse and withdrawal cease

Table 1.4 Retrospective assessments of order of Co-morbid disorder onset

	Percent of Co-morbid cases for whom anxiety began first		
Sample	Alcohol dependence	Drug dependence	Any SUD
NCS (Kessler et al., 1996)	81.1	84.4	79.3
ICPE (U.S. Sample, Fresno)	68.6	72.7	–
ICPE (Germany)	56.7	67.6	–
ICPE (Mexico)	63.5	100	–
ICPE (Netherlands)	75.3	75.5	–
ICPE (Ontario)	76.8	77.9	–
NCS	79.4	83.4	–
ECA	–	–	75.0
Mean	**72.0**	**80.2**	**77.2**

See Table 1.1 notes for abbreviation definitions and citations.

(i.e., anxiety symptoms should persist in the case of independent anxiety disorder and should not persist in the case of induced anxiety disorder).

Grant and colleagues (2004) examined the proportion of independent vs. substance-induced anxiety in the NESARC sample using these criteria. They reported that about 11% of the sample had a 12-month diagnosis of anxiety disorder and that only "a few individuals with mood or anxiety disorders were classified as having substance-induced disorders." (p. 807). In fact, only about 0.2% of co-morbid cases (i.e., virtually none) in this sample had an anxiety disorder that failed to demonstrate independence from the causal or maintaining influence of a co-occurring SUD using strictly applied DSM IV criteria. These findings themselves are subject to critique based on the arbitrary choice (empirically speaking) of a four-week waiting period to rule out SUD effects as a cause of the co-morbid anxiety disorder (e.g., see chapter 2 describing the long-term effect substance abuse can have on the stress system). From this perspective an expanded abstinence period might result in a greater proportion of co-morbid individuals falling into the substance-induced category.

Discussion

As noted at the beginning of the chapter, epidemiology is well equipped to systematically assess changes in risk for an index condition under various naturally occurring circumstances. Several large scale epidemiological surveys of psychiatric disorders and SUDs conducted over the last 20 years leave little question that co-morbid disorders are correlated in the general population. Further, these studies point to sub-grouping characteristics that help to refine our understanding of the parameters of co-morbid associations and provide clues as to the nature of these associations. For example, these studies show that anxiety disorders are more likely to co-occur with drug disorders than with alcohol disorders. This finding is provocative because clinical studies of co-morbidity have overwhelmingly focused on alcohol-disordered samples (c.f., Kushner, Abrams, and Borchardt 2000). These studies also suggest that anxiety disorders are more likely to occur with SUDs involving dependence than those involving abuse. Such findings can serve as a wellspring for hypotheses concerning the mechanisms promoting co-morbidity.

For example, Table 1.4 shows that SUD could not be the cause of co-morbid anxiety disorder for the 75% of cases in which the latter precedes the former. Data from the Grant et al. (2004) study take this a step further by showing that even when SUD begins before anxiety disorder, the anxiety disorder typically persists during periods of abstinence of at least one month in duration. As mentioned above, one month of abstinence might not be enough time to be sure that sub-acute and longer-term withdrawal effects have cleared up. On the other hand, if we presume that a non-trivial

proportion of the co-morbid cases in the NESARC sample reported abstinences of considerably more than the one-month minimum, then it is even more surprising that they found so very few cases in which an anxiety disorder resolved during drug/alcohol abstinence.

Although Grant et al. (2004) concluded from their findings that co-morbid anxiety disorder was rarely substance-induced, we would add the possible alternative conclusion that substance-induced anxiety disorders are resistant to spontaneous recovery even when substance intake is discontinued. Notably, the idea of a semi-autonomous anxiety disorder that originally began as a result of an SUD is virtually never discussed in the literature. This is surprising, in part, because the converse idea that a semi-autonomous SUD could have started with a self-medication process is a commonplace idea. That is, it is commonplace to expect that an SUD would not automatically resolve upon treatment of the anxiety disorder that caused it. Yet the vary standard (i.e., DSM) for establishing a substance-induced anxiety disorder is that it resolves with a brief abstinence from pathological substance use. This asymmetry seems to us to be both arbitrary and potentially misleading, especially for the approximately 25% of co-morbid individuals who report that the SUD began prior to the anxiety disorder.

Although beyond the scope of this chapter, the causal implications of these epidemiological data do dovetail into various clinical aspects of co-morbidity. For example, we have argued elsewhere (Kushner, Abrams, and Borchardt 2000) that treating either the SUD alone or the anxiety disorder alone, while observing the impact on the other condition, offered a quasi-experimental approach to quantifying the degree of causal influence between co-morbid disorders. However, if the causal influences were concentrated at the initiation of the co-morbid disorder (vs. the maintaining influences), then treating the causal disorder would not necessarily resolve the co-morbid (caused) condition. On the other hand, the emergence of maintaining factors that are independent of the etiological origins of a co-morbid condition would not necessarily imply that the two conditions have no functional associations. For example, an SUD that emerged either in response to an anxiety disorder or for reasons unrelated to a co-morbid anxiety disorder could still be maintained, in part, through a self-medication process serving as a functional linkage between the co-morbid conditions.

Limitations and Future Work

In addition to a good deal of information, several problems are also highlighted by the epidemiological data reviewed in this chapter. Perhaps the greatest among these is the overwhelming number of combinations that are possible if one were to represent all of the various parameters that are potentially relevant to co-morbidity. Based on this review, this list could include: dependence vs.

abuse, alcohol vs. drug, one type of drug vs. another, one type of anxiety disorder vs. another, number of anxiety diagnoses, number of SUD diagnoses, induced vs. independent anxiety disorder, variants of alcoholism subtypes not represented in DSM, other co-morbid conditions such as depression, and gender. No survey imaginable could possibly accommodate all the various combinations (i.e., main effects and interactions) that would fully account for these variables. Notably, this problem has been largely ignored in the work of clinical researchers focused on co-morbidity. Indeed, the analytical and conceptual mechanics of handling all possible combinations of more than even two categorical conditions are so daunting as to conceivably inspire a conspiracy of ignorance.

Although the effort to model all combinations of anxiety disorders and SUDs appears to be practically impossible, it may not be necessary. Alternatives include statistical and conceptual models capable of simplifying or otherwise resolving large amounts of information into manageable systems. This was the aim of Kushner et al. (2005) in using multiple regression to partition unique from shared predictive variance associated with multi-morbid anxiety and affective disorders in alcoholism treatment patients. By using a competitive entry strategy, these models allowed the single most predictive anxiety disorders to enter the model with any other anxiety disorder entering the predictive model only if it accounted for additional predictive variance.

Alternatively, Krueger and Markon (2006) suggested a correlated liability conceptualization of co-morbidity as an approach that can potentially characterize complex co-morbid cases. In this conceptualization, co-morbidity can be traced to the existence of a smaller number of etiologically coherent liability spectrums (i.e., latent variables) that give rise to manifest psychopathology. In a meta-analysis of relevant articles, Krueger and Markon (2006) conclude that studies support the existence of a broad "internalizing" liability latent variable that confers risk to a diverse array of unipolar mood and anxiety disorders, on the one hand, and a broad "externalizing" liability conferring risk for substance use and antisocial behavior disorders (c.f., Achenbach & Edelbrock, 1984) on the other hand. Moreover, these liability constructs are also genetically coherent. That is, the structure of genetic risk for common forms of psychopathology parallels the observed internalizing and externalizing spectrums (Kendler, Prescott, Myers, & Neale, 2003).

These constructs are also psychologically coherent when one examines the ways in which personality is linked to psychopathology (see Krueger & Tackett, 2003 for a recent review). Specifically, personality traits in the domain of negative emotionality may confer risk for both internalizing and externalizing disorders, but traits in the domain of disinhibition confer risk specifically for externalizing disorders. The net result is that, in the population at large, the internalizing and externalizing spectra appear to be etiologically, phenotypically, and personologically coherent. From this perspective, the broad personality domain of negative emotionality (vs. the various separate DSM conditions that make it up) is a more parsimonious way to

characterize the co-morbidity between anxiety and SUDs noted in this review.

A second problem that is highlighted by this review is the dearth of prospective data investigating temporal patterning in co-morbidity. Clearly, epidemiological researchers see the importance of these issues as evidenced by their attention to the order of disorder onset (Table 1.4) and changes in anxiety disorder status during periods of SUD abstinence (Grant et al., 2004). However, none of these studies were conducted prospectively, due (presumably) to the added costs and time such data collection would entail. Prospective studies that examine the changes in anxiety symptoms given periods of abstinence of varying lengths would be particularly valuable in further illuminating the substance-induced vs. independent co-morbid disorder question.

Concluding Remarks

Epidemiological data reviewed provide clear evidence that co-morbid disorders co-occur more frequently than would be expected by chance. However, it should also be noted that other psychiatric disorders, including antisocial personality (OR = 21), mania (OR = 6.2) and schizophrenia (OR = 4.0), are much more strongly related to SUDs of all kinds (Helzer & Pryzbeck, 1988). Nonetheless, because anxiety disorders are far more common than disorders such as schizophrenia and mania, the former as a risk for SUD have implications for many more people than do these latter conditions. Epidemiological data have provided key information related to the extent and the nature of this association and has the potential to provide more yet. These data sets will allow for novel symptom clustering methods to be evaluated and have the potential to reveal the temporal topography of co-morbid conditions over time. Such studies should inform and be informed by complementary methodologies such as those highlighted in this volume.

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