

Comorbid Forms of Psychopathology: Key Patterns and Future Research Directions

Magdalena Cerdá^{1,2,3}, Aditi Sagdeo², and Sandro Galea^{2,3,4}

¹ Robert Wood Johnson Foundation Health and Society Scholars Program, Department of Epidemiology, University of Michigan, Ann Arbor, MI.

² Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI.

³ Center for Urban Epidemiologic Studies, New York Academy of Medicine, New York, NY.

⁴ Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY.

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The purpose of this review is to systematically appraise the peer-reviewed literature about clustered forms of psychopathology and to present a framework that can be useful for studying comorbid psychiatric disorders. The review focuses on four of the most prevalent types of mental health problems: anxiety, depression, conduct disorder, and substance abuse. The authors summarize existing empirical research on the distribution of concurrent and sequential comorbidity in children and adolescents and in adults, and they review existing knowledge about exogenous risk factors that influence comorbidity. The authors include articles that used a longitudinal study design and used psychiatric definitions of the disorders. A total of 58 articles met the inclusion criteria and were assessed. Current evidence demonstrates a reciprocal, sequential relation between most comorbid pairs, although the mechanisms that mediate such links remain to be explained. Methodological concerns include the inconsistency of measurement of the disorders across studies, small sample sizes, and restricted follow-up times. Given the significant mental health burden placed by comorbid disorders, and their high prevalence across populations, research on the key risk factors for clustering of psychopathology is needed.

anxiety; comorbidity; conduct disorder; depression; social conditions; substance-related disorders

INTRODUCTION

Psychiatric comorbidity is the presence, simultaneously or in sequence, of two or more disorders in an individual within a certain time period (1, 2). Psychiatric comorbidity is a prevalent phenomenon across age groups and types of populations (3–5). The Epidemiologic Catchment Area (ECA) Survey found that 35 percent of respondents with at least one lifetime disorder had one or more additional disorders during their lifetime (6); the National Comorbidity Survey Replication found that 27.7 percent of the respondents had two or more disorders during their lifetime (7).

Understanding psychiatric comorbidity has important research, clinical, and nosologic implications. From a research perspective, epidemiologic research conducted on isolated disorders may underestimate the burden imposed by mental health problems because this group may represent a select portion of the population that suffers from psychiatric disorders (8). Documenting the relation between key psychiat-

ric disorders over the life course can provide a more accurate assessment of the psychiatric burden experienced by different population groups.

With respect to clinical concerns, comorbidity is associated with more severe psychiatric symptoms, more functional disability, longer illness duration, less social competence, and higher service utilization (9–11). Given the high prevalence of comorbidity and its clinical consequences, research efforts that aim to better understand the patterns of comorbidity over time are clearly essential to help guide its prevention.

Investigation into the distribution of comorbidity across key psychiatric disorders can also help us elucidate the structure of phenotypic psychopathology. The cooccurrence of disorders has called into question the validity of current categorical classifications of mental disorders, with critics suggesting that a dimensional approach to classifying comorbid disorders is more appropriate (12). Studying comorbid patterns can thus help us discern commonalities and

distinctions in the developmental pathways of comorbid disorders and in the etiologic profiles of each comorbid disorder—elements that will provide the basis to understand whether the disorders are different expressions of the same underlying disturbance or are distinct disorders in their own right (13).

This review aims to examine current knowledge on the epidemiology of clustered forms of psychopathology over the life course, focusing on four of the most common mental disorders: anxiety, depression, conduct disorder, and substance abuse. According to the National Comorbidity Survey Replication, 28.8 percent of the US population suffered from an anxiety disorder sometime in their life, whereas 20.8 percent suffered from a mood disorder, 14.6 percent had a substance use disorder, and 9.5 percent presented symptoms of conduct disorder (7). The cooccurrence of these conditions has been consistently documented in clinical and population samples (5).

This paper systematically reviews comorbidity studies within a life course framework, focusing exclusively on prospective population-based studies. This presents a novel approach to address comorbidity and enables us to study similarities and differences in comorbidity patterns at key life stages as well as to understand how the normative developmental trajectories of disorders may influence the magnitude of comorbidity from childhood to adulthood. Focusing on population-based studies overcomes one of the key limitations of clinical studies: selection bias that may determine the patterns of comorbidity observed in the sample.

REVIEW OF THE LITERATURE

This review encompasses the peer-reviewed literature published between 1970 and 2007. We limited our review to these years to reflect current thinking about psychiatric comorbidity and to include studies that use methods considered standard today. The literature reviewed was identified through the Social Science Citation Index and Science Citation Index, and it covered studies about concurrent and sequential comorbidity between anxiety, depression, substance use/abuse, and conduct disorder. We restricted our review to longitudinal, population-based studies that provided information about the temporal associations between disorders. As stated by Kraemer et al. (14), cross-sectional studies, particularly those that use lifetime prevalence with mixed-age samples to estimate comorbidity, run the risk of identifying instances of “pseudocomorbidity” when no real comorbidity exists.

The literature on comorbidity is vast and encompasses many different fields, from medicine to public health to psychology. We restricted our review to psychiatric definitions of the disorders because a wider review would have been beyond the scope of this project. For example, for conduct disorder, we considered measurement of symptoms or diagnoses of conduct disorder, oppositional defiant disorder, and antisocial personality disorder but not aggression or delinquency. The search was limited to English-language studies in biomedical research. Keywords and terms used

for the search included primarily the following: 1) for substance abuse: substance abuse, alcohol abuse, drug abuse, cannabis, cocaine, heroin, street drugs, smoking, injection drug use; 2) for depression: depression, depression symptomatology, depression symptoms, mood disorders; 3) for conduct disorder: conduct disorder, antisocial personality disorder, antisocial, opposition defiant disorder, externalizing behavior/disorder; 4) for anxiety disorder: anxiety, anxiety symptomatology, anxiety symptoms, internalizing disorder; and 5) for comorbidity: comorbidity, joint trajectories, discordant trajectories, concurrent, cooccurrence, risk pathways, chain of risk, launch factors, transitions, risk pathways.

FINDINGS

In this paper, we review concurrent and sequential comorbidity between the four disorders, and we present available data on concurrent comorbidity, sequential comorbidity, and contributions of each disorder to the deflection of developmental trajectories of the other three disorders. This review covers 58 studies, including those using child and adolescent samples, and then adult samples, to present available knowledge on comorbidity at key life stages. The original search provided 103 articles, of which 45 were removed because of the absence of a prospective study design. Although studies such as Kessler et al.'s (15) on the National Comorbidity Survey Replication or the cross-national comparison of comorbidity conducted by Merikangas et al. (16) offer groundbreaking data on the distribution of comorbid disorders in population-based samples, they were not included because they used retrospective measures of disorder onset in cross-sectional study designs.

The studies reviewed here (summarized in tables 1 and 2) approach the issue of causality between comorbid disorders by investigating the relative timing of the onset of each disorder and the impact that the prevalence of one disorder has on the course of the other. The strength of the causal link depends on whether the cooccurrence of the disorders persists after accounting for common risk factors (3, 17).

Anxiety and substance use

The evidence on the link between anxiety and substance use is mixed: most studies have been cross-sectional or retrospective in design and used dimensional rather than diagnostic measures of anxiety. The few existing prospective, diagnostic studies (18–22) propose several alternative causal associations between anxiety and substance abuse: 1) individuals with an anxiety disorder may be more likely to develop or sustain a substance use disorder, in part as a way to manage the symptoms of anxiety (21, 23, 24); 2) having an anxiety disorder may reduce or delay the onset of behavioral problems such as substance abuse either because of the high level of anxious social cognitions that serve as a reminder of the negative consequences of the behavior or because of behavioral inhibition that results from anxiety disorders (25); 3) substance use may exert physiologic effects that increase vulnerabilities to anxiety

disorders; or 4) a third variable may promote the development or maintenance of both (20).

Children and adolescents. Childhood and adolescence is a critical time to investigate the timing of onset of the comorbid disorders since anxiety has a relatively early age at onset (26). Few studies have looked prospectively at the link between anxiety and substance abuse among the younger age groups. Several studies have found support for the “self-medication” thesis: that persons with anxiety use alcohol and drugs to suppress their anxiety symptoms (18, 22, 27–29). Costello et al. (18) found that anxiety predicted later substance use disorders among a representative population sample of adolescent girls, but not among boys. However, several studies have also found support for the reverse association, in which substance dependence promotes the development of anxiety (20, 21). A particularly compelling study that followed children over 21 years and obtained prospective reports of anxiety and substance dependence found that the association between anxiety and substance dependence was largely or entirely noncausal, while substance dependence predicted anxiety disorder at follow-up. Finally, some evidence also exists for a negative relation between anxiety and substance use: Pardini et al. (25) followed the Pittsburgh Youth Study sample of boys from early adolescence to young adulthood, and they found that higher levels of anxiety/withdrawal were inversely related to symptoms and diagnoses of alcohol use disorder; a cohort study of a representative population sample aged 9–13 years at baseline found that anxiety predicted a later onset of smoking (30).

Lack of conclusive evidence is due to the heterogeneity of substance use and anxiety subtypes examined in the few available population-based studies: associations may differ between subtypes. Kaplow et al. (28) proposed that, in studies that consider anxiety as a general syndrome and fail to differentiate within its dimensions, the opposing functions of different types of anxiety may offset each other, resulting in null findings. In fact, Kaplow et al. found opposing effects for generalized anxiety disorder and separation anxiety disorder: whereas generalized anxiety disorder was positively associated with alcohol use initiation, separation anxiety disorder resulted in a lower risk of onset of alcohol use. A study of 2,548 adolescents in Germany also found that the association depended on the type of anxiety disorder examined; although the seven lifetime anxiety disorders taken as a set predicted subsequent onset of hazardous use, abuse, and persistence, only panic and social phobia were independent predictors of hazardous use and abuse and the persistence of an alcohol use disorder (22).

Adults. Studies conducted among adults provide support for a potential reciprocal relation between anxiety and substance abuse. A study of 454 college students followed over 7 years, for example, found that having an anxiety disorder was associated with 3.5–5 times higher odds of developing a new alcohol dependence, while the odds of developing a new anxiety disorder were about four times higher for those diagnosed with alcohol dependence in previous years (24). The direction of the relation between anxiety and substances may depend on the type of substance. The Kushner et al. study (24) was limited by use of a select

population that may have a more similar mental health status than the general population. In a study of a random sample of the adult population, however, Newcomb et al. (31) also found a bidirectional relation between anxiety and substance use: polydrug problems in young adulthood increased anxiety in adulthood, but anxiety was actually associated with fewer cocaine problems later in life—possibly because individuals who experience high levels of arousal would be less likely to use a drug that exacerbated that arousal.

Depression and substance abuse

Depressive symptoms are associated with substance use disorders throughout adolescence and adulthood (25). As with anxiety, the directionality and causal nature of the association remains in question: depression and substance use disorders may be linked through common confounding factors, or the association may be causal—either that alcohol and illegal substances are used as a form of self-medication to manage symptoms of depression or that substance use may increase vulnerability to depression through behavioral changes or neurophysiologic alterations (32).

Children and adolescents. Several studies have reported that depression and substance abuse tend to cooccur in adolescence (18, 19, 21, 33–35). In a study of high school students in western New York, Windle and Davies (35) found that 24–27 percent of adolescents identified as depressed also met the criteria for heavy drinking, whereas Rao et al. (34) found that 21.1 percent of adolescent women with depression also had a substance use disorder. The nature of the association between depression and substance abuse among adolescents remains in question. Several studies found that depressed adolescents were more vulnerable to substance use; this association has been found for marijuana (27), smoking (33), alcohol abuse (25), and substance abuse problems (36). Fergusson et al. (33) and Pardini et al. (25), authors of two of the most promising studies on issues of depression–substance abuse comorbidity among adolescents, highlight the lack of conclusive evidence on this issue. Fergusson et al. followed a birth cohort of 1,265 children from birth to age 21 years and found that major depression was associated with increased rates of daily smoking and nicotine dependence, although the association could be due to confounders that affected the development of both outcomes. Pardini et al. also followed up 506 boys until young adulthood and found that increased depression in early adolescence was associated with more alcohol use disorder symptoms and alcohol abuse and dependence diagnoses by young adulthood, but only for boys with high levels of conduct problems.

Evidence also exists to support the hypothesis that substance use may increase vulnerability to depression. Hayatbakhsh et al. (21) followed a comparable cohort of 3,239 children up to age 21 years and found that symptoms of depression in childhood did not predict use of marijuana, but use of marijuana was associated with depression. A small study of 155 women aged 17–19 years also found that substance use disorders predicted worse depression

TABLE 1. Population studies on comorbid patterns between substance abuse, anxiety, depression and conduct disorder among children and adolescents

Comorbidity	Citation	Sample	Follow-up time	Measurement of disorders	Conclusions
Anxiety and substance use/abuse	Goodwin et al. (20)	1,265 children (635 males, 630 females) from Christchurch, New Zealand	21 years	CIDI* and custom-written survey items used; alcohol dependence: DSM-IV* criteria; illicit drug dependence: DSM-IV criteria; nicotine dependence: DSM-IV; anxiety disorders (generalized anxiety disorders, panic disorder, agoraphobia, social phobia, and specific phobia): CIDI diagnostic to assess DSM-IV criteria	Young people with anxiety disorders are at increased risk of substance dependence; association is largely noncausal and is explained by 1) presence of fixed childhood and family factors associated with both anxiety and substance dependence; and 2) time-dynamic associations including lagged effects of substance dependence and development of comorbid depression. OR* of substance dependence associated with anxiety disorder = 1.8 (95% CI*: 1.2, 2.6).
Anxiety and substance use/abuse	Zimmerman et al. (22)	2,548 adolescents aged 14–24 years in Munich, Germany	4 years	Diagnostic assessment based on the computer-assisted version of the DIA-X/M-CIDI*; DSM-IV anxiety disorders assessed; DSM-IV alcohol use disorders assessed include alcohol abuse without dependence and alcohol dependence without alcohol abuse	Anxiety disorders are significant predictors of the subsequent onset and persistence of regular and hazardous alcohol use and alcohol use disorders. Panic disorder and social phobia are the only anxiety disorders involved in these predictive associations.
Depression and substance use/abuse	Silberg et al. (71)	307 monozygotic and 185 dizygotic same-sex male twin pairs from Virginia; 392 monozygotic and 187 dizygotic like-sex female pairs	4 years	Substance use based on ratings given by multiple informants during a home interview using the DSM-based CAPA,* conduct disorder measured with a composite rating based on child's response to CAPA symptoms, a diagnosis of conduct disorder and oppositional defiant disorder, and ratings on the Olweus aggression scale; depression based on CAPA symptoms associated with a diagnosis of major depressive episode	Among boys, the cross-lagged correlations between conduct disturbance and substance use and between substance use and depression were approximately equal, indicating that a common factor contributed to these behaviors; among girls, there were differences in the pattern of the cross-lagged correlations for conduct disorder and depression, substance use and depression, indicating that conduct disorder preceded substance use and that depression followed substance use. Among girls, the cross-lagged associations were also consistent with conduct disorder leading to depression.
Depression and substance use/abuse	Fergusson et al. (33)	Birth cohort of 1,265 children (635 males, 630 females) born in Christchurch, New Zealand in mid-1977	Assessed at birth, 4 months, 1 year, annually to age 16 years, and at ages 18 and 21 years	Smoking based on written survey, nicotine dependence based on DSM-III-R* criteria at age 16 years and DSM-IV criteria at ages 18 and 21 years; major depression measured with DISC* with DSM-III-R criteria at age 16 years and CIDI with DSM-IV criteria at ages 18 and 21 years	Major depression was associated with increased rates of daily smoking (IRR* = 1.19 (95% CI: 1.03, 1.39)). and elevated rates of nicotine dependence (OR = 1.75 (95% CI: 1.13, 2.70)).

Depression and substance use/abuse	Rao et al. (34)	155 women aged 17-19 years recruited from three high schools in Los Angeles, California	Follow-ups conducted every 6 months up to 5 years	Axis I disorders assessed with the Structured Clinical Interview for DSM-III-R; self-reported depressive symptoms assessed with the Beck Depression Inventory; self-reported problems of substance use assessed at the end of follow-up with the Rutgers collegiate Substance Abuse Screening Test	Depression and substance use disorder were related concurrently; major depressive disorder and substance use disorder were significantly associated in follow-up; substance use disorder problem score and Beck Depression Inventory (self-reported depressive symptoms) during follow-up were also correlated. Major depressive disorder before the study did not predict substance use disorder during the follow-up period, whereas prior substance use disorder did predict major depressive disorder at follow-up. Prior substance use disorder also predicted the worst Beck Depression Inventory score during follow-up.
Depression and substance use/abuse	Windle and Davies (35)	975 high school students from western New York State in the first wave, 220 added in the second wave; average age, 15.54 years (data collected from primary caregivers: 90% mothers)	Time 1: 1 year since study; time 2: 2 years since study	Depression: CES-D* Scale criterion score of >23, "heavy drinking": Quality Frequency Index—adolescents who consumed >45 drinks in the last 30 days	24-27% of adolescents identified as depressed met the criteria for heavy drinking (33-37% of boys, 16-18.5% of girls); 23-27% of adolescent heavy drinkers were depressed (18-20% of boys, 27-33% of girls). Approximately 5% of participants had depression and were heavy drinkers at either wave. The mixed drinking and depression group showed the lowest stability between time 1 and time 2: only 20% of those in the mixed group at time 1 persisted in this group at time 2.
Depression and substance use/abuse	Aseltine et al. (13)	900 adolescents (9th, 10th, and 11th graders) from Boston, Massachusetts	3 years	Depressive symptoms measured with CES-D Scale; measures of alcohol and drug use adapted from Monitoring the Future studies	Rate of cooccurring depression and substance use problems was 4% ($n = 39$); those with prior substance problems were more than twice as likely to develop cooccurring problems (9%) at time 2 than were the depressed (4%).
Anxiety, depression, and substance use/abuse	Kaplow et al. (28)	1,420 children in the total study from western North Carolina; for this analysis, only 936 included who completed child or parent report measures of generalized anxiety, separation anxiety, and depressive symptomatology as well as reported alcohol use at all four time points	4 years	CAPA used to assess psychiatric symptoms	Children with early symptoms of generalized anxiety were found to be at increased risk for initiation of alcohol use (OR = 1.14 (95% CI: 1.03, 1.25)), whereas children with early symptoms of separation anxiety were at decreased risk (OR = 0.71 (95% CI: 0.51, 0.94)); depressive symptomatology was associated with increased risk for initiation of alcohol use in adolescence (OR = 1.60 (95% CI: 1.29, 1.99)).
Anxiety, depression, and substance use/abuse	Hayatbakhsh et al. (21)	3,239 Australian young adults	Birth to age 21 years	Anxiety and depression symptoms in the last 6 months measured in the 21-year follow-up by using the Young Adult Self-Report; cannabis use retrospectively assessed, occasional use = use of cannabis once a month or not in the past month, frequent use = use of cannabis every day or every few days	Frequent use of cannabis, either without (OR = 2.1 (95% CI: 1.1, 4.0)) or with (OR = 2.7 (95% CI: 1.8, 4.1)) use of other illicit drugs, predicts more than a twofold increase in anxiety and depression in young adults. No association was found between symptoms of anxiety and depression at age 14 years and either occasional or frequent use of cannabis by young adults. Frequent use of cannabis and early onset of use are associated with symptoms of anxiety and depression in young adults.

Table continues

TABLE 1. Continued

Comorbidity	Citation	Sample	Follow-up time	Measurement of disorders	Conclusions
Anxiety and depression	Repetto et al. (51)	579 African-American adolescents in Ann Arbor, Michigan, who were at risk of dropping out of school	4 years	Depressive symptoms assessed with items from the Brief Symptom Inventory; anxiety symptoms assessed with six items from the Brief Symptom Inventory	Adolescents who presented consistently high levels of depressive symptoms were more likely to report higher anxiety symptoms compared with adolescent members of other trajectories. Adolescents whose depressive symptoms followed the decreasing trajectory had higher levels of anxiety than those in the consistently low or increasing groups.
Anxiety and depression	Stein et al. (2)	2,548 adolescents and young adults aged 14–24 years from Munich, Germany	One follow-up 34–50 months later	Munich-CIDI used to diagnose by using DSM-IV criteria; social anxiety disorder defined as meeting DSM-IV criteria per the Munich-CIDI diagnostic criteria; depressive disorder defined as meeting DSM-IV criteria for one or more episodes of major depression or dysthymia	Persons with a combination of social anxiety disorder and depression are at the greatest risk of depression in early adulthood. Persons with depression and social anxiety disorder (current or previous) were significantly more likely (OR = 8.7 (95% CI: 4.5, 16.8)) than persons with no mental disorder to have experienced a depressive disorder during the follow-up period.
Anxiety and depression	Wittchen et al. (26)	3,021 adolescents and young adults aged 14–24 years at first interview in Munich, Germany	Three waves over 4–5 years	Diagnostic assessment based on the computer-assisted version of the Munich-CIDI; diagnoses made by using DSM-IV criteria	The proportion of major depressive episodes among those with an anxiety disorder was low for those aged 14–17 years but increased at ages 18–24 years. Almost two thirds of cases with anxiety disorder were comorbid with major depression at follow-up (OR = 3.9 for generalized anxiety disorder, OR = 3.4 for panic disorder, and OR = 1.7 for specific phobia). The number of anxiety disorders, baseline impairment associated with anxiety, the frequency of avoidance, and the presence of panic-like attacks all increased the risk of secondary depression among those with primary anxiety disorders.
Anxiety and depression	Pine et al. (50)	776 young people (aged 9–18 years) in upstate New York	Assessed in 1983, 1985, and 1992: 9 years	Used DISC to assess DSM-III criteria from parents and children at times 1 and 2; at time 3, DISC used with the children only	Major depression at time 2 predicted generalized anxiety disorder at time 3. Overanxious disorder predicted major depression at time 3. Conduct disorder at time 1 was related to major depression at time 3 (OR = 2.54 (95% CI: 1.42, 7.68)). Conduct disorder at time 2 was related to major depression at time 3 (OR = 2.38 (95% CI: 1.10, 5.16)).
Conduct disorder and substance use/abuse	Cohen et al. (60)	749 adolescents aged 13.7 years at the first interview from two upstate New York counties	Interviewed in 1983, 1985–1986, and 1991–1994	Substance use disorders and conduct disorder assessed with DISC-I; instrument administered to both the child and a parent; DSM-III-R diagnoses made	Adolescents with conduct disorder had 2.59 times the hazard of initiating marijuana use over the study period in comparison to adolescents without conduct disorder. Conduct disorder in early adolescence was independently associated with significantly elevated mean symptoms of alcohol abuse/dependency and marijuana use disorder across the age range.

Conduct disorder and substance use/abuse	Juon et al. (75)	952 African-American children who began 1st grade in Woodlawn, Chicago, in 1966-1967 and remained in the Woodlawn school during their 1st year	1966-1967; 1975-1976; 1992-1994	Self-report measures of smoking frequency and quantity (instrument not specified); substance use disorder measured by using the modified version of CIDI based on DSM-III-R criteria; major depressive disorder measured with CIDI; antisocial behavior operationalized as ratings from 1st-grade teachers as aggressive or shy and aggressive	Those who had been rated as aggressive (OR = 2.10) or as both shy and aggressive (OR = 1.93) in the 1st grade were more likely to be current smokers/early adopters than nonsmokers. Those who had comorbidity of major depressive disorder and drug problems (OR = 4.70) were more likely to be current smokers/early adopters than nonsmokers compared with those who had no problems.
Conduct disorder and substance use/abuse	Hussong et al. (66)	461 men from the Dunedin, New Zealand, Multidisciplinary Health and Development Study	8 years, at ages 18, 21, and 26 years	Alcohol abuse and marijuana abuse assessed by symptoms from the DIS*; antisocial behaviors assessed via the self-report offending interview, which ascertains illegal behaviors and conduct problems; DSM-IV criteria used for these measures	Substance abuse exerts both proximal and distal effects on desistance of antisocial behavior over young adulthood. Men with greater substance abuse at the end of adolescence showed greater antisocial behavior across young adulthood. Periods in which men reported greater symptoms of substance abuse corresponded to higher-than-normal levels of antisocial behavior.
Conduct disorder and substance use/abuse	Marmorstein and Iacono (67)	289 families of male twins and 337 families of female twins, first assessed when the twins were approximately 17 years of age in Minnesota	3 years	Conduct disorder measured from an adapted version of the Structured Clinical Interview for DSM-III-R Personality Disorders; substance dependence symptoms assessed by using adolescents' reports on a modified version of the Substance Abuse Module of CIDI; DSM-III-R criteria used	Youths with late-onset antisocial behavior had higher rates of substance dependence than controls for all three classes of substances. The late-onset group also had more nicotine and cannabis dependence than those with desisting behavior. Youths with persisting antisocial behavior had more nicotine, alcohol, and cannabis dependence than youths with no antisocial behavior and youths with desisting antisocial behavior.
Conduct disorder and substance use/abuse	White et al. (64)	506 boys in the Pittsburgh Youth Study	6 years	Drug use: assessed with the 16-item substance-use scale adapted from the National Youth Survey; psychopathologic characteristics: assessed with the Self-Report Delinquency Scale, the Youth Self-Report, and the caretaker-completed DISC-Parent Version; depressed mood = number of symptoms from the Recent Moods and Feelings Questionnaire	Marijuana use was associated with higher overall level of conduct disorder but did not affect the rate of growth of conduct disorder. No association was found between oppositional defiant disorder scores and marijuana use; oppositional defiant disorder was a significant predictor of level of alcohol use. Number of symptoms of depression was positively related to level of alcohol use but not marijuana use.
Conduct disorder and depression	Ingoldsby et al. (68)	431 school-age children from Durham, North Carolina; Nashville, Tennessee; Seattle, Washington; central Pennsylvania	5th-7th grade	Conduct problems: youth completed the 32-item Things You Have Done survey at the end of 5th grade, youth completed the Self-Report Delinquency Scale at the end of 7th grade; parents rated Child Behavior Checklist, teachers completed the externalizing scale on the Teacher's Report Form; depressive symptomatology: youth completed the Reynolds Child Depression Scale at the end of 5th and 7th grades and parents completed a subscale of the Child Behavior Checklist	This study did not find support for the hypothesis that conduct problems predict increases in depression in early adolescence. Cases of comorbid conduct problems and depressive symptoms were significantly persistent over time. A substantial portion of youth in the conduct problems group in 5th grade moved to the cooccurring group by 7th grade. Serious depression or conduct problems by 7th grade occurred more frequently in comorbid cases than in cases with either disorder alone.

Table continues

TABLE 1. Continued

Comorbidity	Citation	Sample	Follow-up time	Measurement of disorders	Conclusions
Conduct disorder and depression	Kim et al. (70)	206 boys recruited through 4th-grade classes (depression studied from ages 14–15 to 23–24 years) from Oregon	10 years	Depressive symptoms: assessed with the CES-D Scale; antisocial behavior in late childhood: antisocial construct from items from the Teacher Child Behavior Checklist, telephone interview scores, peer nominations, home observations, and interviewer impression	Early antisocial behavior was associated with depressive symptoms in adulthood.
Conduct disorder, substance use/abuse, and depression	Measelle et al. (36)	Community sample of 496 female adolescents who varied in age from 13 to 15 years at first assessment from the metropolitan area of the southwestern United States	5 years	Depressive symptoms: adapted version of the K-SADS*; antisocial behavior symptoms: Externalizing Syndrome of the Child Behavior Checklist; substance abuse symptoms: items adapted from Stice et al. (76); DSM-IV criteria used for all	Initial depression level predicted increases in substance abuse symptoms and slower decreases in antisocial behavior; initial levels of antisocial symptoms predicted increases in depression and substance abuse; initial substance abuse level predicted slower decelerations in antisocial behavior.
Conduct disorder, anxiety, and depression	Gregory et al. (49)	1,037 members of a birth cohort in Dunedin, New Zealand (baseline beginning at age 11 years)	21 years: follow-ups at ages 11, 13, 15, 18, 21, 26, 32 years (<i>N</i> = 972 at this follow-up)	At ages 11–15 years, DISC used to diagnose mental health according to DSM-II; at ages 18–32 years, DIS used to assess mental health by using DSM-IV criteria	Adult anxiety cases were also more likely to have experienced juvenile depression relative to those without adult anxiety. Adults with social phobia, agoraphobia, and posttraumatic stress disorder were more likely to have experienced externalizing spectrum disorders than those without these disorders: adults with posttraumatic stress disorder were likely to have met diagnostic criteria for conduct or oppositional defiant disorder.
Conduct disorder, anxiety, and depression	Lavigne et al. (61)	510 children aged 2–5 years at baseline from Chicago, Illinois	5 years	Externalizing and internalizing behavior problems assessed by the Child Behavior Checklist; DSM-III-R diagnoses conducted with the Diagnostic Interview for Children and Adolescents	Single-diagnosis oppositional defiant disorder at wave 1 was associated with later comorbidity of oppositional defiant disorder and mood disorders and of comorbidity of oppositional defiant disorder and an anxiety disorder. There was moderate-to-high stability for oppositional defiant disorder comorbid with anxiety and low stability for oppositional defiant disorder comorbid with mood disorder.
Conduct disorder, anxiety, depression, and substance use/abuse	Loeber et al. (74)	Pittsburgh Youth Study of three samples of boys in grades 1 (age 6.9 years), 4 (age 10.2 years), and 7 (age 13.4 years) (each sample including 250 of the most antisocial boys in each grade plus 250 randomly selected others)	Youngest group assessed at screening and at eight assessment waves spaced at 6-month intervals; middle group assessed at screening and six assessment waves; oldest group assessed at screening and seven assessment waves	Child Behavior Checklist and the DISC-Parent Version administered to caretaker; teachers given the Teacher Report Form; boys assessed with the National Youth Survey 40-item Self-Reported Delinquency Scale and the 16-item Substance Use Scale based on the National Youth Survey; oppositional defiant disorder: DSM-III-R based on DISC-Parent Version	Persistent substance use in preadolescence was predicted by persistent delinquency and internalizing problems, while persistent substance use in adolescence was predicted by persistent delinquency only. Comorbid persistent substance use and delinquency were predicted by oppositional defiant disorder in middle childhood and by persistent internalizing problems in middle-to-late childhood.

Conduct disorder, anxiety, depression, and substance use/abuse	Rohde et al. (77)	1,507 participants selected from high schools in western Oregon aged 14-18 years	Mean = 13.8 months	Adolescents interviewed with a version of K-SADS that combined features of the epidemiologic version (K-SADS-E) to derive diagnoses based on DSM-II-R criteria; alcohol use: four symptoms for alcohol use and seven symptoms for dependence assessed; psychopathology: diagnoses clustered among DSM subdivisions	Of adolescents with alcohol abuse/dependence, 20% had an internalizing disorder, 35% had an externalizing disorder, and 45% had both internalizing and externalizing disorders. 87.5% of the time, anxiety disorders preceded alcohol disorders, and, 80.0% of the time, disruptive behavior disorders preceded alcohol disorders. Comorbidity was associated with an earlier age at onset of alcohol disorder; 16% of adolescents with a current psychiatric disorder moved into a more problematic alcohol use group from time 1 to time 2 vs. 5.8% of adolescents with no diagnosis between the assessment points.
Conduct disorder, anxiety, depression, and substance use/abuse	Pardini et al. (25)	506 boys in the Pittsburgh Youth Study	Average of 12.5 years; boys screened, assessed at ages 13.9, 20.4, and 25.4 years	Depression: assessed with the self-report Recent Moods and Feelings Questionnaire (contains items with DSM-III criteria); anxiety/withdrawal: assessed with a scale that combined the child (youth self-report), teacher (Teacher Report form), and parent-report Child Behavior Checklist; alcohol use disorders (assessed with the DIS on two occasions in early adulthood (DSM-III-R diagnoses)	Early conduct disorder symptoms predicted increased alcohol use disorder symptoms and alcohol dependence diagnosis by young adulthood. Adolescent boys with high levels of anxiety/withdrawal had lower levels of alcohol use disorder symptoms and were less likely to develop alcohol dependence by young adulthood. Increased depression in early adolescence was associated with higher alcohol use disorder symptoms and alcohol abuse and dependence diagnoses by young adulthood, but only for boys with high levels of conduct disorder symptoms.
Conduct disorder, anxiety, depression, and substance use/abuse	Costello et al. (18)	1,420 children from western North Carolina	3-5 years (children aged 9-13 years assessed annually until age 16 years)	CAPA used to assess psychiatric symptoms	Significant comorbidity was found among the behavioral disorders and anxiety and depression; depression was comorbid with conduct disorder in girls but not boys; depression was comorbid with substance use disorder in boys but not girls; anxiety predicted later substance use disorder, but depression did not; in girls, but not boys, anxiety predicted depression even when controlling for current comorbidity.
Conduct disorder, anxiety, depression, and substance use/abuse	Krueger et al. (8)	961 members of an unselected birth cohort from Dunedin, New Zealand	Aged 18-21 years	Mental disorders (in the prior 12 months) assessed by using the DIS to generate diagnoses according to DSM-III-R criteria	A two-factor model provided the best fit to the data: major depressive disorder, dysthymia, generalized anxiety disorder, agoraphobia, social and simple phobia, and obsessive compulsive disorder were presumed to reflect internalizing problems; conduct disorder and marijuana and alcohol dependence were presumed to reflect externalizing problems. Subjects retained their positions regarding the latent factors over the 3-year period.

Table continues

TABLE 1. Continued

Comorbidity	Citation	Sample	Follow-up time	Measurement of disorders	Conclusions
Conduct disorder, anxiety, depression, and substance use/abuse	Wittchen et al. (27)	1,395 community subjects from Munich, Germany, aged 14–17 years at baseline	Three waves over 10 years	Substance use, abuse, and dependence, as well as mental disorders, assessed with the DIA-X/M-CIDI, according to DSM-IV	Major depression was associated with a higher risk of cannabis use and dependence: (OR for cannabis use = 2.2 (95% CI: 1.3, 3.7); OR for cannabis dependence = 2.4 (95% CI: 1.3, 4.5)). Hypomania and mania were associated with incident cannabis use and cannabis dependence (OR for cannabis use = 2.4 (95% CI: 1.0, 5.4); OR for cannabis dependence = 2.7 (95% CI: 1.1, 6.3)). Among anxiety disorders, only panic-anxiety was associated with cannabis use (OR = 3.1 (95% CI: 1.4, 6.8)). Conduct problems predicted cannabis use (OR = 2.3 (95% CI: 1.2, 4.2)).
Conduct disorder, anxiety, depression, and substance use/abuse	Dierker et al. (19)	173 high- and low-risk youths in New Haven, Connecticut (identified on the basis of parental history of substance abuse) aged 7–17 years	1988–1998	Child diagnoses based on K-SADS and independent ratings from DSM-III-R obtained from a child and adolescent psychiatrist; tobacco assessed using K-SADS	Psychiatric disorders were significantly associated with nicotine dependence: the association between having a psychiatric disorder and dependence vs. lower levels of use were as follows: OR for anxiety = 4.5 (95% CI: 1.71, 11.94), OR for affective disorder = 10.7 (95% CI: 3.79, 30.25), OR for conduct disorder = 5.0 (95% CI: 1.6, 15.73), OR for oppositional defiant disorder = 5.8 (95% CI: 1.80, 18.43); in the low-risk population, oppositional defiant disorder was the only risk factor that predicted transition to nicotine dependence.
Conduct disorder, anxiety, depression, and substance use/abuse	Costello et al. (30)	1,420 children from western North Carolina	Followed from ages 9, 11, and 13 years to age 16 years	CAPA used to assess psychiatric symptoms	Disruptive behavior disorders and depression were associated with a higher rate and earlier onset of substance use and abuse in both sexes, but anxiety predicted later onset of smoking. Onset of conduct disorder and anxiety was well before the first use of any substance. Substance use and abuse of every type were more common among girls with behavior disorders; depressed boys, compared with nondepressed boys, had significantly higher rates of every type of substance use.
Conduct disorder, anxiety, depression, and substance use/abuse	Sung et al. (62)	1,420 children aged 9, 11, and 13 years from North Carolina	3–7 years (until participant aged 16 years, reviewed annually)	CAPA used in interviews; substance use, abuse, and dependence items used; psychiatric disorders classified by using DSM-IV criteria for symptoms experienced in the past 3 months	Conduct disorder, particularly at earlier ages (14 and 15 years) was the strongest psychiatric predictor of transition from substance use to a disorder (OR = 2.0 (95% CI: 1.2, 3.6)). Boys, but not girls, with a history of depression were at increased risk of substance use disorder; anxiety increased the risk of substance use disorder in girls at age 16 years.

* CIDI, Composite International Diagnostic Interview; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; OR, odds ratio; CI, confidence interval; DIA-X/M-CIDI, Munich-Composite International Diagnostic Interview; CAPA, Child and Adolescent Psychiatric Assessment; DSM-III-R, *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised; DISC, Diagnostic Interview Schedule for Children; IRR, incidence rate ratio; CES-D, Center for Epidemiological Studies Depression; DIS, Diagnostic Interview Schedule; K-SADS, Schedule for Affective Disorders and Schizophrenia and School-Age Children.

symptoms at follow-up, but depression did not predict substance use disorders at follow-up (34).

Adults. Comorbidity between depression and substance use persists until adulthood: there is a two- to four-fold higher risk of developing one disorder if the other has occurred (37, 38). As has been detected in adolescence and young adulthood, support also exists for the use of alcohol and illegal substances as a way to manage depressive symptoms in adulthood (37, 39–41). Several studies also document a reciprocal association between the two, as was the case with anxiety (42, 43). Gilman and Abraham (42) followed up participants from the Epidemiologic Catchment Area Survey and found that, although the odds of alcohol dependence increased in relation to baseline depressive symptoms, the odds of major depression also increased in response to the number of alcohol symptoms and a diagnosis of alcohol dependence.

Anxiety and depression

High rates of comorbidity have been found between anxiety and depression. An important fraction of depression cases also present symptoms of anxiety, to the point that Krueger et al. (8) proposed that “pure” cases of depression or anxiety would be unrepresentative of the entire spectrum of these disorders. In a 40-year follow-up of levels of anxiety and depression, the probability of having anxiety for those who already suffered from depression ranged from 0.54 to 0.98, while, for those who did not suffer from depression, the probability ranged from 0.03 to 0.10 (44). Anxiety and depression function in a cohesive manner and have been classified as internalizing disorders, which are stable over time (8, 45). The comorbidity of these disorders has raised some controversy. While some argue that anxiety and depression are distinct disorders with different etiologic profiles and high levels of cooccurrence, others interpret the overlap as indicative of similar psychopathologic processes and shared risks or as different manifestations of the same disease (26, 46).

Children and adolescents. Strong heterotypic continuity exists between depression and anxiety from childhood to adulthood (2, 18, 26, 47–51). In the Great Smoky Mountains study that followed a cohort of children aged 9–13 years for 5 years, anxiety predicted depression and vice versa, even when controlling for current comorbidity (18). A gender-specific analysis indicated, however, that the associations independent of current comorbidity persisted among girls only. Another study that followed those aged 9–18 years over 9 years found that overanxious disorder in adolescence was associated with adult major depression, while major depression in adolescence predicted generalized anxiety in adulthood (50). These associations were independent of gender.

The degree of comorbidity between depression and anxiety may vary as a function of age. Wittchen et al. (26) followed 3,021 respondents aged 14–24 years at baseline over 4 years and found that, although only 9 percent of those with an anxiety disorder at ages 14–17 years also had major depressive episodes, the proportion was considerably higher among those aged 18–24 years. Moreover, depression in-

creased considerably among those with anxiety disorder at final follow-up: almost two thirds of cases were comorbid with major depression. The variation in comorbidity by age might be a function of age at onset of the two disorders; whereas anxiety disorders tend to start in childhood and early adolescence, depressive disorders increase in late adolescence and continue to rise in those aged 20 years or older (2, 26, 52).

The frequency and type of comorbidity differ by disorder. Wittchen et al. (26) found that the odds ratio for presenting major depression at follow-up ranged from 1.7 for specific phobia to 3.4 for panic disorder and 3.9 for generalized anxiety disorder. Pine et al. (50) also found that major depression predicted generalized anxiety disorder but not simple or social phobia.

Comorbidity is related to symptom severity, degree of impairment, course, and outcome. Wittchen et al. (26) found, in a study of 3,021 respondents aged 14–24 years at first interview followed over 4–5 years, that the number of anxiety disorders present, persistence of anxious avoidance behavior, and degree of psychosocial impairment were the characteristics most strongly associated with development of secondary depression. Repetto et al. (51) confirmed, in a more restricted study of African-American adolescents at risk of school dropout, that adolescents who presented consistently high levels of depressive symptoms were more likely to present a higher number of anxiety symptoms.

Adults. Most studies have identified anxiety as a primary disorder that precedes secondary depression, perhaps related to the difference in ages at onset as well as to the higher degree of stability of anxiety. A critical review of longitudinal studies of representative samples, however, indicates that this question remains unsettled and may depend on life stage examined, length of study follow-up, and type of anxiety disorder studied. A follow-up of a representative population sample over 10 years from early adolescence to young adulthood found that social anxiety disorder was temporally primary relative to depression in most of the cases and that the risk of subsequent depression was twofold for individuals with social anxiety disorder in comparison to those without social anxiety disorder (53). However, a study that followed up a birth cohort until age 32 years (54) found that major depression preceded generalized anxiety disorder almost as often as generalized anxiety disorder preceded major depression. Two studies in older adulthood found that anxiety preceded depression within short time intervals. A study of older Swedish twins found that over two 3-year intervals, anxiety symptoms led to depressive symptoms, while the opposite did not occur (46). The same phenomenon was reported among the elderly for depression and generalized anxiety disorder: a follow-up of a sample of community-living elderly over 3 years found that generalized anxiety disorder either remitted or progressed into depression or mixed anxiety/depression, whereas subjects with depression or depression/generalized anxiety disorder were unlikely to develop noncomorbid generalized anxiety disorder at follow-up (12).

Comorbid disorders may be more stable than “pure” cases of disease. A study that followed adults aged 19–20 years at baseline over 15 years found that substantial

TABLE 2. Population studies on comorbid patterns between substance abuse, anxiety, depression and conduct disorder among adults

Comorbidity	Citation	Sample	Follow-up time	Measurement of disorders	Conclusions
Anxiety and substance use/abuse	de Graaf et al. (78)	7,076 adults aged 18–64 years from the Netherlands	Retrospective; used age at onset data	Diagnoses based on DSM-III-R* from the CIDI*	The association between major depression and alcohol or drug dependence was stronger than that for alcohol or drug abuse. Men were more likely than women to report major depression temporally secondary to any other disorder; of those who had ever experienced a mood disorder, 46% of males and 57% of females had a history of anxiety disorders, and 43% of males and 15% of females had a substance use disorder; in most anxiety-comorbid cases, mood disorder arose after anxiety disorder.
Anxiety and substance use/abuse	Kushner et al. (24)	454 incoming freshmen at a large university	At years 1, 4, and 7	Anxiety disorders (generalized anxiety disorder, social phobia, agoraphobia with panic attacks, panic attacks in the absence of agoraphobia): assessed with DIS* version III-R to use criteria from DSM-III; alcohol abuse/dependence: used DIS and DSM-III	Strong evidence was found for reciprocal causal influences between anxiety disorders and alcohol dependence; having an anxiety disorder at years 1 or 4 quadrupled the risk for new onset of alcohol dependence at year 7.
Anxiety and substance use/abuse	Newcomb et al. (31)	470 adults from Los Angeles, California	4 years	Polydrug problems assessed with items based on DSM-IV* criteria for drug abuse and dependence; anxiety (included in the agitation measure) measured by three items on a 5-point Likert rating scale, taken from the Hopkins Symptom Checklist	Early dysphoria directly increased agitation as an adult. Polydrug problems in young adulthood increased anxiety in adulthood. Social conformity accounted fully for the relation between polydrug problems and agitation. Marijuana problems in early adulthood increased later suicidal ideation. Early cocaine problems increased later hostility. Dysphoria in young adulthood increased alcohol problems but decreased cocaine abuse in later adulthood.
Anxiety and substance use/abuse	Sartor et al. (79)	1,269 offspring (average age, 20.1 years) of male twins from the Vietnam Era Twin Registry in the United States	Retrospective	Drinking outcomes measured with Semi-Structured Assessment for the Genetics of Alcoholism (onset defined as age at which full DSM-IV criteria were met); lifetime diagnoses for DSM-IV mood, anxiety, and conduct-related disorders also obtained	Nicotine dependence (HR* = 3.91 (95% CI*: 2.48, 6.17)) and generalized anxiety disorder (HR = 3.45 (95% CI: 2.08, 5.72)) were robust predictors of progression from first drink to alcohol dependence; conduct disorder (HR = 1.75 (95% CI: 1.10, 2.77)) and cannabis abuse (HR = 1.88 (95% CI: 1.22, 2.90)) were also associated with rapid transition to alcohol dependence.
Anxiety and substance use/abuse	Sonntag et al. (29)	2,548 individuals aged 14–15 years at baseline from Munich, Germany	Average, 19.7 months	Psychopathologic and diagnostic assessments based on the computer-assisted personal interview version of the DIA-X/M-CIDI*	When age/gender/comorbid depressive disorder were controlled for, baseline nonusers with at least one social fear but no social phobia diagnosis showed elevated odds for an occurrence of nicotine dependence in the follow-up period (OR* = 3.85 (95% CI: 1.34, 11.00)). All baseline, nondependent, regular smokers with social fears but not social phobia also showed higher odds for nicotine dependence (OR = 1.5 (95% CI: 1.01, 2.23)).
Anxiety and substance use/abuse	Bovasso (80)	1,920 individuals in the Baltimore (Maryland) Epidemiologic Catchment Area Survey	15 years	DIS assessed symptoms of DSM-III disorders at baseline and DSM-III-R symptoms at baseline; outcomes measured by using the 20-item version of Goldberg's General Health Questionnaire to assess general distress, DIS for psychiatric disorders, and DIS for symptoms of substance abuse/dependence	Anxiety/depression did not predispose individuals to substance use, and substance use did not predispose individuals to anxiety/depression.

Depression and substance use/abuse	Crum et al. (40)	1,920 adults from Baltimore, Maryland (average age, 41.7 years at baseline; range, 18-86)	Median 12.6 years of follow-up	Depression measured with DIS by using DSM-III criteria; alcohol dependence measured as 1) lifetime and 2) new onset; DSM-III criteria used at baseline and 1 year follow-up, DSM-III-R criteria used at 12.6-year follow-up	Depressive syndrome was associated with lifetime prevalence of alcohol dependence: for women, OR = 1.89 (95% CI: 1.16, 3.06), while, for men, OR = 1.83 (95% CI: 1.14, 2.93). Depressive syndrome was not associated with onset of alcohol dependence. Having a current or prior anxiety disorder increased the odds of alcohol dependence among women: OR = 2.35 (95% CI: 1.28, 4.32).
Depression and substance use/abuse	Dixit and Crum (41)	1,383 women from Baltimore, Maryland, ranging in age from 18 to ≥65 years, who did not report heavy alcohol use at baseline	1 year	Center for Epidemiologic Studies Depression Scale heavy alcohol use measured as five or more drinks at least once in the past month; depression measured with DIS by using DSM-III criteria	The estimated risk of heavy alcohol use for women with major depression, depressive syndrome, and/or dysthymia was 2.22 greater than the risk for women without such a history (95% CI: 1.00, 4.92). The adjusted relative risk of heavy alcohol use associated with an incremental number of lifetime-experienced depressive symptoms was estimated to be 1.09 (95% CI: 1.01, 1.18).
Depression and substance use/abuse	Gilman and Abraham (42)	14,480 respondents not meeting DSM-III criteria for alcohol dependence or lifetime major depression, mean age, 43 years (range, 18-96), in five US community sites located near Duke University; Johns Hopkins University; University of California, Los Angeles; Washington University; and Yale University	1 year	Both alcohol dependence and major depression measured with the DIS by using DSM-III criteria; administered by nonclinician interviewers	The odds of alcohol dependence associated with number of baseline depressive symptoms were, for females, 1-3 symptoms, OR = 2.75 (95% CI: 1.52, 5.00), 4-6 symptoms, OR = 3.52 (95% CI: 1.86, 6.66), ≥7 symptoms, OR = 7.88 (95% CI: 2.86, 21.70); for males, 1-3 symptoms, OR = 1.50 (95% CI: 1.08, 2.08). The odds of depression associated with 1-3, 4-6, and ≥7 alcoholic symptoms, respectively, were, for females, OR = 1.66 (95% CI: 1.05, 2.64), OR = 3.98 (95% CI: 2.37, 6.69), and OR = 4.32 (95% CI: 1.92, 9.75); for males, OR = 1.19 (95% CI: 0.76, 1.88) OR = 2.49 (95% CI: 1.26, 4.92), and OR = 2.12 (95% CI: 0.90, 5.00). The odds of major depression corresponding to a DSM-III alcohol dependence diagnosis were 3.52, 95% CI: 2.16, 5.72 for females and 1.77 (95% CI: 1.08, 2.91) for males.
Depression and substance use/abuse	Hettema et al. (43)	2,926 male and 1,929 female adult twin subjects aged 21-62 years in Richmond, Virginia	Retrospective (based on age-at-onset data)	Lifetime diagnoses for DSM-III-R major depressive disorder, generalized anxiety disorder, panic disorder, phobias, alcohol dependence, and psychoactive substance use disorder assessed via telephone and face-to-face structured psychiatric interviews based on the modified SCID*	Generalized anxiety disorder and major depressive disorder had the highest same-year onsets (about 41%); panic disorder tends to occur after major depressive disorder in females but before major depressive disorder in males; the majority of phobias precede major depressive disorder in both genders. Onset of alcohol dependence precedes that of major depressive disorder in about one third of cases; for psychoactive substance use disorder, onset for females was about evenly divided between those occurring before (44%) and after (49%) major depressive disorder, significantly more males (54%) reported onset before that of major depressive disorder. Generalized anxiety disorder and panic disorder cases had the highest risk of developing concurrent major depressive disorder, with same-year-onset HRs of 38.07 and 12.28, respectively.

Table continues

TABLE 2. Continued

Comorbidity	Citation	Sample	Follow-up time	Measurement of disorders	Conclusions
Depression and substance use/abuse	Kuo et al. (37)	7,477 twins, including 3,302 females with a mean age when last assessed of 36.5 years and 4,175 males with a mean age of 37.0 years in Virginia	Two measurements: waves 1 and 4 for female-to-female twin pairs and waves 1 and 2 for male-to-male and male-to-female twin pairs	DSM-III-R diagnoses of major depression and alcohol dependence assessed by using adapted versions of standard structured interviews (not specified)	Risk of developing alcohol dependence associated with lifetime or concurrent major depression was higher for males than for females. Risk of alcohol dependence in year 1 associated with major depression onset in the prior year was higher than that associated with lifetime major depression: twofold for males and fourfold for females. Among females, the risk of alcohol dependence associated with prior major depression was higher than that associated with concurrent major depression (HR = 5.1 vs. HR = 3.1). Lifetime alcohol dependence predicted increasing HR of major depression for both genders, and the effect was stronger for females. Concurrent alcohol dependence had the highest effects on major depression risk. However, compared with lifetime alcohol dependence, preceding alcohol dependence did not increase major depression risk.
Anxiety, depression, and substance use/abuse	de Graaf et al. (81)	4,796 adults from the Netherlands	Baseline, 1 year, 3 years	CIDI used	Of respondents who developed an incident disorder, 16.1% developed comorbid disorders; anxiety-comorbid mood disorder was the most frequent incident comorbid disorder among females, and both anxiety-comorbid and substance use-comorbid mood disorders were the most frequent among males.
Anxiety, depression, and substance use/abuse	John et al. (38)	Random adult population sample aged 18–64 years ($n = 4,075$) from northern Germany (Lubeck and surrounding communities)	Baseline, 30 months, and 36 months	Nicotine dependence, affective and anxiety disorders according to DSM-IV assessed with the computer-assisted DIA-X/M-CIDI	Male former or current daily smokers had higher odds ratios of affective and anxiety disorders: compared with male never smokers, male current daily smokers had 4.5 higher odds of having an anxiety disorder. Having 1–2 nicotine dependence symptoms was associated with higher odds of affective (OR = 1.7 (95% CI: 1.2, 2.4)) and anxiety (OR = 1.6 (95% CI: 1.2, 2.2)) disorders; having ≥ 3 symptoms was associated with 3.6 times higher odds of affective disorders (95% CI: 2.6, 5.0) and 3.7 higher odds of anxiety disorders (95% CI: 2.8, 5.0).
Anxiety and depression	Beesdo et al. (53)	3,021 individuals from Munich, Germany, aged 14–24 years at baseline and 21–34 years at follow-up	10 years	Individuals assessed with the DIA-X/M-CIDI	Social anxiety disorder was consistently associated with subsequent depression, independent of age at onset of social anxiety disorder (relative risk range: 1.49–1.85).
Anxiety and depression	Breslau et al. (48)	1,007 individuals from a list of all members of a large health maintenance organization aged 21–30 years in Michigan	3.5 years	DIS used, following DSM-III-R criteria	Higher lifetime prevalence of major depressive disorder in females vs. males was primarily for major depressive disorder comorbid with anxiety; prior history of an anxiety disorder was associated with increased risk of major depressive disorder in males and females. Prior anxiety disorder accounted for the higher prevalence of major depressive disorder in females.

Anxiety and depression	Breslau et al. (47)	1,007 individuals from a list of all members of a large health maintenance organization aged 21–30 years in Michigan	3.5 years	DIS used, following DSM-III-R criteria	Prior anxiety was associated with a higher risk of major depressive disorder in both sexes. Women were not more vulnerable than men to depression because of an anxiety disorder. Substance use disorder does not play the comparable role in men that anxiety plays in women in contributing to depression onset.
Anxiety and depression	de Graaf et al. (9)	7,065 adults aged 18–65 years in the Netherlands	Baseline, 1 year, 3 years	CIDI used	15.2% of pure mood, 10.5% of anxiety, and 6.8% of substance use disorder cases became comorbid; half the transitions from pure substance use disorders were into mood-comorbid and half into anxiety-comorbid.
Anxiety and depression	Grant et al. (57)	102 undergraduates with an average age of 18.64 years from an undergraduate college in the United States	1 year	Social anxiety measured by using the Social Phobia and Anxiety Inventory; depressive symptoms measured by using the Beck Depression Inventory	22% of the total effect of time 1 social anxiety on time 2 depressive symptoms was accounted for by avoidance of expressing emotions. Individuals with social anxiety disorder may develop depressive symptoms to the extent that they withhold strong emotions, which may lead to a feeling of loss of self.
Anxiety and depression	Merikangas et al. (55)	4,547 subjects (2,201 men and 2,346 women) aged 19 and 20 years representative of the canton of Zurich, Switzerland	15 years	The Structured Diagnostic Interview for Psychopathologic and Somatic Syndromes used to make diagnoses according to DSM-III and DSM-III-R criteria for most major categories	Concurrent comorbidity between anxiety and depression was highly stable across the 15 years of the study (OR range: 3.0–6.0); subjects with anxiety only had a moderate probability of developing depression only (OR range: 1.5–7.8), whereas those with depression only did not develop anxiety only (OR range: 0.3–1.8); substantial transitions from pure anxiety or pure depression to comorbid depression/anxiety (OR range: 1.5–10.0); women were more likely than men to transition from pure anxiety or depression to comorbid conditions at follow-up.
Anxiety and depression	Moffitt et al. (54)	1,037 members of a birth cohort (972 were assessed by the last measurement) in New Zealand	21 years (studied at ages 11, 13, 15, 18, 21, 26, and 32 years)	At ages 11, 13, and 15 years, diagnoses with DSM-III criteria made with the DISC*-Child Version and, at older ages, with the DIS (at ages 18 and 21 years, DSM-III-R; at ages 26 and 32 years, DSM-IV); both generalized anxiety disorder and major depressive disorder diagnosed	Cumulative prevalence of adult comorbid major depressive disorder + generalized anxiety disorder was 12% in the cohort; sequential and cumulative comorbidity was balanced: ≤37% of cases of depression were preceded by anxiety disorders, but 63% were not; the two disorders had strong cumulative lifetime comorbidity from ages 11 to 32 years (OR = 5.3 (95% CI: 3.9, 7.2)); of lifetime major depressive disorder cases, 48% had lifetime anxiety disorder; of lifetime anxiety cases, 72% had lifetime major depressive disorder.
Anxiety and depression	Wetherell et al. (46)	1,391 Swedish twins with an average age of 60.9 years at first measurement	Interviewed in 1987, 1990, and 1993	Depressive symptoms assessed with the Center for Epidemiologic Studies Depression Scale; anxiety assessed with the State Anxiety subscale of the State-Trait Personality Inventory	A two-factor model with latent depression and anxiety factors provided the best fit to the data; the two factors were highly correlated (0.84). Between 1987–1990 and 1990–1993, the parameters for the paths linking anxiety to subsequent depression were significant, whereas the paths linking depression to subsequent anxiety were not significant and could be dropped from the model.
Anxiety and depression	Wilhelm et al. (56)	156 young adults enrolled in a postgraduate teachers' training program in the United States	15 years	DIS and subsequently its newer form, CIDI, used to find cases of depression and anxiety; DIS and CIDI used to generate DSM-III and then DSM-III-R diagnoses	Subjects with two or more episodes of major depression had higher rates of meeting "major anxiety" and "all anxiety" status than those with one episode. Those with one episode had higher rates than subjects in the "no depression" group. Mean age at onset of simple phobia was significantly younger among those who had multiple episodes of depression. One of the best predictors to distinguish between "no depression" and "one or more episodes" was major anxiety.

Table continues

TABLE 2. Continued

Comorbidity	Citation	Sample	Follow-up time	Measurement of disorders	Conclusions
Anxiety and depression	Schoevers et al. (12)	2,173 subjects aged 65–84 years from the Amsterdam Study of the Elderly	3 years	Dutch translation of the Mini-Mental State Examination, the Geriatric Mental State Examination, the Activities of Daily Living scale, the Instrumental Activities of Daily Living scale, and the Cambridge Mental Disorders of the Elderly Examination interview used; diagnoses of depression, organic “caseness,” and generalized anxiety reached by use of the Geriatric Mental State–AGECAT system	Depression and generalized anxiety disorder together had a significantly worse prognosis (27% remission) than the “pure” categories: 4 of 199 subjects with depression developed generalized anxiety disorder (pure generalized anxiety disorder), but 27 (13.6%) developed pure depression/generalized anxiety disorder; subjects with pure depression/generalized anxiety disorder at baseline were more likely to keep the combined disorder than have it change into pure forms.
Conduct disorder and substance use/abuse	Nock et al. (82)	3,199 respondents aged 18–44 years in the National Comorbidity Survey Replication in the United States	Retrospective study (based on age-at-onset data)	Mental disorders assessed by using CIDI to generate diagnoses according to DSM-IV criteria and the ICD-10* diagnostic system	Oppositional defiant disorder is associated with substantial risk of secondary mood, anxiety, impulse-control, and substance use disorders; 92.4% of respondents with lifetime oppositional defiant disorder met criteria for at least one other lifetime disorder; oppositional defiant disorder was significantly comorbid with agoraphobia without panic disorder (OR = 2.1) and conduct disorder (OR = 12.6). The ORs for impulse control disorders were 4.0–12.6, and the ORs for anxiety disorders were 2.1–4.5.
Conduct disorder and substance use/abuse	Angst et al. (39)	591 adults (aged 19–20 years at baseline) selected from a representative sample of Zurich, Switzerland: two thirds were high scorers in the Symptom Checklist 90-R Global Severity Index (GSI), and one third were a random sample of those whose GSI score was below the 85th percentile	20 years	Alcohol abuse and dependence classified according to DSM-IV criteria; major depressive episodes defined by DSM-III criteria in the first two interviews (1979 and 1981) and DSM-III-R criteria in the last four interviews (1986, 1988, 1993, and 1999)	Major depressive episodes were associated with alcohol dependence but not with alcohol abuse: for men, OR = 3.8 (95% CI: 2.0, 7.1); for women, OR = 5.2 (95% CI: 1.8, 14.5).
Conduct disorder and substance use/abuse	Kratzer and Hodgins (63)	6,449 males and 6,268 females from Sweden	30 years	Conduct problems in school: teachers rating students on a 3-point scale at grades 6 and 9; conduct problems in the community: defined as children referred to the Child Welfare Committee; mental disorders: Stockholm county register screened to document admissions to psychiatric wards	Males identified with conduct problems in childhood were more likely than the no-conduct-problems group to develop substance abuse in adulthood; females identified with conduct problems in childhood were at greater risk than no-conduct-problems females for crime and for mental disorders in adulthood; a diagnosis of substance abuse accounted for most of the mental disorders among conduct-problem-school but not conduct-problem-community females.
Conduct disorder and depression	Johnson et al. (69)	658 individuals from New York	18–21 years total: assessed in 1983, 1985–1986, 1991–1993, and finally in 2001–2004	Axis I disorders assessed with DISC-I, the nonpatient version of the structured clinical interview for DSM-IV (SCID-IV-NP) at age 33 years; assessment of personality disorders with items from the Personality Diagnostic Questionnaire, the Structured Clinical Interview for Personality Disorders (SCID-II) and DISC-I	Individuals with a DSM-IV cluster A (paranoid, schizoid, or schizotypal) or cluster C (avoidant, dependent, obsessive-compulsive) panic disorder by mean age 22 years were at elevated risk of recurrent or chronic unipolar depression; antisocial, borderline, dependent, depressive, histrionic, and schizotypal panic disorder traits, identified between the ages of 14 and 22 years, were significantly associated with risk of dysthymic disorder or major depressive disorder.

Conduct disorder and anxiety	Johnson et al. (72)	658 individuals from Albany and Saratoga counties, New York	18–21 years total: assessed in 1983, 1985–1986, 1991–1993, and finally in 2001–2004	Axis I disorders assessed with DISC-I at ages 14–21 years, the nonpatient version of the structured clinical interview for DSM-IV (SCID-IV-NP) at age 33 years; personality disorders: Personality Diagnostic Questionnaire, the Structured Clinical Interview for Personality Disorders (SCID-II), and DISC-I used	Antisocial disorder between 14 and 22 years of age was associated with elevated risk of anxiety disorders by mean age 33 years. Antisocial personality traits were associated with risk of agoraphobia at age 33 years (OR = 1.68 (95% CI: 1.14, 2.47)).
Conduct disorder and anxiety	Nock et al. (82)	3,199 adults aged ≥ 18 years in the coterminous United States	Retrospective	CIDI to diagnose based on DSM-IV and ICD-10	Conduct disorder typically precedes mood and substance use disorders but occurs most often after impulse and anxiety disorders; presence of conduct disorder is associated with an elevated risk of substance use disorders (OR = 5.9); conduct disorder predicted the presence of comorbid anxiety disorders (OR = 1.5, $p = 0.038$).

* DSM-III-R, *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised; CIDI, Composite International Diagnostic Interview; DIS, Diagnostic Interview Schedule; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; HR, hazard ratio; CI, confidence interval; DIA-X/M-CIDI, Munich-Composite International Diagnostic Interview; OR, odds ratio; SCID, Structured Clinical Interview for DSM-III-R; DISC, Diagnostic Interview Schedule for Children; ICD-10, *International Statistical Classification of Disease and Related Health Problems*, Tenth Revision.

transitions occurred from anxiety and depression alone to comorbidity; an average of 21 percent of those with depression alone and 24 percent of those with anxiety alone developed comorbid anxiety and depression at baseline, and, once comorbidity developed, the recurrence of either disorder alone was much lower (55).

Specificity also exists in the degree of comorbidity between different types of anxiety disorders and depression. Generalized anxiety disorder has been identified as the type of anxiety disorder most closely connected with major depression (54). Wilhelm et al. (56) followed a cohort of subjects involved in teacher training in 1978–1993 and found a stronger association between number of depressive episodes and panic disorder, generalized anxiety disorder, and agoraphobia than between number of depressive episodes and either simple or social phobia. Gregory et al. (49) followed a representative birth cohort from ages 11 to 32 years and found that adult anxiety cases were more likely to have experienced juvenile depression than those without adult anxiety, except for specific phobia and panic disorder cases.

The specific nature of the associations between depression and anxiety may depend on certain interpersonal features of anxiety disorders. Two studies have found, for example, that behavioral inhibition (53) and avoidance of expressing emotions (57), rather than lack of assertion or interpersonal dependency, explained part of the transition from social anxiety disorder to depression. Grant et al. (57) hypothesized that inhibition of strong emotions to significant others as a strategy to maintain associations may lead to a loss of self, which may increase depressive symptoms.

Conduct disorder and substance use

Conduct disorder has been defined in the *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV* as a pervasive pattern of aggressive and deceptive behavior that begins in adolescence (58). Conduct disorder and substance use have been classified under the same latent construct of externalizing disorders (8). Measelle et al. (36) found, for example, that an externalizing factor accounted for 79 percent and 95 percent of the baseline levels of antisocial behavior and substance abuse, respectively. Both disorders tend to increase through late adolescence and peak in young adulthood, and they are more prevalent among males (59). Several studies have proposed that a major fraction of the association can be attributed to common genetic factors (45).

Children and adolescents. Most studies on conduct disorder and substance use concern adolescence and young adulthood. Similar to anxiety and depression, the directionality of the link between these conditions and conduct seems to vary across studies (18, 30, 49, 60–62). Cohen et al. (60) followed up 749 adolescents from ages 13 to 24 years and found that participants with conduct disorder in early adolescence experienced significantly elevated rates of alcohol abuse/dependency and marijuana use disorder between early adolescence and young adulthood. Kratzer and Hodgins (63) found a similar phenomenon when they followed an unselected birth cohort from pregnancy to 30 years of age: childhood conduct problems were associated with a higher risk of severe substance abuse. White et al. (64) moved

beyond examining the influence of conduct disorder on levels of substance abuse and investigated its influence on both mean levels of use and change in use over time. Although conduct disorder was associated with higher overall levels of alcohol and marijuana use throughout the study period, it predicted change in levels of alcohol use only. Participants with higher levels of conduct disorder began adolescence with higher levels of alcohol use, but their level of alcohol use grew slower than that among participants who had lower initial levels of conduct disorder—possibly because of regression to the mean.

Some of the most promising studies on comorbidity have investigated the impact that conduct disorder and substance abuse have on the developmental patterns of the comorbid disorder. Conduct disorder, for example, has been found to play an important role in the shift from substance use to substance use disorders (30, 65). The Great Smoky Mountains study found that conduct disorder, particularly at earlier ages (14 and 15 years), was the strongest psychiatric predictor of the transition from substance use to a disorder (62). Substance abuse can play a role in crime desistance in young adulthood (45, 66). Hussong et al. (66) found that substance abuse may exert both proximal and distal effects on antisocial desistance over young adulthood: 1) substance abuse early in young adulthood can slow an individual's pattern of criminal desistance relative to the lifetime pattern of criminality; and 2) substance abuse can result in "time-specific" elevations in antisocial behavior relative to an individual's own antisocial trajectory. A community sample of female adolescents aged 13–15 years found that, although initial levels of antisocial behavior predicted increases in substance abuse, substance abuse also predicted slower deceleration in antisocial behavior (36); a study of female and male twin pairs reported that youths with late-onset and persisting antisocial behavior had higher rates of substance use than youths in groups without a history of antisocial behavior or a pattern of antisocial desistance (67).

Adults. We found one study that examined the influence of conduct disorder on substance abuse but used retrospective reports of age at onset for comorbid disorders. The National Comorbidity Survey Replication indicated that lifetime conduct disorder was associated with 5.9 times higher odds for substance use disorders (58). Conduct disorder was more likely to occur before substance use disorders 88.5 percent of the time. Although both active and remitted conduct disorder were significant predictors of substance use disorders, the risk of substance use disorders was significantly higher for those with active conduct disorder. The persistent effect of remitted conduct disorder may indicate that conduct disorder is a risk marker for unmeasured common causes of substance use disorders or that active conduct disorder has long-lasting consequences that persist even after the disorder has remitted. The higher risk associated with active conduct disorder may also, however, point to a causal role that conduct disorder plays in related disorders.

Conduct disorder and anxiety and depressive disorders

The limited number of studies identified that addressed the connections between conduct disorder and either depres-

sion or anxiety led us to group the review of these disorders into one section. Factor analyses of internalizing disorders, notably anxiety and depression, and externalizing disorders, of which conduct disorder constitutes an important fraction, have identified distinct developmental patterns for these two groups of disorders but have also detected a correlation across time between the two types of disorders (8, 45). Little is understood about the mechanisms that may connect conduct disorder with mood disorders. Conduct disorder may disrupt interpersonal functioning, contributing to greater conflict with parents and peers and greater social rejection and academic failure, which may generate a sense of repeated failure and feelings of anxiety or depression (68). At the same time, depression and anxiety may impede social development and generate interpersonal conflict, which may contribute to the onset of conduct problems. Common etiologic factors may also underlie both types of disorders (69).

The developmental course of conduct disorder tends to be intertwined with internalizing problems, particularly depression (36). For example, a study involving a community sample of female adolescents followed from early to late adolescence found that initial depressive and antisocial behavior symptoms predicted future increases in the other: while initial levels of antisocial symptoms predicted increases in depressive symptoms, initial levels of depression predicted a slower deceleration in antisocial problems (36). Early antisocial problems have also been found to predict depressive symptoms in adulthood (69–71). Kim et al. (70) found that, among young men followed from early adolescence to young adulthood, early antisocial behavior was associated with depressive symptoms in adulthood; Silberg et al. (71) detected a correlation between early conduct problems and later depression among adolescent female twin pairs. The link may be explained by a failure model, whereby early developmental failures associated with antisocial behavior increase vulnerability to depressive symptoms (36).

Some evidence also exists of a link between conduct disorder and specific types of anxiety (49, 58, 61, 72). A birth cohort of a representative sample followed from ages 11 to 32 years showed an association between a juvenile history of conduct disorder and posttraumatic stress disorder at age 32 years (49). A longitudinal study of a population sample assessed from ages 14 to 33 years also found that the presence of antisocial personality disorder traits at ages 14–22 years was associated with a higher risk of anxiety disorders by age 33 years, most particularly for agoraphobia (72). The National Comorbidity Survey Replication found mixed evidence about the temporal order between conduct disorder and anxiety: conduct disorder occurred after specific and social phobia but prior to all other types of anxiety disorders (58). The findings from the National Comorbidity Survey Replication require replication within a longitudinal study because they are based on retrospective reports of age at onset.

Putting it all together: internalizing and externalizing disorders as predictors of substance abuse

Most studies on comorbidity assess the interaction between pairs of disorders concurrently and over time, but

they fail to determine how clusters of disorders may promote onset of psychopathology. One exception has been the area of youth risk behaviors; selected studies have investigated the relative influence of externalizing and internalizing disorders on the prevalence of substance abuse or conduct disorder. Adolescence has long been considered the stage at which risk behaviors such as delinquency and substance use are initiated and when disorders such as substance abuse become consolidated (36, 73). It is a time when multiproblem youth emerge, characterized by persistent substance use, persistent delinquency, and/or persistent internalizing problems (74). This peak in comorbidity has motivated studies of the intersections between multiple forms of psychopathology in adolescence and young adulthood.

Loeber et al. (74), for example, used longitudinal data from three samples of the Pittsburgh Youth Study to examine the cooccurrence of persistent substance use with delinquent and persistent internalizing problems in boys aged 7–18 years. The joint occurrence of mood dysregulation, in the form of internalizing problems, and behavioral dysregulation, in the form of delinquency, emerged in preadolescence and played a significant role in the persistence of substance use. During adolescence, however, only persistent delinquency predicted persistent substance use. Another publication using the Pittsburgh Youth Study expanded this investigation by examining how the cooccurrence of conduct disorder and depressive symptoms identified high-risk youth (25). The authors found that higher levels of depression led to the development of alcohol use disorder symptoms but among only those subjects who had high levels of early conduct disorder symptoms. The interaction between depression and conduct disorder may indicate a need to manage negative affective states without a high regard for social norms, or it may indicate a subgroup of individuals at particularly high risk of developing a severe form of substance use.

Summary

Prospective population studies that investigate the sequential links between comorbid disorders remain scarce. The bulk of prospective studies assess the influence of the prevalence of one disorder on the future prevalence of the comorbid disorder. Few studies actually move beyond this topic to investigate the influence that comorbidity may have on changes in the state of psychopathology, that is, in shifts from persistence to desistance, or from substance use to abuse, or from disorder-free status to onset. Such information would provide initial evidence of the specific mechanisms by which disorders influence each other. Moreover, differences in the duration of study follow-up, choice of age groups, and selections of measurement instruments and diagnostic criteria make comparability across studies more difficult.

Despite these limitations, several points emerge from our review of population-based studies of comorbid disorders. The concurrent and sequential links among conduct disorder, substance use/abuse, anxiety, and depression are neither random nor a result of bias from help-seeking clinical sam-

ples. The nature of comorbidity is specific to the type of disorder under study: evidence exists for a reciprocal relation between substance use and depression, anxiety, and conduct disorder, while the bulk of studies on depression and anxiety indicate that anxiety may precede onset of depression. The studies that address comorbidity of conduct disorder with anxiety and depression indicate that conduct disorder may precede these mood disorders, but the paucity of studies that test a reciprocal association impede us from making conclusive statements.

The mechanisms that connect disorders remain in question. Three hypotheses link comorbid disorders: 1) the association may be indirectly causal, so that a primary disorder may exert neurophysiologic, individual, or social changes that increase vulnerability to the secondary disorder; 2) disorders may be directly linked, so a primary disorder may, for example, exert neurophysiologic changes that contribute to onset of the secondary disorder; or 3) a set of common risk factors, such as common genes or the experience of childhood trauma, may explain the connection between two disorders. However, these hypotheses are difficult to distinguish from one another. For example, a social factor such as affiliation with deviant peers could predispose adolescents to both substance use disorder and conduct disorder (hypothesis 3), but conduct disorder could also lead to association with deviant peers, which would contribute to substance use disorder (hypothesis 1). A review of the risk factors associated with the initiation and maintenance of comorbid conditions can help illuminate the mechanisms that underlie comorbidity in psychopathology.

CONCLUSIONS

Understanding patterns of comorbidity is essential in order to evaluate psychiatric nosology and fully understand the developmental trajectories of key forms of psychopathology. To date, a number of studies have shown that anxiety, depression, substance abuse, and conduct disorder cluster in individuals across the life course. This critical review is one of the first focused on population-based, longitudinal studies of comorbidity between these four key disorders.

The four psychiatric disorders we reviewed have been classified under two latent constructs: externalizing and internalizing disorders. Although factor analyses indicate a higher correlation between disorders within each construct, clustering also exists between externalizing and internalizing disorders. Approaching first the issue of internalizing disorders, anxiety and depression function jointly from childhood to adulthood. Comorbidity seems to be a function of age; it increases from late adolescence onward, possibly because of the later age at onset of depression relative to anxiety. Comorbidity also depends on the type of anxiety disorder concerned: several studies found a higher clustering between major depressive disorder and generalized anxiety disorder, for example, than with other anxiety disorders. In terms of externalizing disorders, conduct disorder and substance abuse show a strong reciprocal link, particularly in adolescence and young adulthood.

Conduct disorder and substance abuse not only influence the onset and prevalence of the other but also influence the shift between developmental stages of the other disorder, that is, in shifts from substance use to a substance use disorder, or in the likelihood of moving from conduct disorder to desistance.

Studies have documented a link between disorders across the internalizing/externalizing divide. Studies indicate that the relation between substance abuse and anxiety or depression is reciprocal: substance abuse alone or depression/anxiety alone predicts onset of the other disorder. The impact of anxiety on substance abuse remains in question: anxiety disorders have been associated with both a higher and a lower likelihood of substance use disorders. The direction of the association may depend on the type of anxiety disorder and substance in question. Research has also addressed the question of clustering between conduct disorder and anxiety/depression, although research is less developed in this area. Depression and conduct disorder play a role in shaping the developmental trajectory of the other. Initial levels of depression have been associated with a slower rate of desistance from conduct disorder, while conduct disorder predicted increases in depressive symptoms from adolescence to adulthood. The links between anxiety and conduct disorder are less understood. The few existing studies focus on adolescence and young adulthood and have indicated that initial levels of conduct disorder were associated with higher levels of anxiety.

Existing research on comorbidity has a number of strengths. Prospective studies linking the presence of one disorder to onset of the other, as well as examining the influence that a disorder may have on developmental shifts in comorbidities, are growing, and they offer promise in enabling us to understand the specific ways in which comorbid disorders are linked over the life course. Moreover, research is shifting from a focus on a pair of disorders to a more holistic approach that analyzes how clusters of disorders interact with each other. We think this line of investigation will be key in understanding the complexity of comorbid relations and in estimating the health burden that results from multiple comorbidities.

At the same time, the epidemiologic literature falls short in its consideration of key issues within comorbidity research. First, although early research in this area is promising, a need exists for study designs that make it possible to test the timing and specific nature of comorbid relations—that is, shifting from merely investigating whether disorders are “associated” with each other to understanding the ways that disorders deflect a comorbid pair from specific stages in its normative trajectory. This process involves studying the influence of disorders in promoting qualitative shifts in the comorbid disorder, from alcohol use initiation to abuse to dependence, for example. It also implies accounting for the spectrum of relevant comorbid disorders within the same study to control for spurious associations and understand how the presence of a third disorder may influence the causal link between comorbid pairs.

Second, our understanding is limited in terms of the specific comorbid patterns between subtypes of disorders. Although we recognize that specific types of anxiety disorders,

for example, may show different comorbidity patterns with depression, or that alcohol abuse may have different levels of comorbidity with anxiety than illicit drug abuse does, the scarcity of available, population-based, longitudinal studies on each specific subtype combination prevented us from making critical distinctions between comorbid patterns. Studies that compare comorbid patterns between disorder subtypes across key developmental stages, from childhood to adulthood, offer a promising way to address this gap.

Third, one of the key questions that remains relates to the causes of comorbidity: the direction and mechanisms underlying causal links, as well as the potential spurious nature of such links. Investigating factors at multiple levels of influence as potential confounders, mediators, triggers, or modifiers of comorbid associations would enable us to identify groups at highest risk of the presentation of multiple disorders and distinguish features of the individual and his or her environment that are most malleable to preventive intervention. Moreover, it would enable us to establish whether associations between comorbid disorders are truly causal or are spurious phenomena resulting from common risk factors. Little effort has been invested in systematically documenting the associations between these disorders across different age groups or in reviewing the factors associated with the cooccurrence of such comorbid forms of psychopathology. Multilevel multivariate models that consider the joint influence of factors at the individual, family, and community levels on a set of comorbid disorders provide a promising avenue to attack the question of common versus distinct etiologies of comorbid disorders.

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REFERENCES

1. de Graaf R, Bijl RV, Smith F, et al. Risk factors for 12-month comorbidity of mood, anxiety, and substance use disorders: findings from the Netherlands Mental Health Survey and Incidence Study. *Am J Psychiatry* 2002;159:620–9.
2. Stein MB, Fuetsch M, Muller N, et al. Social anxiety disorder and the risk of depression—a prospective community study of adolescents and young adults. *Arch Gen Psychiatry* 2001;58:251–6.
3. Angold A, Costello EJ, Erkanli A. Comorbidity. *J Child Psychol Psychiatry* 1999;40:57–87.
4. Angst J. Comorbidity of mood disorders: a longitudinal prospective study. *Br J Psychiatry* 1996;168:31–7.
5. Kendler KS, Prescott CA, Myers J, et al. The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Arch Gen Psychiatry* 2003;60:929–37.

6. Bourdon KH, Rae DS, Locke BZ, et al. Estimating the prevalence of mental disorders in U.S. adults from the Epidemiologic Catchment Area Survey. *Public Health Rep* 1992;107:663–8.
7. Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005;62:593–602.
8. Krueger RF, Caspi A, Moffitt TE, et al. The structure and stability of common mental disorders (DSM-III-R): a longitudinal-epidemiological study. *J Abnorm Psychol* 1998;107:216–27.
9. de Graaf R, Bijl RV, ten Have M, et al. Pathways to comorbidity: the transition of pure mood, anxiety and substance use disorders into comorbid conditions in a longitudinal population-based study. *J Affect Disord* 2004;82:461–7.
10. Bakken K, Landheim AS, Vaglum P. Axis I and II disorders as long-term predictors of mental distress: a six-year prospective follow-up of substance-dependent patients. *BMC Psychiatry* 2007;7:29–41.
11. Renouf AG, Kovacs M, Mukerji P. Relationship of depressive, conduct, and comorbid disorders and social functioning in childhood. *J Am Acad Child Adolesc Psychiatry* 1997;36:998–1004.
12. Schoevers RA, Deeg DJH, van Tilburg W, et al. Depression and generalized anxiety disorder—co-occurrence and longitudinal patterns in elderly patients. *Am J Geriatr Psychiatry* 2005;13:31–9.
13. Aseltine RH, Gore S, Colten ME. The co-occurrence of depression and substance abuse in late adolescence. *Dev Psychopathol* 1998;10:549–70.
14. Kraemer HC, Wilson KA, Hayward C. Lifetime prevalence and pseudocomorbidity in psychiatric research. *Arch Gen Psychiatry* 2006;63:604–8.
15. Kessler RC, Chiu WT, Demler O, et al. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005;62:617–27.
16. Merikangas KR, Angst J, Eaton W, et al. Comorbidity and boundaries of affective disorders with anxiety disorders and substance misuse: results of an international task force. *Br J Psychiatry Suppl* 1996;Jun:58–67.
17. Kushner MG, Abrams K, Borchardt C. The relationship between anxiety disorders and alcohol use disorders: a review of major perspectives and findings. *Clin Psychol Rev* 2000;20:149–71.
18. Costello EJ, Mustillo S, Erkanli A, et al. Prevalence and development of psychiatric disorders in childhood and adolescence. *Arch Gen Psychiatry* 2003;60:837–44.
19. Dierker LC, Avenevoli S, Merikangas KR, et al. Association between psychiatric disorders and the progression of tobacco use behaviors. *J Am Acad Child Adolesc Psychiatry* 2001;40:1159–67.
20. Goodwin RD, Fergusson DM, Horwood LJ. Association between anxiety disorders and substance use disorders among young persons: results of a 21-year longitudinal study. *J Psychiatr Res* 2004;38:295–304.
21. Hayatbakhsh MR, Najman JM, Jamrozik K, et al. Cannabis and anxiety and depression in young adults: a large prospective study. *J Am Acad Child Adolesc Psychiatry* 2007;46:408–17.
22. Zimmermann P, Wittchen HU, Hofler M, et al. Primary anxiety disorders and the development of subsequent alcohol use disorders: a 4-year community study of adolescents and young adults. *Psychol Med* 2003;33:1211–22.
23. Costello EJ, Egger HL, Angold A. The developmental epidemiology of anxiety disorders: phenomenology, prevalence, and comorbidity. *Child Adolesc Psychiatr N Am* 2005;14:631–48.
24. Kushner MG, Sher KJ, Erickson DJ. Prospective analysis of the relation between DSM-III anxiety disorders and alcohol use disorders. *Am J Psychiatry* 1999;156:723–32.
25. Pardini D, White HR, Stouthamer-Loeber M. Early adolescent psychopathology as a predictor of alcohol use disorders by young adulthood. *Drug Alcohol Depend* 2007;88(suppl):S38–49.
26. Wittchen HU, Kessler RC, Pfister H, et al. Why do people with anxiety disorders become depressed? A prospective-longitudinal community study. *Acta Psychiatr Scand* 2000;102:14–23.
27. Wittchen HU, Frohlich C, Behrendt S, et al. Cannabis use and cannabis use disorders and their relationship to mental disorders: a 10-year prospective-longitudinal community study in adolescents. *Drug Alcohol Depend* 2007;88(suppl):S60–70.
28. Kaplow JB, Curran PJ, Angold A, et al. The prospective relation between dimensions of anxiety and the initiation of adolescent alcohol use. *J Clin Child Psychol* 2001;30:316–26.
29. Sonntag H, Wittchen HU, Hofler M, et al. Are social fears and DSM-IV social anxiety disorder associated with smoking and nicotine dependence in adolescents and young adults? *Eur Psychiatry* 2000;15:67–74.
30. Costello EJ, Erkanli A, Federman E, et al. Development of psychiatric comorbidity with substance abuse in adolescents: effects of timing and sex. *J Clin Child Psychol* 1999;28:298–311.
31. Newcomb MD, Vargas-Carmona J, Galaif ER. Drug problems and psychological distress among a community sample of adults: predictors, consequences, or confound? *J Community Psychol* 1999;27:405–29.
32. Chinet L, Plancherel B, Bolognini M, et al. Substance use and depression. Comparative course in adolescents. *Eur Child Adolesc Psychiatry* 2006;15:149–55.
33. Fergusson DM, Goodwin RD, Horwood LJ. Major depression and cigarette smoking: results of a 21-year longitudinal study. *Psychol Med* 2003;33:1357–67.
34. Rao U, Daley SE, Hammen C. Relationship between depression and substance use disorders in adolescent women during the transition to adulthood. *J Am Acad Child Adolesc Psychiatry* 2000;39:215–31.
35. Windle M, Davies PT. Depression and heavy alcohol use among adolescents: concurrent and prospective relations. *Dev Psychopathol* 1999;11:823–44.
36. Measelle JR, Slice E, Hogansen JM. Developmental trajectories of co-occurring depressive, eating, antisocial and substance abuse problems in female adolescents. *J Abnorm Psychol* 2006;115:524–38.
37. Kuo PH, Gardner CO, Kendler KS, et al. The temporal relationship of the onsets of alcohol dependence and major depression: using a genetically informative study design. *Psychol Med* 2006;36:1153–62.
38. John U, Meyer C, Rumpf HJ, et al. Smoking, nicotine dependence and psychiatric comorbidity—a population-based study including smoking cessation after three years. *Drug Alcohol Depend* 2004;76:287–95.
39. Angst J, Gamma A, Endrass J, et al. Is the association of alcohol use disorders with major depressive disorder a consequence of undiagnosed bipolar-II disorder? *Eur Arch Psychiatry Clin Neurosci* 2006;256:452–7.

40. Crum RM, Storr CL, Chan YF. Depression syndromes with risk of alcohol dependence in adulthood: a latent class analysis. *Drug Alcohol Depend* 2005;79:71–81.
41. Dixit AR, Crum RM. Prospective study of depression and the risk of heavy alcohol use in women. *Am J Psychiatry* 2000;157:751–8.
42. Gilman SE, Abraham HD. A longitudinal study of the order of onset of alcohol dependence and major depression. *Drug Alcohol Depend* 2001;63:277–86.
43. Hettema JM, Prescott CA, Kendler KS. The effects of anxiety, substance use and conduct disorders on risk of major depressive disorder. *Psychol Med* 2003;33:1423–32.
44. Murphy JM, Horton NJ, Laird NM, et al. Anxiety and depression: a 40-year perspective on relationships regarding prevalence, distribution, and comorbidity. *Acta Psychiatr Scand* 2004;109:355–75.
45. Krueger RF, Hicks BM, Patrick CJ, et al. Etiologic connections among substance dependence, antisocial behavior, and personality: modeling the externalizing spectrum. *J Abnorm Psychol* 2002;111:411–24.
46. Wetherell JL, Gatz M, Pedersen NL. A longitudinal analysis of anxiety and depressive symptoms. *Psychol Aging* 2001;16:187–95.
47. Breslau N, Chilcoat H, Schultz LR. Anxiety disorders and the emergence of sex differences in major depression. *J Genet Specif Med* 1998;1:33–9.
48. Breslau N, Schultz L, Peterson E. Sex differences in depression: a role for preexisting anxiety. *Psychiatry Res* 1995;58:1–12.
49. Gregory AM, Caspi A, Moffitt TE, et al. Juvenile mental health histories of adults with anxiety disorders. *Am J Psychiatry* 2007;164:301–8.
50. Pine DS, Cohen P, Gurley D, et al. The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. *Arch Gen Psychiatry* 1998;55:56–64.
51. Repetto PB, Caldwell CH, Zimmerman MA. Trajectories of depressive symptoms among high risk African-American adolescents. *J Adolesc Health* 2004;35:468–77.
52. Wittchen HU, Nelson CB, Lachner G. Prevalence of mental disorders and psychosocial impairments in adolescents and young adults. *Psychol Med* 1998;28:109–26.
53. Beesdo K, Bittner A, Pine DS, et al. Incidence of social anxiety disorder and the consistent risk for secondary depression in the first three decades of life. *Arch Gen Psychiatry* 2007;64:903–12.
54. Moffitt TE, Harrington H, Caspi A, et al. Depression and generalized anxiety disorder—cumulative and sequential comorbidity in a birth cohort followed prospectively to age 32 years. *Arch Gen Psychiatry* 2007;64:651–60.
55. Merikangas KR, Zhang HP, Avenevoli S, et al. Longitudinal trajectories of depression and anxiety in a prospective community study—the Zurich cohort study. *Arch Gen Psychiatry* 2003;60:993–1000.
56. Wilhelm K, Parker G, Dewhurst-Savellis J, et al. Psychological predictors of single and recurrent major depressive episodes. *J Affect Disord* 1999;54:139–47.
57. Grant DM, Beck JG, Farrow SM, et al. Do interpersonal features of social anxiety influence the development of depressive symptoms? *Cogn Emot* 2007;21:646–63.
58. Nock MK, Kazdin AE, Hiripi E, et al. Prevalence, subtypes, and correlates of DSM-IV conduct disorder in the National Comorbidity Survey Replication. *Psychol Med* 2006;36:699–710.
59. Hicks BM, Blonigen DM, Kramer MD, et al. Gender differences and developmental change in externalizing disorders from late adolescence to early adulthood: a longitudinal twin study. *J Abnorm Psychol* 2007;116:433–47.
60. Cohen P, Chen H, Crawford TN, et al. Personality disorders in early adolescence and the development of later substance use disorders in the general population. *Drug Alcohol Depend* 2007;88(suppl):S71–84.
61. Lavigne JV, Cicchetti C, Gibbons RD, et al. Oppositional defiant disorder with onset in preschool years: longitudinal stability and pathways to other disorders. *J Am Acad Child Adolesc Psychiatry* 2001;40:1393–400.
62. Sung MJ, Erkanli A, Angold A, et al. Effects of age at first substance use and psychiatric comorbidity on the development of substance use disorders. *Drug Alcohol Depend* 2004;75:287–99.
63. Kratzer L, Hodgins S. Adult outcomes of child conduct problems: a cohort study. *J Abnorm Child Psychol* 1997;25:65–81.
64. White HR, Xie MG, Thompson W, et al. Psychopathology as a predictor of adolescent drug use trajectories. *Psychol Addict Behav* 2001;15:210–18.
65. Robins LN, McEvoy L. Conduct problems as predictors of substance abuse. In: Robins LN, Rutter M, eds. *Straight and devious pathways from childhood to adulthood*. Cambridge, United Kingdom: Cambridge University Press, 1990:182–204.
66. Hussong AM, Curran PJ, Moffitt TE, et al. Substance abuse hinders desistance in young adults' antisocial behavior. *Dev Psychopathol* 2004;16:1029–46.
67. Marmorstein NR, Iacono WG. Longitudinal follow-up of adolescents with late-onset antisocial behavior: a pathological yet overlooked group. *J Am Acad Child Adolesc Psychiatry* 2005;44:1284–91.
68. Ingoldsby EM, Kohl GO, McMahon RJ, et al. Conduct problems, depressive symptomatology and their co-occurring presentation in childhood as predictors of adjustment in early adolescence. *J Abnorm Child Psychol* 2006;34:603–21.
69. Johnson JG, Cohen P, Kasen S, et al. Personality disorder traits associated with risk for unipolar depression during middle adulthood. *Psychiatry Res* 2005;136:113–21.
70. Kim HK, Capaldi DM, Stoolmiller M. Depressive symptoms across adolescence and young adulthood in men: predictions from parental and contextual risk factors. *Dev Psychopathol* 2003;15:469–95.
71. Silberg J, Rutter M, D'Onofrio B, et al. Genetic and environmental risk factors in adolescent substance use. *J Child Psychol Psychiatry* 2003;44:664–76.
72. Johnson JG, Cohen P, Kasen S, et al. Personality disorders evident by early adulthood and risk for anxiety disorders during middle adulthood. *J Anxiety Disord* 2006;20:408–26.
73. Wiesner M, Windle M. Young adult substance use and depression as a consequence of delinquency trajectories during middle adolescence. *J Res Adolesc* 2006;16:239–63.
74. Loeber R, Stouthamer-Loeber M, White HR. Developmental aspects of delinquency and internalizing problems and their association with persistent juvenile substance use between ages 7 and 18. *J Clin Child Psychol* 1999;28:322–32.
75. Juon HS, Ensminger ME, Sydnor KD. A longitudinal study of developmental trajectories to young adult cigarette smoking. *Drug Alcohol Depend* 2002;66:303–14.
76. Stice E, Barrera M Jr, Chassin L. Prospective differential prediction of adolescent alcohol use and problem use: examining mechanisms of effect. *J Abnorm Psychol* 1998;107:616–28.

77. Rohde P, Lewinsohn PM, Seeley JR. Psychiatric comorbidity with problematic alcohol use in high school students. *J Am Acad Child Adolesc Psychiatry* 1996;35:101–9.
78. de Graaf R, Bijl RV, Spijker J, et al. Temporal sequencing of lifetime mood disorders in relation to comorbid anxiety and substance use disorders—findings from the Netherlands Mental Health Survey and Incidence Study. *Soc Psychiatry Psychiatr Epidemiol* 2003;38:1–11.
79. Sartor CE, Lynskey MT, Heath AC, et al. The role of childhood risk factors in initiation of alcohol use and progression to alcohol dependence. *Addiction* 2007;102:216–25.
80. Bovasso G. The long-term treatment outcomes of depression and anxiety comorbid with substance abuse. *J Behav Health Serv Res* 2001;28:42–57.
81. de Graaf R, Bijl RV, ten Have M, et al. Rapid onset of comorbidity of common mental disorders: findings from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Acta Psychiatr Scand* 2004;109:55–63.
82. Nock MK, Kazdin AE, Hiripi E, et al. Lifetime prevalence, correlates, and persistence of oppositional defiant disorder: results from the National Comorbidity Survey Replication. *J Child Psychol Psychiatry* 2007;48:703–13.