Relationships Among Independent Major Depressions, Alcohol Use, and Other Substance Use and Related Problems Over 30 Years in 397 Families

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ABSTRACT. Objective: Although heavy drinking is related to sadness on multiple levels, the link between alcohol use disorders (AUDs) and major depressive episodes (MDEs) is more controversial. One complicating factor is that some MDEs are temporary and only occur in the context of heavy drinking, whereas other MDEs are longer lasting and occur independently of intense alcohol intake (i.e., independent depressive episodes [IDEs]). We hypothesized that a longitudinal study that uses validated interviews with subjects and relatives and distinguishes between IDEs and alcohol-induced depressive episodes would reveal little evidence of a link between IDEs and AUDs. **Method:** Histories of AUDs, IDEs, and substance-induced depressions were prospectively evaluated over 30 years in 397 male probands from the San Diego Pro-

spective Study and in their 449 offspring using questions extracted from the Semi-Structured Assessment for the Genetics of Alcoholism interview. **Results:** The rate of IDEs over 30 years in the 397 probands was 15.3% overall. Among probands who developed AUDs, 31% of their depressive episodes were substance induced, not IDEs. For these men followed over 3 decades, those with IDEs had no increased rate of AUDs and evidenced no higher rate of use or abuse/dependence on illicit substances. Similar conclusions applied to their 449 offspring ages 12 years and older. **Conclusions:** These data support the importance of distinguishing between IDE and substance-induced depressions when evaluating the relationship between AUDs and depression syndromes. (*J. Stud. Alcohol Drugs*, 74, 271–279, 2013)

MOOD DISTURBANCES, INCLUDING major depressive episodes (MDEs), have been reported to be related to heavy drinking and alcohol use disorders (AUDs) (Crum et al., 2005, 2008; Mueller et al., 1994; Schuckit, 2006, 2009; Weissman et al., 2006). The most consistent data are seen for the link between AUDs and mania, where both the clinical course and family histories of the two disorders overlap, several gene variations have been reported to potentially affect both conditions, and at least one genetically influenced characteristic that increases the risk for later AUDs—the low level of response (or low sensitivity) to alcohol—has been documented in individuals at a high risk for manic episodes (Schuckit et al., 2003; Yip et al., 2012).

The relationship of heavy drinking and alcohol problems to MDEs is more controversial. Epidemiological studies have reported that MDEs and AUDs often occur together (Grant et al., 2004; Hasin and Grant, 2002). The comorbidity between these conditions may be particularly obvious because MDEs and AUDs are among the most common psychiatric disorders in Western societies, with lifetime rates approaching 15% for each, a finding that could contribute to a high prevalence of their comorbidity even if no cause-and-effect

relationship exists (Bierut et al., 1999; Hasin et al., 2005; Prescott et al., 2000; Schuckit et al., 2007). Any relationship between MDEs and AUDs may also stand out to researchers and clinicians because the coexistence of these two conditions may contribute to relapses for both disorders and may make the treatment of the mood condition and the alcohol-related problems more challenging (Crum et al., 2005, 2008; Hasin et al., 1996; Schuckit, 2006).

Also, alcohol itself can produce temporary negative mood swings (not necessarily independent MDEs), especially when consumed in high doses (Birnbaum et al., 1983; Howland et al., 2010; Isbell et al., 1955; Tamerin and Mendelson, 1969), in part by increasing life stresses associated with alcohol problems, causing elevations in stress hormones, and activating brain regions related to stress and negative moods (Childs et al., 2011; King and Chassin, 2008; Schuckit et al., 1988; Sommer et al., 2008). Such effects might be particularly important in individuals predisposed toward major depression, in whom heavy drinking could facilitate the expression of those depressive syndromes (Caspi et al., 2010; Kahler et al., 2002; Wu et al., 2008).

A link between mood disorders and AUDs would suggest that MDEs earlier in life might increase the risk for later heavy drinking and AUDs (Crum et al., 2008; Dixit and Crum, 2000). It has been hypothesized that depressed individuals might use alcohol to reduce tension and stress, perhaps through learning to imbibe alcohol as a way of coping after observing similar behaviors among relatives and peers (Crum et al., 2008; Henry et al., 2005; Palfai et al., 2007; Schuckit et al., 2009). Early life depressive episodes

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might also interfere with educational achievement and job performance, potentially producing stresses associated with lower incomes and fewer social supports, with a resulting heavier use of alcohol to cope with life problems (Childs et al., 2011; King and Chassin, 2008). Some support for the role of MDEs as precursors of later alcohol disorders comes from follow-up studies of alcohol-related outcomes in individuals with earlier onset major depressions (e.g., Crum et al., 2008). On the other hand, at least one report noted a tendency for a decrease in alcohol use following depressive syndromes (Hartka et al., 1991), and several studies found no significant increase in later AUDs for individuals with childhood and adolescent depressive episodes, while these same subjects demonstrated the expected increased risk for major depressions at follow-up (Ferguson and Woodward, 2002; Harrington et al., 1990; Rao et al., 1995; Weissman et al., 1999).

A related approach for evaluating the comorbidity between mood disorders and alcohol problems takes advantage of the fact that both major depressions and AUDs are genetically influenced (McGuffin et al., 2007; Schuckit, 2009). These studies have looked at the potential familial crossover between major depressive and alcohol-related syndromes but with mixed results. Some studies reported an increased risk for AUDs in offspring of parents with MDEs (e.g., Weissman et al., 2006), but in others, having a relative with major depressions that occurred in the absence of heavy intake of alcohol or other drugs (i.e., independent depressive episodes [IDEs]) did not correlate significantly with a person's own risk for heavy drinking and alcohol problems (Jacob and Windle, 2000; Schuckit et al., 2006). In addition, there has not been consistent support for an increase in MDEs in children of alcoholics (Gilder et al., 2002; Jacob and Windle, 2000; Newcomb and Bentler, 1988). Our own work from both the Collaborative Study on the Genetics of Alcoholism as well as the longitudinal San Diego Prospective Study demonstrated little evidence of an increased risk for MDEs in offspring of alcoholic parents when the parents had no histories of IDEs themselves (Preuss et al., 2002; Schuckit et al., 2000, 2006). Further complicating the interpretation of the familial overlap between depressive symptoms and AUDs are data indicating that exposure to alcohol in utero may affect the offspring's later risk for mood syndromes and alcohol consumption (O'Connor and Kasari, 2000). As a result of these diverse findings, several groups have hypothesized that the relationship between AUDs and depressive conditions may reflect social and family characteristics rather than a direct genetic or psychological cause-and-effect relationship (Fergusson and Woodward, 2002; Prescott et al., 2000).

The inconsistencies in the literature regarding how MDEs and AUDs might be related may reflect several factors. Many studies have used the less informative cross-sectional or retrospective data, often gathering information through a

family history method, whereas others have used prospective studies with direct interviews of multiple relatives. Investigations also differ on how the MDEs were defined, with some investigations taking steps to distinguish between substance-induced and independent mood conditions and others not. As defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV; American Psychiatric Association, 1994), a substance-induced disorder is a psychiatric syndrome that closely resembles an independent major psychiatric disorder (e.g., an IDE) but that only developed in the context of severe intoxication or withdrawal from a substance capable of mimicking the psychiatric symptoms (e.g., alcohol). It has been estimated that more than a third of the major depressions observed among heavy drinking individuals may be temporary and substance induced (Gilder et al., 2004; Hasin et al., 2002; Hesselbrock et al., 1999; Schuckit et al., 1997a, 2007). Such alcohol-induced MDEs, although sharing the same symptoms and suicide risks associated with independent major depressive conditions (Conner et al., 2007; Ramsey et al., 2004; Schuckit et al., 2007), are likely to greatly diminish in intensity and fall below the severity appropriate for an MDE within 1 month or less of abstinence (Brown and Schuckit, 1988; Schuckit, 2006).

In summary, there is ample evidence of important relationships between heavy drinking and mood changes as well as between AUDs and MDEs. However, the mechanisms that underlie these relationships and the clinical implications of these syndromes are complex. This article presents data from a 30-year longitudinal study of almost 400 families where careful efforts were made to identify independent depressions separately from substance-induced depressions. We hypothesized that a longitudinal study that uses validated interviews with subjects and relatives and focuses on IDEs, not alcohol-induced depressive episodes, would reveal little evidence of a link between IDEs and AUDs.

Method

The original subjects (probands) for these analyses were 397 men from the San Diego Prospective Study who completed all phases of that research protocol from baseline (Time 1 or T1) at ~age 20 through follow-ups at 10 years (T10) and all subsequent 5-year epochs (T15–T30) (Schuckit and Gold, 1988; Schuckit and Smith, 1996). When originally selected, these men were healthy, non-alcohol-dependent but drinking European American or Hispanic 18- to 25-year-olds who were chosen among respondents to a questionnaire distributed to random students and nonacademic staff at the University of California, San Diego. The probands were composed of equal numbers of sons of alcohol-dependent fathers and family history–negative controls matched on demography, drinking histories, and substance use histories, with, at T1, no proband meeting lifetime criteria for dependence on alcohol or any illicit substance and in the absence

of any current major depressive or anxiety conditions or psychotic disorders. During the 30 years of this project, 11 subjects died (2.4%), and the T30 follow-up had data from all epochs for 397 of 442 survivors, an overall rate of complete data of 90%.

At baseline and during each follow-up, subjects were evaluated with semi-structured instruments, which at T1 were based on the Reynard Diagnostic Interview (Robins et al., 1981) and for follow-ups beginning in 1988 were modified based on the Structured Clinical Interview for DSM-III-R (Spitzer et al., 1992) and the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) interview. Overall, SSAGA validities and 1-week retest reliabilities for alcohol, illicit substance, and mood disorders are $\sim .75$ (Bucholz et al., 1994; Hesselbrock et al., 1999). This includes a κ of .63 for alcohol dependence when compared with the SCAN and .73 to .85 for cocaine and opioid dependence (Hesselbrock et al., 1999). At each evaluation, data were gathered regarding the interval (e.g., prior 5-year) pattern of use and problems associated with alcohol and illicit substances as well as nicotine, and subjects were screened for all substance use disorders (SUDs). Sections of the interviews also reviewed DSM major mood and anxiety conditions as well as psychotic symptoms. Similar interviews with spouses established the spouse's interval histories of the same conditions. For all diagnoses, the age at onset was the age at which the person first met the criteria for the full relevant syndrome. For follow-ups from T10 through T25, face-to-face inter-

views about the probands were used with both probands and a resource person (usually a spouse or first-degree relative), but because of financial constraints, at T30 these were carried out by telephone. In the current analyses, subjects who during the follow-up met criteria for at least one DSM-IV MDE that occurred outside the context of heavy drinking were labeled as having had an IDE, whereas alcohol-induced MDEs were those that met DSM-IV criteria in the context of heavy drinking.

At T15 and each follow-up thereafter, subjects also filled out a retrospective report of the number of drinks required for up to four possible effects actually experienced, using the Self-Rating of the Effects of Alcohol (SRE) questionnaire. Two scores were generated, one for the approximate first five times of drinking (the SRE5) and the other the number of drinks for effects averaged across the first five times, the period of heaviest drinking, and the most recent 3 months (the SRET) (Ray et al., 2011; Schuckit et al., 1997b). This instrument, with a Cronbach's $\alpha > .90$ and 12-month to 5-year reliabilities between .6 and .8, recorded the number of standard drinks required for first feeling effects, slurring speech, impairing coordination, and passing out.

Throughout the follow-ups, information was also gathered from direct interviews of biological sons and daughters of probands ($\geq$ age 12) using the SSAGA version developed for adolescents (the C-SSAGA-A). This instrument has similar 1-week reliabilities for alcohol and mood-related items as observed in the adult SSAGA (Kuperman et al., 2001).

TABLE 1. Demography at the 30-year follow-up for 397 men, comparing those with and without IDEs during the follow-up

Variable	IDE ($n = 61$) $M (SD)$ or %	No IDE ($n = 336$) $M (SD)$ or %	t test or χ^2
Age, in years	52.3 (3.53)	50.7 (3.81)	3.07**
Length of follow-up, in years	28.9 (2.59)	27.8 (2.80)	2.83**
Education, in years	17.7 (2.24)	17.7 (2.10)	-0.02
Income ^a	10,010.9 (10,022.62)	13,369.1 (13,014.35)	-1.87
Occupation type			2.38
M.D./Ph.D./law./etc.	34.4%	37.5%	
Banker/large bus. exec.	27.9%	26.5%	
Sales/small bus.	29.5%	31.0%	
Skilled/semi-skilled	6.6%	4.8%	
Other	1.6%	0.3%	
Unemployed ≥ 1 mo. in prior 5 years	16.4%	8.3%	3.88*
Current marital status			5.38
Married	68.9%	81.0%	
Div./separated	19.7%	10.1%	
Never married	11.5%	8.9%	
Has ≥ 1 children	59.0%	76.8%	8.48**
T30 religion			8.53*
None	50.8%	47.9%	
Protestant	32.8%	31.5%	
Catholic	8.2%	18.2%	
Other	8.2%	2.4%	

Notes: IDE = independent (not substance-induced) major depressive episode; law. = lawyer; bus. = business; exec. = executive; mo. = month; div. = divorced; T30 = Time 30 (30-year follow-up).

^aU.S. dollars per month in prior year.

* $p < .05$; ** $p < .01$.

TABLE 2. Histories of IDEs and related conditions

Variable	No IDE		<i>t</i> test or χ^2
	IDE (<i>n</i> = 61) <i>M</i> (<i>SD</i>) or %	(<i>n</i> = 336) <i>M</i> (<i>SD</i>) or %	
Follow-up diagnosis			
Any anxiety disorder	4.9%	1.2%	4.14*
Panic	3.3%	0.6%	3.73
General anxiety	0.0%	0.3%	0.18
OCD	0.0%	0.3%	0.18
PTSD	1.6%	0.3%	1.85
IDE history			
Age at onset, in years	33.8 (6.58)	N.A.	N.A.
No. of depression symptoms	5.8 (2.21)	0.5 (1.41)	24.60***
No. of epochs with IDE	1.6 (0.98)	N.A.	N.A.
See mental health worker	75.4%	39.6%	26.76***
Antidepressants ever	50.8%	5.7%	95.67***
Attempted suicide	3.3%	0.6%	3.73
Psychiatric hospitalized	4.9%	0.3%	11.05***

Notes: IDE = independent (not substance-induced) major depressive episode; OCD = obsessive-compulsive disorder; PTSD = posttraumatic stress disorder; N.A. = not applicable.

* $p < .05$; *** $p < .001$.

Offspring with experience with alcohol also filled out the SRE. Approximately 85% of eligible offspring participated in relevant every-5-year interviews.

Data analyses compared probands who did and did not meet follow-up criteria for a DSM-IV major depressive episode outside the context of an AUD (i.e., an IDE) and

offspring who did and did not have a parent with an IDE. Differences across the groups were evaluated using *t* tests for continuous variables and chi-square for categorical data.

Results

The 397 probands, 97.8% of whom were European American or White Hispanic, were divided into 61 individuals (15.4%) who experienced at least one IDE that occurred outside the context of heavy drinking during the follow-up and 336 who reported no follow-up IDE. The men in the IDE group consisted of 93.6% who fulfilled criteria for at least one independent major depression and 6.4% who met criteria for an independent dysthymia. As shown in Table 1, at the 30-year follow-up (T30), the subjects were about 50 years old (those in the IDE group were 1.6 years older than the remaining subjects), the men had been followed for almost 30 years (slightly longer for those with an IDE), and the subjects reported an average of almost 18 years of education. The average incomes during T30 were about U.S. \$13,000 per month across the two groups (with a trend toward lower earnings for those with IDE, $p = .07$), and more than half of the subjects in each group were professionals or business executives. During the 5-year epoch of T30, about 10% of the subjects had experienced at least 1 month of un-

TABLE 3. Thirty-year histories of alcohol use, drug use, and related problems for men with and without IDEs

Variable	No IDE		<i>t</i> test or χ^2
	IDE (<i>n</i> = 61) <i>M</i> (<i>SD</i>) or %	(<i>n</i> = 336) <i>M</i> (<i>SD</i>) or %	
SID during follow-up	4.9%	2.7%	0.88
Alcohol			
Max. drinks in follow-up	14.8 (10.01)	13.6 (6.83)	-1.15
Usual drinks/drinking day	1.8 (1.93)	2.0 (1.48)	0.71
Usual days/month drank	11.6 (11.05)	13.6 (10.52)	-0.22
Max. alcohol problems	2.4 (2.91)	2.0 (2.18)	1.04
Any AUD			2.68
None	67.2%	57.1%	
Abuse	11.5%	17.3%	
Dependence	21.3%	25.6%	
SRE			
SRE5	3.2 (1.32)	3.4 (1.58)	-0.73
SRET	4.3 (1.86)	4.3 (1.69)	-0.15
Drugs			
Use any drug	72.1%	69.6%	0.15
Cannabinols	85.2%	82.7%	0.23
Amphetamine/cocaine	32.8%	28.6%	0.44
Any SUD	19.7%	20.8%	0.04
Cannabinols SUD	4.9%	15.5%	4.82*
Amphetamine/ cocaine SUD	14.8%	8.9%	1.98
Smoke in follow-up	50.8%	44.9%	0.72

Notes: IDE = independent (not substance-induced) major depressive episode; SID = substance-induced depression (alcohol or other drug-induced major depressive episode); max. = maximum; AUD = alcohol use disorder; SRE = Self-Rating of the Effects of Alcohol; SRE5 = SRE for the number of drinks for effects the first five times of drinking; SRET = the number of drinks for effects averaged across the first five times, the period of heaviest drinking, and the most recent 3 months; SUD = substance use disorder.

* $p < .05$.

employment, with a twofold higher rate for individuals with IDE histories. At the time of follow-up, there was a trend ($p = .07$) for men with histories of independent depressions to be more likely to be separated, divorced, or never married, and those with independent depressive histories were less likely to have children, a ratio that was unchanged if only married subjects were considered. Finally, regarding demographic backgrounds, those who had reported an IDE were less likely to report a current religion.

Table 2 presents information on the pattern of psychiatric symptoms and diagnoses for the two proband groups. For those with IDE histories, their first IDE occurred at an average age of 34 years, and during the period between T1 and T30 they experienced at least one IDE in two of the

five follow-up epochs. Over the 30 years, their most severe depressive syndrome involved six of the nine possible DSM-IV MDE symptoms, three quarters of the 61 men had been treated by a mental health worker, half had been prescribed an antidepressant, almost 5% had been psychiatrically hospitalized, and 3% had attempted suicide. Although not shown in the table, 1 of the 11 deaths in the San Diego Prospective Study probands was a suicide. Some men in the non-IDE group also saw mental health workers and some reported depressive symptoms and related conditions, but the rates were significantly lower than for the IDE group. Men with IDEs were also more likely to meet criteria for a major anxiety disorder, with a trend in that direction for the specific diagnosis of panic disorder ($p = .054$).

TABLE 4. Demography, substance use, and mental health-related issues for offspring age 12 and older with an IDE mother or father versus non-IDE parents

Offspring variable	Parent with IDE ($n = 110$) M (SD) or %	No IDE parent ($n = 339$) M (SD) or %	t test or χ^2
Demography			
Age at interview, in years	19.9 (5.38)	18.7 (5.26)	2.16*
Female	39.1%	49.9%	3.86*
Education, in years	11.9 (3.13)	11.3 (3.12)	1.17
Alcohol history			
Ever drank	55.5%	41.0%	7.02**
Max. drinks ($n = 200$)	10.6 (6.29)	11.7 (8.05)	-1.02
Usual drinks/drinking day	3.1 (1.66)	3.9 (2.90)	-2.13*
Usual days/month drank	9.4 (7.86)	9.0 (7.74)	0.31
Max. DSM-IV alc. probs.	1.5 (2.24)	2.02 (2.49)	-1.29
Any AUD			0.08
None	80.0%	79.6%	
Abuse	8.2%	7.7%	
Dependence	11.8%	12.7%	
SRE			
SRE5	2.9 (1.30)	3.3 (1.48)	-2.02*
SRET	3.6 (1.49)	4.2 (1.91)	-2.41*
Drugs			
Use any drug	35.5%	32.4%	0.34
Cannabinols	21.8%	18.6%	0.56
Amphetamine/cocaine	12.7%	8.0%	2.27
Any SUD			
Cannabinols	8.2%	8.0%	0.01
Amphetamine/cocaine	0.9%	2.9%	1.45
Smoke	10.0%	8.0%	0.44
Mental health			
IDE	8.2%	3.2%	4.76*
SID	6.4%	2.1%	5.08*
Conduct diagnosis	3.6%	2.1%	0.86
ADHD	7.3%	2.7%	4.86*
See mental health worker	17.3%	9.1%	5.54*
Antidepressants	6.9%	4.4%	1.04
Attempt suicide	0.6%	0.0%	0.65
Psychiatric hospitalized	0.9%	0.3%	0.71

Notes: IDE = independent (not substance-induced) major depressive episode; max. = maximum; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; alc. probs. = alcohol problems (the 11 DSM-IV alcohol abuse or dependence criteria endorsed); AUD = alcohol use disorder; SRE = Self-Rating of the Effects of Alcohol; SRE5 = SRE for the number of drinks needed for effects the first five times of drinking; SRET = the number of drinks for effects averaged across the first five times, the period of heaviest drinking, and the most recent 3 months; SUD = substance use disorder; SID = substance-induced depression (alcohol or other drug-induced major depressive episode); ADHD = attention-deficit/hyperactivity disorder.

* $p < .05$; ** $p < .01$.

The relationships among a history of an IDE and substance-related experiences are presented in Table 3. As shown at the top of the table, 5% of men with an IDE history and 3% of those with no IDEs experienced an alcohol or related substance-induced major depression. Individuals with and without an IDE were similar on the usual and maximum drinks consumed over the 30 years, their drinking frequencies, the maximum number of DSM-IV AUD criterion items experienced in any epoch during the 3 decades, and regarding the probands who fulfilled criteria for an AUD. In addition, men with and without IDEs were also similar on another risk factor for heavy drinking and alcohol problems, the number of drinks required for effects both early in their drinking careers and across their life span as measured by their SRE5 and SRET scores.

Although not shown in the table, overall among the subset of 20 men with IDE and 144 in the non-IDE group who had developed an AUD, 12.2% reported an IDE, and 5.5% reported an alcohol-induced syndrome only, for a total of 17.7% with a major depression. Thus, for men in the full sample with alcohol abuse or dependence, 31.1% of their MDEs were alcohol induced. These alcohol-induced depressive episodes were similar in most ways to the characteristics reported for IDEs in Table 2 in that these probands reported 5.7 (2.12) of the 9 possible depressive symptoms, 88.9% saw a mental health worker, and 44.4% had been prescribed antidepressants, although none of this subsample had been psychiatrically hospitalized. Among the 20 subjects in the IDE group who had both an IDE and an AUD, for 50.0% the alcohol diagnosis developed at a younger age than the alcohol-induced IDE, for 15.0% the IDE and the AUD developed at approximately the same age, and for 35.0% the alcohol dependence or abuse developed later than the IDE.

Table 3 also presents information related to patterns of smoking and the use of illicit drugs during the 30 years for subjects in the two IDE groups. There were no significant differences across subjects with and without IDEs regarding their prevalence of smoking, their use of illicit substances (primarily cannabinoids, amphetamines, or cocaine), or their overall rate of abuse or dependence on these drugs. However, regarding specific substances, those with IDEs reported a lower rate of dependence on cannabinoids.

Table 4 explores the relationships among parental IDEs and substance use, mental health, and related issues in their offspring. These data were available for 110 offspring age 12 years and older who had a mother or father with an IDE (including 55 offspring of the 61 IDE probands in Tables 1–3) and 339 offspring of probands and spouses with no IDE histories. The two groups of offspring were similar generally in age (although those with IDE parents were 1.2 years older) and years of education; fewer offspring of IDE parents, however, were female. Offspring of parents with an IDE were generally similar to offspring of non-IDE parents regarding most drinking variables, although offspring of IDE

parents were more likely to be drinkers but had fewer usual drinks per drinking day.

Approximately 20% of the sons and daughters in the two groups ever met criteria for alcohol abuse or dependence, but offspring of IDE parents reported requiring fewer drinks for effects on the SRE, a characteristic known to be related to a lower AUD risk. The two offspring groups were also similar in the proportions who used illicit drugs, met the criteria for an SUD, and had used cigarettes. However, as might be expected, offspring of IDE parents had an increased rate of IDEs themselves, as well as higher rates of substance-induced depressions. They also were more likely to be diagnosed with attention-deficit/hyperactivity disorder and were more likely than offspring of non-IDE parents to have been treated by a mental health worker. If only offspring who themselves had an AUD or SUD were considered, the proportions with substance-induced depressions were 31.8% for the group with parental IDE versus 9.5% for the comparison group ($\chi^2 = 6.81, p < .01$). All significant differences across the two offspring groups remained so after covarying for sex.

Discussion

Relationships between major depressive episodes and heavy drinking are widely supported and clinically important, but those relationships are complex. This study evaluated several layers of the link between depressive syndromes and heavy alcohol use, with a focus on distinguishing between independent and substance-induced major depressions in a 30-year longitudinal study that repeatedly used validated interviews to distinguish between men with and without a family history of IDEs, while also characterizing their offspring.

Overall, the rate of major depressive episodes in the 397 probands was 17.6%, including 15.3% with IDEs and an additional 2.3% with alcohol-induced depressions only. The 15% rate of IDEs over 3 decades was similar to the lifetime rate for men reported in several large-scale studies, although higher than some other reports (Hasin et al., 2005; Jacobi et al., 2004; Kessler et al., 1996, 2003; Prescott et al., 2000). The IDE syndromes observed in this study were clinically severe conditions, with subjects reporting five of the nine potential symptoms and 75% receiving treatment, including 50% who were prescribed antidepressants and 5% who were psychiatrically hospitalized. Consistent with other studies, men with IDEs had some indication of impaired life functioning, as they were less likely to be married at follow-up, tended to be less likely to have children, and had a trend toward lower recent incomes (e.g., Angermeyer et al., 2002).

The overall rate of an alcohol-induced depressive episode in the 397 men (~3%) is similar to the low prevalence of these syndromes in the general population reported in a prior study (Grant et al., 2004). However, the rate of alcohol-induced syndromes is most relevant for subjects who

themselves had AUDs. Here, among the subset of 164 men who had alcohol abuse or dependence across the IDE and non-IDE groups, 31% of the depressions they experienced were substance induced, not independent. Prior studies have reported similar or even higher percentages of substance-induced depressive syndromes in such populations (Hasin et al., 2002; Schuckit et al., 1997a, 2007). The relatively high prevalence of alcohol-induced versus independent MDEs in individuals with alcohol abuse or dependence is important to clinicians because the clinical course, overall prognoses, and optimal treatments for these induced conditions are different from IDEs (Brown and Schuckit, 1988; Schuckit, 2006). This distinction is also important for researchers because the environmental and genetic contributors to the major depressions may also be different for individuals with independent versus substance-induced disorders. Thus, the current article using data from a 30-year longitudinal study that incorporated repeated personal interviews based on a validated semi-structured instrument supports the importance of distinguishing between IDE and substance-induced conditions.

On several levels, the current data do not indicate a close relationship between AUDs and IDEs in these subjects. Probands with an IDE had no higher rate of AUDs than men with no IDE history. This occurred despite the high rate of AUDs in this population, half of whom were enrolled in the study because of a family history of alcohol dependence. Also, contrary to a recent study of subjects at risk for mania who demonstrated a greater number of drinks needed for effects—a risk factor for heavy drinking (Yip et al., 2012)—no such potential vulnerability as measured by higher scores on the SRE were seen for the probands with IDEs. Nor were the men with independent depressions more likely to use illicit substances or to fulfill criteria for a related SUD.

The relative absence of indications that having an IDE was related to AUDs also applied to the offspring of these probands. Comparing the 110 sons and daughters of mothers or fathers with an independent depression with the 339 offspring of non-IDE parents revealed no evidence of an increased rate of AUDs in the former group and no need for more drinks for effects, nor was there evidence of an increased risk for substance use or SUDs. However, as reported in prior studies of offspring of individuals with major depressions (Harrington et al., 1990; Rao et al., 1995; Weissman et al., 1999), the sons and daughters of parents with independent depressions demonstrated higher rates for independent depressions themselves and were more likely to receive psychiatric treatment compared with individuals with non-IDE parents.

Several factors may have contributed to why our current study and some additional investigations have noted little relationship between MDEs and AUDs while other studies have reported a potential link between the two conditions. Perhaps the most important distinction is the steps taken with

probands and offspring in the current study to distinguish between MDEs that occurred outside versus within the context of heavy substance use. This distinction was facilitated by repeated personal interviews over 30 years in probands, spouses, and offspring based on the SSAGA interview that was structured to follow the same algorithm outlined in DSM-IV to distinguish between substance-induced and independent depressive disorders.

The current data also shed some light on whether an individual with a history of an IDE might carry an increased risk for an alcohol-induced depression when drinking heavily, although the answer may be different across the two generations. Regarding the probands, their rate of an alcohol-induced disorder was a bit, but not significantly, higher in those with IDEs. However, offspring of parents with IDEs who themselves had an AUD or SUD were significantly more likely to have a substance-induced disorder themselves. Although the numbers of subjects involved in these analyses were relatively small, the significant finding in offspring with nonsignificant results in a similar direction for parents supports the possibility that alcohol-induced depressions may be more common in young men and women who have histories of independent depressive disorders. Perhaps at age 19 and younger, the stages of brain development associated with adolescence may make heavy drinking and drug-using subjects more vulnerable to associated mood problems compared with the probands who were studied at ages 20, 30, and beyond. Future studies will be required to evaluate this hypothesis.

There were several potential validators of the distinction between IDE and substance-induced conditions in this population. In offspring, despite their young age, those who had a parent with an independent depression were themselves more likely to demonstrate an IDE than those without a similar family history. Also, the rate of IDEs in the probands, half of whom had an alcohol-dependent father, was not higher than what might be expected in the general population, despite the high familial rate of AUDs.

The current study has several strengths that facilitated the analyses reported here. Most notable are the longitudinal nature of the work, the repeated evaluations of probands every 5 years, and the use of an interview structured to distinguish between substance-induced and independent disorders. At the same time, the data on depression, as only one component of a larger study, were primarily descriptive, and the use of 5-year epochs of follow-up makes it difficult to disentangle cause and effect when both heavy drinking and depressive episodes occur in the same 5-year period. The results of this study must also be viewed from the perspective of the population evaluated because the subjects were relatively highly educated men with an overrepresentation of those who came from families with alcohol dependence. These characteristics, the emphasis on full criteria for MDEs, and the retrospective nature of reports may have

contributed to the relatively older than expected age at onset for IDEs in this population. Different results might be seen in women, those with family histories of independent depressions, or subjects with lower education. In addition, although the population studied here included almost 400 probands and 450 offspring, the number of subjects with independent and alcohol-induced depressions was relatively low, and the results need to be validated in larger studies.

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