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CORRELATES OF CO-OCCURRING ADHD IN DRUG-DEPENDENT SUBJECTS: PREVALENCE AND FEATURES OF SUBSTANCE DEPENDENCE AND PSYCHIATRIC DISORDERS

Albert J. Arias[a], **Joel Gelernter**[b], **Grace Chan**[a], **Roger D. Weiss**[c], **Kathleen T. Brady**[d], **Lindsay Farrer**[e], and **Henry R. Kranzler**[a*]

a*Department of Psychiatry, University of Connecticut School of Medicine, Farmington, CT 06030, USA*

b*Department of Psychiatry, Yale University School of Medicine, New Haven, CT and VA CT Healthcare Center, West Haven, CT 06516, USA*

c*Department of Psychiatry, Harvard Medical School, Boston, MA, and McLean Hospital, Belmont, MA 02178, USA*

d*Department of Psychiatry, Medical University of South Carolina, Charleston, SC 29425, USA*

e*Departments of Medicine (Genetics Program), Neurology, Genetics & Genomics, Epidemiology, and Biostatistics, Boston University Schools of Medicine and Public Health, Boston, MA 02118, USA*

Abstract

We examined the prevalence and course of psychiatric and substance dependence (SD) disorders in subjects with SD and attention deficit hyperactivity disorder (ADHD).

Method—We interviewed 1,761 adults with a lifetime diagnosis of cocaine and/or opioid dependence using the Semi-Structured Assessment for Drug Dependence and Alcoholism. Generalized linear regression with generalized estimating equation analysis was used to examine the associations between a lifetime diagnosis of ADHD and indicators of clinical course, and to identify unique correlates of ADHD.

Results—Lifetime ADHD prevalence in the SD sample was 5.22% (vs. 0.85% in a group of individuals without SD). ADHD was associated with an earlier age of first substance use, more SD and psychiatric diagnoses, a greater likelihood of attempted suicide, and more hospitalizations. After controlling for conduct disorder and bipolar type I disorder, there were unique effects of ADHD on age of first substance use and number of SD diagnoses.

Conclusion—In subjects with cocaine or opioid dependence, ADHD is associated with greater SD and psychiatric comorbidity and a more severe course of illness.

Keywords

Attention Deficit-Hyperactivity Disorder; ADHD; Substance Dependence; Comorbidity; Adult ADD

*Correspondence: Department of Psychiatry, University of Connecticut Health Center, Farmington, CT 06030-2103; email: kranzler@psychiatry.uchc.edu; telephone: 860-679-4151; fax: 860-679-1316.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a common, highly heritable, neurobehavioral disorder, beginning in childhood but often persisting into adulthood, which is associated with significant impairment in psychosocial function (Biederman, 2005). Estimates of the worldwide lifetime prevalence of childhood ADHD in the general population usually range from less than 5%, to 12% (Kessler et al., 2005a; Fayyad et al., 2007; Polanczyk et al., 2007; and Faraone et al., 2003). The prevalence of ADHD is thought to be considerably higher among individuals with a substance use disorder (SUD) than in the general population (see Kalbag and Levin, 2005 for a review). The prevalence of childhood and adult ADHD in substance abusing populations has been estimated to be three times that in the general population (Rounsaville et al., 1991; Levin et al., 1998; King et al., 1999; Clure et al., 1999). Similarly, rates of SUDs among individuals with adult ADHD, which are as high as 40% (Kalbag and Levin, 2005; Biederman et al., 1995), are substantially higher than those in the general population, estimated to be 14.6% for any SUD (Kessler et al., 2005a). Examination of non-treatment-seeking ADHD samples reveals findings similar to those obtained in clinical samples (Biederman et al., 1995).

The National Comorbidity Survey Replication study (NCS-R) is the only study to date that reports on the co-occurrence of SUD and ADHD in a general, non-treatment seeking SUD population (Kessler et al., 2005a; 2005b; 2006). This national survey yielded overall prevalence rates of 8.1% and 4.4% for childhood (i.e., lifetime) ADHD and adult ADHD, respectively. Although the prevalence of childhood ADHD among individuals with a lifetime SUD was not reported, the prevalence of adult ADHD in this subgroup was 10.8%, compared to 3.8% among individual without a lifetime SUD.

Adults with a history of ADHD (including those with adult ADHD) have double the risk of developing a SUD as adults without ADHD (Biederman et al., 1998). A co-occurring ADHD diagnosis is also associated with an earlier onset and more severe course of a SUD, poorer treatment adherence, more difficulty achieving treatment goals and progress in treatment, and higher rates of relapse (Carroll and Rounseville, 1993; Wise et al., 2001; Levin et al., 2004; Wilens et al., 1997). In a study by Kolpe and Carlson, (2007), the presence of clinically significant ADHD symptoms just prior to admission to a methadone program was associated with a poorer outcome in that program. Despite these associations, the specific nature of the relationship between ADHD and SUDs is unclear, and there are few data on their co-occurrence in non-treatment seeking SUD populations. Prior studies have also linked ADHD to increased suicidal behaviors and/or self-mutilation, though the nature of this relationship remains unclear (Kelly et al., 2004, Fulwiler et al., 1997).

The influence of other psychiatric disorders that frequently co-occur with ADHD [e.g., oppositional defiant disorder, conduct disorder (CD), and antisocial personality disorder (ASPD)] on risk for the development of a SUD further complicates the picture. The co-occurrence of ADHD with CD, in particular, is of interest, since in a number of studies showing them to be associated, results for ADHD are not significant when comorbid CD is taken into account, raising the question of whether it is CD rather than ADHD that accounts for the increased risk of a SUD (Flory and Lynam, 2003). However, other studies have provided evidence for a direct link between ADHD and risk for the age of onset and presence of a SUD, after controlling for CD (Biederman et al., 1995; Wilens et al., 1997; Milberger et al., 1997). The co-occurrence and effects of ADHD and CD on a child's development, including the impact on the risk and features of SUDs, requires further research. ADHD and CD could make unique contributions to the risk of a SUD; these disorders could also interact developmentally with social difficulties faced by ADHD, increasing the risk of the individual affiliating with

deviant peer groups and thereby modify the phenotypic expression of a SUD (Marshal and Molina, 2006).

It has been proposed that ADHD and SUDs may share common genetic risk factors, as well as similar etiologies based in personality factors or psychosocial environmental factors, or that co-occurrence of SUDs may stem from "self-medication" of ADHD (Kalbag and Levin, 2005). To date, however, there is little evidence to support a shared genetic etiology, possibly because the complex relationship between ADHD and SUDs complicates etiologic and pathophysiologic analysis (Johann et al., 2003; Kim et al., 2006; Lasky-Su et al., 2006). A recent study by Wilens et al., (2007), reported no difference in rates of drug use for self-medication or for getting high between ADHD subjects and controls, when motivations for drug use were examined, arguing against a strong role for self-medication in the link between ADHD and SD.

Because there are few published studies examining the impact of ADHD on the course of SD course and on its outcome, despite a comparatively high rate of co-occurrence, studies in the population of patients with these co-occurring disorders are clinically important. This study explores the association with ADHD of a number of psychiatric and SD-related variables, some of which serve as proxy measures of course and outcome, while others are descriptive and serve to characterize this population more fully. Of particular interest is whether ADHD itself (and not co-occurring disorders or other associated factors) is associated with a more severe phenotypic expression of psychiatric and substance use disorders, as is suggested by the literature reviewed above. The population studied here is unique in that in contains subjects recruited largely from the community, as opposed to a primary treatment sample.

To examine the correlates of co-occurring ADHD with regard to substance dependence (SD), psychiatric disorders, and related features, we studied a sample of subjects recruited as small nuclear families, ascertained on the basis of sibling pairs affected with cocaine and/or opioid dependence to participate in linkage studies of cocaine and opioid dependence (Gelernter et al., 2005; 2006). We predicted that the prevalence of ADHD in this population of SD subjects would be elevated relative to a comparison group screened to exclude individuals with a lifetime SUD. We hypothesized that a lifetime history of ADHD would be associated with a more severe course of SUD and more co-occurring SD and psychiatric disorders, including outcomes associated with impulsivity (often a prominent feature of ADHD), such as suicidal behaviors. We also hypothesized that ADHD would be associated with these indicators of more severe substance and psychiatric disorder even when the particularly important confounding effect of CD is taken into account. As an exploratory analysis, we also examined whether there is a preference for certain types of drugs in drug-dependent individuals with ADHD, as such information could inform further studies designed to understand and the link between ADHD and substance use disorders.

2. Methods

2.1. Study sample

A total of 2 047 individuals from 984 small nuclear families were ascertained on the basis of a sibling pair, in which both individuals were affected with cocaine and/or opioid dependence. Subjects were recruited to participate in one of two multi-site studies of the genetics of SD (Gelernter et al., 2005; 2006). Once an affected sibling pair was ascertained, all other biological nuclear family members were invited to participate. Subjects were recruited from four sites: the University of Connecticut Health Center (Farmington, CT), Yale University School of Medicine (New Haven, CT), McLean Hospital (Belmont, MA), and the Medical University of South Carolina (Charleston, SC). A total of 1 761 subjects met lifetime criteria for cocaine and/or opioid dependence. These individuals represented a total of 964 small nuclear families, the

largest of which included 5 individuals. Approximately 30% of the families were recruited in treatment facilities, the rest were recruited through advertisements in newspapers, notices in public places, and by word of mouth.

Table 1 shows the demographic characteristics of the 1 761 individuals included in the analysis. There were slightly more males (51.9%) than females; Non-Hispanic Black (48.7%) was the most frequently self-identified race, 60.1% of individuals were single, and 34.8% of individuals were currently employed, with a preponderance of individuals (69.0%) reporting their annual income to be less than $20 000. The mean age of the sample was 38.4 (standard deviation, s.d. = 7.67), with an average of 11.4 (s.d. = 1.97) years of education.

The primary analysis was performed only on the SD subjects, by dividing them into two groups for comparison: ADHD(+), and ADHD(−). For comparison only with respect to the lifetime prevalence of ADHD, we also included a group of 705 subjects who were screened to exclude those with a SUD. These individuals included unaffected family members of SD subjects, as well as individuals recruited to serve as a control group for case-control genetic studies. Of the 705 control subjects, only 6 are ADHD(+). The low prevalence of ADHD in this non-SD group did not allow its use in the analysis of factors associated with ADHD.

2.2 Diagnostic instrument

We used the Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA) to obtain information on demographics and substance use and psychiatric symptoms and disorders. A detailed description of the instrument, the methods used to administer it, and data showing its diagnostic reliability can be found in Pierucci-Lagha et al. (2005). Most of the SD diagnoses derived from the SSADDA have good-to-excellent reliability, and the reliability of psychiatric diagnoses varies from fair to excellent. Included among the diagnoses available with the SSADDA is a lifetime DSM-IV diagnosis of ADHD (American Psychiatric Association, 1994). The ADHD section of the SSADDA includes detailed information on childhood symptoms of the disorder, its persistence into adulthood, and the history of its treatment during both childhood and adulthood. The inter-rater reliability of the ADHD diagnosis derived from the SSADDA was good (kappa = .66) to excellent (Yule's Y = .88; Yule's Y may be a better estimate of reliability given the low prevalence of the diagnosis in the reliability sample) (Pierucci-Lagha et al., 2005).

2.3. Study variables

The main response variable of interest for this report was the diagnosis of childhood ADHD. To estimate the likelihood of ADHD among cocaine and/or opioid dependent subjects, we examined a range of explanatory variables in four domains: demographics, substance use symptoms and disorders, psychiatric symptoms and disorders, and number of hospitalizations for either psychiatric-and/or substance abuse-related problems.

2.3.1. Substance use symptoms and disorders—We compared ADHD(+) and ADHD (−) groups on: 1) the prevalence of dependence on nicotine, alcohol, cocaine, opioids, cannabis, stimulants, and sedatives; 2) the age of first use of any of these substances, and 3) the age of first dependence on any of these substances. The diagnosis of stimulant dependence included non-medical use of prescription drugs such as methylphenidate.

2.3.2. Psychiatric symptoms and disorders—We also compared ADHD groups on the prevalence of 10 psychiatric disorders: ASPD, CD, major depressive disorder, bipolar disorder type I, posttraumatic stress disorder (PTSD), generalized anxiety disorder, obsessive compulsive disorder, social phobia, panic disorder, and pathological gambling. Moreover, we compared the groups on three variables related to self-harm: "suicidal ideation" was based on

the subject's response to the question *"Have you ever thought about killing yourself?"*; "attempted suicide" was based on the subject's response to the question *"Have you ever tried to kill yourself?"*; and "intentionally self-injurious behavior" was based on the subject's response to *"Other than when you tried to take your own life, did you ever hurt yourself on purpose, for example, by cutting or burning yourself?"*

2.3.3. Hospitalization for substance use and psychiatric disorders—Finally, we compared ADHD groups on their response to the following question: *"How many times have you been an inpatient in a psychiatric hospital or ward or in a chemical dependency program where you stayed overnight?"*

2.4. Data analysis

The logistic model, which is a special kind of generalized linear regression model (McCullagh and Nelder, 1989), was used to examine the relationships between the binary response variable, presence or absence of an ADHD diagnosis, and the potential explanatory variables mentioned above. In addition, generalized estimating equations (GEE)[1] were employed to fit the logistic model to account for the potential dependence among individuals within the same nuclear family. All logistic GEE regression models assume an exchangeable correlation structure among individuals within the same nuclear family.

First, descriptive univariate sample statistics were computed for each of the study variables based on the entire sample of 1 761 individuals. Second, 32 (unadjusted) pair-wise relationships between each of these variables and the presence or absence of ADHD were examined using Wald statistics for type 3 GEE analysis. In this preliminary analysis, Bonferroni multiple comparison correction at an overall 10% level of significance was used to determine the strength of these 32 relationships. That is, each of these 32 p-values was compared using a significance level of $p < 0.003$.

Logistic GEE regression analysis was also used to explore the (adjusted) relationships in each of four groups of characteristics: demographics, substance use symptoms and disorders, psychiatric symptoms and disorders, and treatment for substance use and psychiatric disorders. A final logistic GEE regression analysis was used to examine all group-specific significant predictors in a number of combined models. The final logistic GEE regression model included only characteristics that were deemed to be clinically important or that were statistically significant at the $p < 0.05$ level. In the logistic GEE regression analyses, the treatment variable was included in both the substance use and psychiatric disorder variable groups.

Next, two sets of *exploratory* analyses were conducted. The first set explored whether the ADHD groups differed with respect to their drug preference. Simple logistic GEE regression analysis was used to examine responses to the following two questions in relation to the diagnosis of ADHD: "*Which substance is the major problem?*" and *"Of all the drugs you have used, which one was your favorite (including opiates, cocaine, and alcohol)?"* As an indicator of drug preference, we also examined whether the ADHD groups differed with respect to the first substance on which they developed dependence. The second analysis compared subjects with childhood-only ADHD to those whose symptoms continued into adulthood (i.e., those with Adult ADHD). Logistic GEE analysis was used to compare these groups on four domains: demographic, substance use symptoms and disorders, psychiatric symptoms and disorders, and treatment for substance use and psychiatric disorders.

[1]Liang and Zeger (1986) introduced generalized estimating equations (GEEs) as a method of dealing with correlated data in fitting the generalized linear model. In the present study, the SAS procedure GENMOD was used to fit generalized linear models to correlated data by the GEE method.

To determine whether ADHD has a unique relationship with the course and severity of SD after controlling for the presence of comorbid CD, the number of SD disorders and the age of first substance use were regressed on age, CD, and ADHD separately. This analysis was conducted to disentangle the collinear effects of ADHD and CD, as they do not appear as independent variables in the final model. Due to the counting nature of the first response and the skewness of the second response, three distributional assumptions were considered: Normal, Poisson, and Negative Binomial[2]. For the two latter distributional assumptions, the response variables were log transformed. In all regressions, GEE with exchangeable correlation structure was used to model the nuclear familial dependence. The results were essentially the same under the three distributional assumptions, hence only the Normal models on (untransformed) response were reported.

3. Results

3.1. Prevalence and characteristics of ADHD

The prevalence of childhood ADHD in the selected sample of 1 761 individuals with either cocaine and/or opioid dependence was 5.22% (i.e., 92 subjects met lifetime criteria for childhood ADHD). This compares with a prevalence of ADHD of 0.85% among 705 individuals with no lifetime SD disorder (odds ratio = 6.42).

Among the 92 individuals with childhood ADHD, 79.5% reported symptoms that persisted beyond the age of 18, i.e., they met criteria for Adult ADHD. Only 52.2% of the childhood ADHD subjects had ever received any treatment for ADHD, and only 28.3% of them had ever received pharmacological treatment for the disorder. Of the subjects with ADHD, 19/92 subjects (20.7%) with ADHD were of the inattentive type, 28/92 (30.4%) were of the hyperactive type, and 45/92 (48.9%) were of the combined type. Six-hundred sixty-three subjects from the entire sample had three SD diagnoses (37.65%); that included 54 (58.70%) of the ADHD(+) subjects, and 609 (36.49%) of the ADHD(−) subjects.

3.1.1. Demographic Characteristics—Table 1 presents demographic data for the total sample and the ADHD groups. Logistic GEE regression of ADHD diagnosis on the seven demographic characteristics showed that the ADHD groups differed only on age ($p = 0.0043$) and race ($p = 0.0020$).

3.1.2. Substance use symptoms and disorders—Table 2 presents the prevalence of various SD diagnoses in the entire sample and by subjects' ADHD diagnosis. Although the prevalence of each of these seven SD diagnoses was higher among individuals with ADHD, after controlling for multiple comparisons, only the prevalence of dependence on alcohol ($p = 0.0005$), cannabis ($p = 0.0004$), and stimulants ($p = 0.0012$) was significantly increased.

Four other characteristics related to SD are also presented in Table 2. Those with ADHD had a significantly earlier age of onset of substance use ($p < 0.0001$), age of first SD diagnosis ($p < 0.0001$), were dependent on significantly more substances ($p < 0.0001$), and had been hospitalized more due to either substance or psychiatric problems ($p = 0.0018$) than ADHD(−) individuals.

The logistic GEE regression of ADHD diagnosis on these 11 substance use disorder characteristics indicates that, after adjustment, only the age of onset of substance use ($p < 0.0001$) and the number of SD diagnoses ($p = 0.0001$) differed significantly by ADHD group.

[2]McCullagh and Nelder (1989, ch. 6) suggested that two special kinds of generalized linear models (Poisson and Negative Binomial log-linear models) be used for analysis of responses that may not be normally distributed.

3.3. Psychiatric symptoms and disorders

Table 3 shows the prevalence of 10 psychiatric disorders and the rate of endorsement of three measures of suicidal ideation or self-harm. Controlling for multiple comparisons, there was a significantly greater prevalence of four disorders among subjects with ADHD: CD ($p < 0.0001$); ASPD ($p = 0.0006$); bipolar disorder, type I ($p < 0.0001$); and PTSD ($p = 0.0028$). ADHD(+) subjects also had a greater total number of psychiatric disorders ($p < 0.0001$), and had been hospitalized more due to either substance or psychiatric problems ($p = 0.0018$). Among the 1,761 subjects, nearly half had thought about killing themselves, about one-fifth attempted suicide, and about one in 15 had purposely hurt themselves without intending to kill themselves; ADHD(+) subjects were significantly more likely to endorse all three of these symptoms (p-value < 0.0001).

The logistic GEE regression analysis of ADHD diagnosis on these 15 psychiatric variables showed that only five differentiated the groups significantly: number of psychiatric disorders ($p < 0.0056$), suicide attempts ($p = 0.0138$), intentionally self-injurious behavior ($p = 0.0042$), ASPD ($p = 0.0164$), and CD ($p = 0.0007$).

3.4. Combined logistic regression analysis

We combined the nine significant predictors from the three groups of variables described above in a single logistic GEE regression analysis. The best model included only five of the predictors (See Table 4). The only significant demographic predictor of ADHD was age, with younger subjects having a slightly greater risk of ADHD. In addition, two substance use characteristics were retained in the model: age of first use of any substance, with later substance use individuals having a reduced risk of ADHD, and number of SD disorders, with the risk of ADHD increasing with the number of SD disorders. Finally, two psychiatric variables were significant predictors: number of positive psychiatric diagnoses, with the risk of ADHD increasing with the number of psychiatric disorders, and suicide attempt, with the risk of ADHD being greater among individuals who had attempted suicide.

3.5. Exploratory analyses

Additional bivariate GEE analyses examining drug of choice, the most problematic substance, and the first substance of dependence yielded only one potentially significant result: ADHD (+) subjects were significantly more likely than ADHD(−) subjects to report that alcohol was the substance that presented the greatest problem for them (18.5% vs. 9.7%, $p = 0.0066$). There was also a greater likelihood for ADHD(+) subjects to be dependent first on cannabis (32.6% vs. 21.1%, $p = 0.0131$). Although there were no significant differences between subjects with childhood-only ADHD and those whose ADHD symptoms persisted into adulthood, the statistical power of these tests was low due to the small size of the childhood-only ADHD group ($n = 18$).

3.6. Analysis of the effects of co-occurring ADHD and CD on SD risk

Two aspects of substance use disorder were considered in these supplemental analyses: the age of onset of substance use and the total number of SD disorders. The analyses controlled for the presence of a lifetime diagnosis of CD (either in the presence or absence of ASPD), yielding a lifetime prevalence of CD in the entire sample of 17.52%, including 41.30% in the ADHD group and 16.19% in the non-ADHD group.

The predicted age of onset of substance use increased as age at the time of the interview increased. Individuals with both CD and ADHD had the earliest onset of substance use, followed approximately one year later by individuals with CD but not ADHD and two years later by individuals with ADHD but not CD. Subjects with neither CD nor ADHD had the

latest onset. There were independent contributions of both CD ($p < 0.0001$) and ADHD ($p = 0.0001$) on the number of SD diagnoses. Specifically, the number of SD diagnoses was, respectively, 2.9, 3.5, and 4.1 for individuals with neither CD nor ADHD, with either CD or ADHD (but not both), and with both CD and ADHD. In predicting the age of first substance use, age at interview ($p = 0.002$), a diagnosis of CD ($p < 0.0001$), and a diagnosis of ADHD ($p < 0.0001$) all made substantial independent contributions. Specifically, the mean ages of first substance use for the diagnostic groups were; 10.29 years (s.d. = 2.25) for CD with co-occurring ADHD, 10.75 years (s.d. = 3.06) for CD only, 11.37 years (s.d. = 2.98) for ADHD only, and 13.15 years (s.d. = 3.24) for neither ADHD nor CD.

4. Discussion

The findings reported here are consistent with a growing body of literature showing that the presence of ADHD is associated with more severe expressions of substance use and psychiatric disorders (Fulwiler et al., 1997; Izutsu et al., 2006; Wilens et al., 2005). Bivariate GEE analyses showed ADHD to be associated with greater likelihood of a variety of specific substance use and psychiatric disorders. However, when the contribution of co-occurring factors was taken into account (including CD, ASPD, and bipolar disorder, type I), ADHD was associated only with an earlier age of first substance use, greater number of co-occurring SD and psychiatric diagnoses, a higher rate of suicide attempts, and a greater number of hospitalization due to either substance or psychiatric problems. These findings support the hypothesis that ADHD could influence the expression of co-occurring disorders by contributing to a more severe phenotype, in which the individual initiates substance use at an earlier age and experiences a more severe SD and psychiatric course. The present study extends the existing literature by showing that these associations are present in a population with serious SD disorders (i.e., opioid and/or cocaine dependence).

The results of logistic GEE regression analysis showed that ADHD is associated with a more severe expression of SD, including an earlier use of substances and a greater number of SD diagnoses. Although these findings were evident even after attempting to control for the effects of co-occurring CD, ASPD, and bipolar disorder, type 1 (using the stepwise logistic GEE regression analysis), we were unable to disentangle fully the relationship between SD and ADHD given the significant impact on ADHD risk of the number of co-occurring psychiatric disorders. Indeed, whether ADHD itself, as distinguished from co-occurring CD, actually has an impact on the development and expression of SUDs remains controversial. However, additional analyses that we performed indicate that ADHD is uniquely associated with an earlier age of first substance use and a greater number of SD diagnoses and that this effect is additive to that of co-occurring CD.

In contrast to the report by Wilens et al. (1997) of an earlier onset of a SUD among individuals with ADHD, we did not find that ADHD(+) subjects had an earlier onset of SD after controlling for age of onset of substance use and number of substance dependence diagnoses. However, we did find that ADHD(+) subjects had an earlier onset of substance use. The difference in findings between studies may be explained by the fact that Wilens et al. (1997) included both substance abuse and dependence diagnoses, while we examined SD only. Alternatively, the relatively small number of ADHD cases in our sample may have limited the statistical power to detect a significant correlation between ADHD and an earlier onset of a SD diagnosis. Because this study is observational in design, and we lacked a comparison group with ADHD but no SD, the contribution of ADHD to the risk of developing a SUD could not be evaluated. However, despite the limitations, analysis of the correlation of ADHD with substance use and psychiatric disorders in this large dataset could potentially inform future prospective studies examining the contribution of ADHD to risk of developing a SUD, as well as studies of the genetic risk shared by ADHD and substance use disorders.

The logistic GEE regression analysis supports our hypothesis that ADHD is associated with a more severe phenotypic expression of SD, including an earlier onset of substance use and a greater number of SD diagnoses. We would hypothesize that these findings could be explained by greater levels of impulsivity or novelty seeking in ADHD(+) subjects, though this hypothesis requires empirical validation. Future research should consider the use of these putative endophenotypes, as well as measures of physiologic or neurocognitive function, which could help to disentangle the specific contributions to risk of SD of ADHD, as well as the disorders that commonly occur with ADHD.

Most of the ADHD(+) subjects in our sample reported never having received treatment for the disorder and the vast majority had persistent ADHD symptoms into adulthood. These results are generally consistent with findings from the literature suggesting that ADHD symptoms often persist into adulthood, and that treatment of ADHD could protect against the risk of developing a co-occurring SUD (Biederman, 2005; Wilens et al., 2003). Persistence of ADHD into adulthood may have particularly detrimental effects on the course and outcome of substance use and co-occurring psychiatric disorders (Kalbag and Levin, 2005). However, in the sample examined here, the effects of drug dependence may have confounded the diagnosis of adult ADD, as they may induce either transient or lasting deficits in attention. Consequently, although our results could be interpreted as being consistent with the hypothesis that ADHD subjects use alcohol and drugs to self-medicate symptoms of ADHD or of psychiatric disorders that commonly co-occur with ADHD, this hypothesis requires further exploration. The exploratory comparison of childhood ADHD subjects with adult ADD subjects yielded no convincing evidence of differences between the groups, suggesting that they are a homogenous group, at least in the population that we studied. However, it should be acknowledged that the small sample sizes in this comparison (n=18 for the childhood-only ADHD group) provided limited statistical power.

The prevalence of ADHD in our sample of drug-dependent subjects (5.2%) is lower than that seen in other studies, including those in the general population (Faraone et al., 2003; Kessler et al., 2005a; Biederman, 2005). However, in comparison with the prevalence of the disorder in our screened control group (0.8%), the risk of ADHD in the SD subjects was substantially elevated (OR = 6.4), as is widely reported in the literature. Although the difference in prevalence of ADHD compared with that obtained in prior studies may raise concerns about the diagnostic method used in the present study, as noted above, the reliability of the ADHD diagnosis derived using the SSADDA was good to excellent. Further, we found that ADHD had a significant, independent association with SD outcomes, providing evidence of the construct validity of the diagnosis.

There appears to be a bi-directional over-representation of ADHD and SUDs (i.e., a higher prevalence of ADHD in SUD samples and of SUDs in ADHD samples) (Wilens 2004). Although studies in substance-abusing populations have focused mainly on treatment-seeking patients, the subjects included in the present study were recruited from a variety of sources. Individuals with SUDs and co-occurring ADHD may be particularly likely to seek treatment, leading to notably high prevalence estimates of ADHD in these treatment-seeking SUD populations. The substantial proportion of subjects in our study that were recruited from the community may help to explain the relatively low prevalence of ADHD. Further, criteria for participants in the genetic linkage studies for which the present sample was recruited excluded individuals who had ever received a clinical diagnosis of schizoaffective disorder or schizophrenia, which may have decreased the prevalence of a number of co-occurring disorders, possibly including ADHD. Although strict DSM-IV diagnostic criteria were applied in the diagnosis of ADHD (Pierucci-Lagha et al., 2005), the use of a retrospective diagnostic method could have led to an underestimation of the prevalence of ADHD in this sample (in cases as well as controls); this, however, runs counter to research suggesting that retrospective

recall is likely to overestimate the prevalence of ADHD (Manuzza et al., 2002; McGough and Barkley, 2004).

The lack of an experimental design and non-SD ADHD+ comparison group limit the conclusions that can be drawn from this study with regard to a causal link between SD and ADHD. However, the fact that in our study, ADHD was associated with earlier substance use, more SD diagnoses, more psychiatric diagnoses, more suicide attempts, and more hospitalizations due to either substance use or psychiatric problems potentially implicates impulsivity as a feature that could underlie all of these phenomena. This hypothesis also requires empirical validation. Insofar as both ADHD and SD occur commonly in the general population and in the face of evidence that their co-occurrence has important clinical implications, more research into the complex relationship between these disorders is needed to help guide diagnosis and improve treatment outcomes in patients with these co-occurring disorders.

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Table 1

Demographic Variables

Variable[†]	Entire sample (N)	Entire sample % or mean ± s.d.	ADHD (N)	ADHD % or mean ± s.d.	Non-ADHD (N)	Non-ADHD % or mean ± s.d.	GEE p-value [ρ][‡]
Sex	(1761)		(92)		(1669)		0.0381
Male	(914)	51.90	(57)	61.96	(857)	51.35	[0.0586]
Age	(1761)	38.37 ± 7.67	(92)	35.26 ± 8.14	(1669)	38.54 ± 7.61	**< 0.0001** [0.0404]
Race (self-report)	(1760)		(92)		(1668)		**< 0.0001** [0.0496]
NHB	(857)	48.69	(25)	27.17	(832)	49.88	
NHC	(587)	33.35	(52)	56.52	(535)	32.07	
Hispanic	(212)	12.05	(11)	11.96	(201)	12.05	
Marital status	(1761)		(92)		(1669)		0.7309
Married	(248)	14.08	(12)	13.04	(236)	14.14	[0.0504]
Single	(1058)	60.08	(59)	64.13	(999)	59.86	
Years of education	(1760)	11.40 ± 1.97	(92)	11.48 ± 2.07	(1668)	11.39 ± 1.97	0.6620 [0.0539]
Employment	(1760)		(92)		(1668)		0.1092
Yes	(613)	34.83	(25)	27.17	(588)	35.25	[0.0533]
Annual income	(1731)		(87)		(1644)		0.3293
<$20,000	(1194)	68.98	(55)	63.22	(1139)	69.28	[0.0683]
$20,000 – $39,999	(347)	20.05	(20)	22.99	(327)	19.89	
$40,000 – $74,999	(142)	8.20	(8)	9.20	(134)	8.15	
$75,000 – $149,999	(45)	2.60	(3)	3.45	(42)	2.55	
≥ $150,000	(3)	0.17	(1)	1.15	(2)	0.12	

[†]Variables that were significant in the logistic GEE regression analysis in which all of these variables were included are in bold italics. NHB = Non-Hispanic Black; NHC = Non-Hispanic Caucasian

[‡]P-values in bold are those that were significant on bivariate analysis, after correction for multiple comparisons. The symbol ρ denotes the estimated correlation coefficient under the GEE exchangeable structure assumption.

Table 2

Lifetime Prevalence of Substance Dependence (SD) Diagnoses and Related Features

Variable[†]	Entire sample (N)	Entire sample % or mean ± s.d.	ADHD (N)	ADHD % or mean ± s.d.	Non-ADHD (N)	Non-ADHD % or mean ± s.d.	GEE p-value[ρ][‡]
Cocaine	(1761)		(92)		(1669)		0.4171
Dependence	(1627)	92.39	(87)	94.57	(1540)	92.27	[0.0557]
Nicotine	(1760)		(92)		(1668)		0.0232
Dependence	(1252)	71.14	(75)	81.52	(1177)	70.56	[0.0553]
Alcohol	(1759)		(92)		(1667)		**0.0005**
Dependence	(865)	49.18	(62)	67.39	(803)	48.17	[0.0568]
Opioid	(1761)		(92)		(1669)		0.4052
Dependence	(842)	47.81	(48)	52.17	(794)	47.57	[0.0523]
Cannabis	(1757)		(92)		(1665)		**0.0004**
Dependence	(509)	28.97	(42)	45.65	(467)	28.05	[0.0586]
Sedative	(1758)		(91)		(1667)		0.0548
Dependence	(139)	7.91	(12)	13.19	(127)	7.62	[0.0315]
Stimulant	(1759)		(92)		(1667)		**0.0012**
Dependence	(117)	6.65	(14)	15.22	(103)	6.18	[0.0609]
Number of SD diagnoses	(1761)	3.04 ± 1.27	(92)	3.70 ± 1.36	(1669)	3.00 ± 1.26	**< 0.0001** [0.0589]
Age of onset of substance use	(1757)	12.67 ± 3.33	(92)	10.92 ± 2.74	(1665)	12.77 ± 3.33	**< 0.0001** [0.0506]
Age of first SDdiagnosis	(1755)	21.31 ± 6.62	(92)	18.30 ± 4.89	(1663)	21.48 ± 6.66	**< 0.0001** [0.0283]
Number ofhospitalizations	(1741)	3.95 ± 7.46	(92)	6.26 ± 8.80	(1649)	3.83 ± 7.36	**0.0018** [0.0448]

[†]Variables that were significant in the logistic GEE regression analysis in which all of these variables were included are in bold italics.

[‡]P-values in bold are those that were significant on bivariate analysis, after correction for multiple comparisons. The symbol ρ denotes the estimated correlation coefficient under the GEE exchangeable structure assumption.

Table 3

Lifetime Prevalence of Psychiatric Disorders and Related Features

Variable[†]	Entire sample (N)	Entire sample % or mean ± s.d.	ADHD (N)	ADHD % or mean ± s.d.	Non-ADHD (N)	Non-ADHD % or mean ± s.d.	GEE p-value [ρ][‡]
Antisocial Personality	(1741)		(92)		(1649)		**0.0006**
Disorder	(246)	14.13	(25)	27.17	(221)	13.40	[0.0387]
Major Depressive	(1729)		(90)		(1639)		0.6154
Disorder	(236)	13.65	(14)	15.56	(222)	13.54	[0.0145]
Posttraumatic Stress	(1754)		(91)		(1663)		**0.0028**
Disorder	(234)	13.34	(22)	24.18	(212)	12.75	[0.0661]
Pathological Gambling	(1743)		(87)		(1656)		0.0204
	(172)	9.87	(15)	17.24	(157)	9.48	[0.0633]
Panic Disorder	(1752)		(88)		(1664)		0.0061
	(122)	6.96	(13)	14.77	(109)	6.55	[0.0586]
Bipolar Disorder, Type I	(1751)		(92)		(1659)		< **0.0001**
	(92)	5.25	(17)	18.48	(75)	4.52	[0.0505]
Social Phobia	(1721)		(86)		(1635)		0.2906
	(63)	3.66	(5)	5.81	(58)	3.55	[0.0668]
Conduct Disorder	(1740)		(92)		(1648)		< **0.0001**
	(59)	3.39	(13)	14.13	(46)	2.79	[0.0540]
Obsessive Compulsive	(1751)		(88)		(1663)		0.4072
Disorder	(37)	2.11	(3)	3.41	(34)	2.04	[0.0400]
Generalized Anxiety	(1758)		(90)		(1668)		NA
Disorder	(7)	0.40	(0)	0.00	(7)	0.42	
Number of psychiatric disorders	(1761)	0.72 ± 0.93	(92)	1.38 ± 1.01	(1669)	0.68 ± 0.91	< **0.0001**
							[0.0542]
Number of hospitalizations	(1741)	3.95 ± 7.46	(92)	6.26 ± 8.80	(1649)	3.83 ± 7.36	0.0018
							[0.0448]
Suicidal ideation	(1759)		(92)		(1667)		< **0.0001**
	(765)	43.49	(61)	66.30	(704)	42.23	[0.0223]
Attempted suicide	(1754)		(91)		(1663)		< **0.0001**
	(329)	18.70	(7)	40.66	(291)	17.50	[0.0055]
Intentionally self-injurious behavior	(1754)		(91)		(1663)		< **0.0001**
	(124)	7.07	(19)	20.88	(105)	6.31	[0.0333]

[†]Variables that were significant in the logistic GEE regression analysis in which all of these variables were included are in bold italics.

[‡]P-values in bold represent are that were significant on bivariate analysis, after correction for multiple comparisons. The symbol ρ denotes the estimated correlation coefficient under the GEE exchangeable structure assumption.

Table 4

Final logistic GEE regression results (estimated exchangeable correlation within nuclear family ρ, = 0.0017)

Domain	Predictor	Estimated odds ratio	p-value
Demographics	Age	0.953	0.0003
Substance Use	Age of first use of any substance	0.881	0.0001
	Number of substance dependence disorders	1.242	0.0091
Psychiatric Features	Number of psychiatric disorders	1.442	0.0003
	Attempted suicide	2.248	0.0015