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The "Younger-Sibling-at-Risk Design": a Pilot Study of Adolescents with ADHD and an Older Sibling with Substance Use Disorder

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Abstract

Introduction—This article introduces a "younger at-risk sibling" design to study progression from other psychopathologies to their substance use disorder (SUD) complications. The design selects not-yet-SUD adolescents with high-risk-for-SUD psychopathology only if an older sibling has SUD. This "proof of concept" pilot study examines the design's feasibility if the younger sibling has attention deficit hyperactivity disorder (ADHD).

Method—Subjects were recruited from families at substance abuse treatment centers that had a non-SUD younger child with ADHD, from families at behavior disorder clinics that had a younger child with ADHD and SUD older child, and through general advertisements. Subjects were seen weekly for at least 3 months and monthly thereafter for 3 months. All were treated with open-label *lisdexamfetamine* dimesylate 30–70 mg per day. Outcomes explored were recruitment, compliance, diversion, ADHD improvement, and substance use interest.

Results—25 families were screened, 13 evaluated, and 8 began medication. ADHD Rating Scale-IV scores obtained by parent adolescent consensus improved as expected with a stimulant. Rating forms could quantify substance use interest in subjects with some drug culture exposure but encountered a floor effect in those without. The design's complexity and implicit commentary on family dynamics complicated recruitment but may have facilitated retention.

Conclusion—Sibling pairs in which the older sibling has substance use and the younger sibling has ADHD exist. Such younger siblings can be recruited into a treatment study. The design may shed light on the pathogenesis and prevention of SUD complications from ADHD and theoretically other SUD comorbidities.

Keywords

comorbidity; pathogenesis; family; siblings

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

Introduction

Mental disorders [e.g., bipolar, unipolar depression, schizophrenia, and attention deficit hyperactivity disorder (ADHD)] are often comorbid with substance use disorders (SUDs) (1). The associations have been intensively studied (1), but the pathogeneses remain poorly understood gene environment interactions. Recently, a large number of epidemiologic studies have exploited the ability of siblings to amalgamate gene and stable aspects of family environment for various purposes (2). These considerations lead us to experiment with extending sibling studies into the family peer environment of adolescence (2).

Siblings aggregate risk from genes and shared environment, and several studies suggest siblings influence substance use patterns even more than parents (3), presumably because the environment relevant to substance use is age specific. Parents do not experience the relevant environment as teenagers, but siblings do. Motivated by this, we propose to examine a “younger sibling at risk design” to follow the emergence of SUD complications from preexisting risk factors. This design designates the older sibling’s SUD plus the younger sibling’s mental disorder as high-risk markers and the non-SUD younger sibling’s progression or nonprogression to SUD as the outcome. Thus, a not-yet-SUD younger sibling eligible for this design has the genetic/environmental risk of an older sibling with SUD plus the risk of a psychiatric condition associated with SUD (e.g., ADHD).

This approach has the potential to identify and prospectively focus resources on the prevention of SUD in subjects who are at very high risk. Where treatment for the younger sibling’s psychiatric disorder is not possible, it could also be an efficient design within which to prospectively study the process through which children at risk develop SUD. The design should be feasible because many adolescents with SUD will have younger siblings of a given age who are at risk for SUD, and of those, a proportion will have the psychiatric risk factor of interest.

As a “proof of concept” exploration of this “younger sibling at risk design,” we select ADHD as the psychiatric risk factor because it is present well before the age of risk for substance use, facilitating tracking of pathogenesis. ADHD is a disorder of self-regulation, first evident in childhood, and long associated with an increased risk of conduct problems and substance use in adolescence and on into adulthood (4). Inattention, impulsivity, and hyperactivity are the core features of ADHD and affect initiation and persistence of substance use (5,6). We assumed that the best developmental period to study ADHD SUD progression is early to mid-adolescence (ages 11–16) because it is when exposure to substances, a prerequisite for SUD, typically begins. Because progression to SUD must involve different choices than those made by similar subjects who do not follow this progression, these choices must be assessed, preferably in real time. We report our experience with rating scales of “perceived benefit” (7) (validated in junior and senior high school) and the ability to “resist” drug and alcohol use during common adolescent stressors (validated in senior high school) (8). We also report on our experience tracking ADHD in young adolescents, individuals too young for self-report but under less parental observation than children.

The exploratory questions in this open-label proof of concept design are as follows:

1. Whether families with a younger sibling with ADHD and an older sibling with SUD can be found, recruited, retained, and, in this study, pharmacologically treated
2. Whether substance use and interest in alcohol/substances can be quantified in subjects who do not have an SUD
3. Whether ADHD symptoms can be tracked in young adolescents

Method

The Institutional Review Board at the New York State Psychiatric Institute/Columbia University approved this study. After full explanation of this study, the parent signed a consent form and the adolescent an assent form.

Sibling pairs were recruited where the elder had an SUD and the younger had ADHD but not an SUD, although experimentation was admissible. Once ascertained, evaluated, and consented, the younger sibling started pharmacotherapy with open-label *lisdexamfetamine dimesylate* (*Vyvanse*R, Shire US Inc., Wayne Pennsylvania). This medication was chosen for convenience. Shire Pharmaceuticals funded this study and supplied the medication. It is equivalent in efficacy for ADHD to other amphetamine products. This study was not designed to examine whether *lisdexamfetamine* is better than other amphetamine preparations.

Recruitment

We prepared flyers and gave talks to parents at an adolescent substance use treatment center discussing this study in the context of the problems their younger children might have. A reciprocal approach was used with parents of children with ADHD, with whom we discussed substance use risk from ADHD and whether there were older children who might have substance use problems. Interested community pediatricians and child psychiatrists supplemented this approach, and this study was registered on Web sites such as ClinicalTrials.gov. Referred families were screened over the telephone and those that met the study requirements were invited for initial evaluation.

Assessments and Outcome

Initial evaluation included a full psychiatric/medical evaluation [with baseline and follow-up electrocardiograms (EKGs)] and a structured interview (schedule for affective disorders and schizophrenia for school aged children (K-SADS), with ADHD module). All information about the older sibling was obtained indirectly, through the parent.

ADHD symptom severity was assessed weekly for the first 3 months and at least monthly thereafter. ADHD symptoms are often not fully evident to the adolescent patient. We attempted to involve teachers, but expected, based on previous studies of adolescent aggression (9), that parents would be the only reliable other collateral informant in adolescents. A clinician read aloud the items of the ADHD Rating Scale-IV (ADHD-RS-IV) to parent and adolescent seeking consensus about ADHD symptoms the previous week, making a best estimate when consensus was not obtained on an item.

The adolescent was interviewed alone and in confidence about substance use. The Time Line Follow-Back (10) collected substance use data. Modified Pretcher and Nash scales assessed the adolescent's "perceived benefit" of drug/alcohol use (7) and "drug avoidance self-efficacy" (8). The clinician read questions (e.g., True or False – Drinking/Drug use helps me "forget my problems," "be friendly," "feel good about myself") and scenarios that asked the adolescent to imagine the situations (parties, loss of a good job, fight with a loved one, etc.) in which temptations to use substances would be high and rate how well he/she could resist these temptations. Summary scores reflect the adolescent's current state of "interest" and "self-efficacy" or resistance.

Parental and self-reports provided the main estimate of adherence to the protocol. There were additional sources of verification that could prompt further investigation of the reports. First, pill counts from returned vials placed an upper limit on compliance. Second, absence of amphetamine in urine was confirmatory of nomcompliance at least in the past 24–48 h.

Third, pill counts also placed an upper limit of possible diversion of medication for illicit use.

Treatment

Subjects received doses of 30, 50, and 70 mg of *lisdexamfetamine dimesylate (LDX)* over a period of 3 weeks and were then maintained on the dose that provided maximum benefit and fewest side effects. After oral ingestion, the inactive prodrug LDX is converted, primarily in the blood (11), to L-lysine and D-amphetamine, the latter being responsible for the therapeutic effect.

Results

Recruitment

Twenty-five referrals (substance use centers – 5, child psychiatry practitioners and clinics – 12, advertisement/public notice – 8) were screened by telephone. Of these, 13 (11 males, 2 females of varied socioeconomic status) were further evaluated. Primary reasons for initial respondents who were not studied further were (1) not interested in medication, (2) had no older sibling with SUD, (3) the younger sibling already had SUD, and (4) not willing to travel to the research site weekly. Of the 13 [mean age (SD) 14.5 ± 2.0 (range 10–17)] evaluated, all were sibling pairs of interest and offered study participation, 8 [age range 10–17, mean (SD) 14.2 ± 2.1, 7 males, 1 female] accepted. The five families that declined participation cited the impracticality of weekly visits ($N = 3$) or the adolescent's oppositional behavior ($N = 2$) as primary reasons for nonparticipation.

Assessments and Outcome

Diagnostic—Of the 13 younger siblings, 8 were full siblings, 5 were half siblings. All met criteria for ADHD. Five met criteria for oppositional defiant disorder. One had a past history of depression not otherwise specified (NOS), one met criteria for past dysthymia lasting 1 year. By admission criteria, none had SUD.

ADHD—We found that, as in previous studies of aggression (9), peers were impractical and junior high school teachers were unresponsive, but parents and adolescent were able to reach consensus on ADHD symptoms as long as the questions were not seen as a venue to deliver criticism. Of the eight patients who allowed us to treat and follow them, five completed both phases (12 weeks), one dropped out at week 2 for oppositional behavior, one was removed from this study after week 3 (adverse event), one completed phase I (at least 6 weeks). Response of ADHD symptoms by ADHD-RS-IV was a function of compliance. Six subjects were judged fully or adequately compliant during the period of treatment as evidenced by parent report, return of pills, and the presence of amphetamine in the urine. The ADHD-RS scores in these six subjects declined from 28.2 ± 8.3 to 4.3 ± 7.1 on last assessment.

Substance use and vulnerability to substance use—Reports from the Time Line Follow-Back were consistent with urine toxicologies. As a group, there was little substance use reported before and throughout the period of observation. One subject disclosed intermittent use of marijuana during this study; one disclosed intermittent use of alcohol, and one use of both.

The efforts to quantify substance abuse "perceived benefit" (7) and "drug avoidance self-efficacy" (8) encountered a floor effect. Originally designed as surrogates for unreported adolescent substance use, the Petchers and Nash assessments rely on scenarios to detect changes in resistance to substance use in the face of certain stressors. These scenarios presuppose some familiarity with the culture surrounding recreational alcohol/drug use.

Three subjects lacked such exposure and could not relate to the questions. Five subjects could relate to the questions, either vicariously or through direct experimentation, and were able to produce scores. Of the three subjects who acknowledged experimentation, two registered increased resistance to substance/alcohol during the period of treatment, whereas one showed decreased resistance for several weeks before an alcohol/marijuana binge. The two patients with no reported experimentation or detected use registered high resistance to substance use on the Petchers and Nash assessments throughout the period of observation.

Medication Diversion and Compliance—The study physician gave the medication directly to a parent and collected used bottles from them. Ninety percent of the unreturned medication was accounted for by the patients presumably having taking the pills as prescribed. Explanations for unaccounted medication provided by parents included misplaced empty bottles and dropping out of this study. Conversely, 80% of the excess pill returns were attributable to two individuals. Their parents consistently reported intermittent compliance and marginal response of ADHD symptoms. These subjects accounted for 80% of amphetamine negative urines. Oppositional behavior in the adolescent was present and appeared to be the main explanation for noncompliance.

Adverse Events—The medication was well tolerated. Decreased appetite led to weekend drug holidays in two subjects. One patient's EKG changed after 1 week on medication, which required an echocardiogram before study continuation, which the family did not obtain, necessitating removal from this study.

Discussion

There has been a resurgence of sibling designs in epidemiology, using the gene environment amalgam they represent in various ways (2). In this younger sibling at risk design, an older sibling represents both the genetic risk of a pathologic progression (to SUD) and the risk from age-specific family and larger social environment the younger sibling experiences as a teenager. The age-specific nature of the risk is especially relevant to SUDs. In this design, the older sibling can also directly influence the younger sibling in addition to being a marker for age-specific risk. We believe this is an intriguing concept with potential for application. It is therefore important to report on pilot studies indicating the concept's feasibility, identifying the barriers and assessing its potential. This is the purpose of this report.

The results here suggest the "younger sibling at risk design" could be used to study the progression and/or intervention efficacy in cases of ADHD likely to lead to SUD. Families that enter treatment generally comply with study requirements (attend visits and complete ratings). In these highly motivated families receiving open-label treatment, pill counts, parental reports, amphetamine positive (or negative) urines, and response of symptoms provided a consistent picture of general compliance or noncompliance.

Five of the 13 younger siblings were half siblings. On the one hand, the presence of half siblings poses a problem in that it dilutes the genetic contribution to the risk for SUD. However, the presence of half siblings could have informative potential, because it varies the genetic contribution while keeping the stable aspects of family and social environment the same. This would not be relevant in a small study, but in large studies, this could be informative.

Modifications in administration of ADHD rating forms (consensus ratings) may improve tracking of ADHD symptoms in young adolescents. Concerning real-time assessments of adolescent drug use choices, the Pretcher scale was validated in junior and senior high school students. The Nash scale was validated in high school students. We found that both

scales could be used in junior high school adolescents provided they have some exposure to the adolescent drug culture, either direct or vicarious. If there is no evidence of familiarity with drug culture, the scales should probably be avoided because they are evocative of temptations that one would not want to introduce. One option would be to exclude naïve patients in future studies on the theory that if the older sibling is influencing the younger sibling, one would expect at least vicarious familiarity, and we are hypothesizing a gene environment amalgam at work. However, if one wants to extend this study to younger children, where the older sibling's influence could be present but not yet expressed in substance use risk in the younger sibling, then the literature suggests that the number of conduct disorder symptoms is a reasonable surrogate for later substance abuse risk and a cutoff for the number of antisocial spectrum symptoms could be set for entry and monitored (12).

We found two major recruitment barriers. First, the design is complex. "There is an older sibling and a younger sibling and the older one has SUD and the younger one has ADHD but not SUD but could be experimenting" is difficult to convey as sound bytes. New forms of advertisement are needed to convey this information, and the Internet seems the most promising. A second recruitment problem is this study's premise that if nonsubstance psychopathology is adequately treated, substance use and dependence will not inevitably occur. Families easily take this premise as criticism of their earlier failure to prevent their older child's drug problem. We dealt with this implied criticism by conveying the problem as a warning: we are investigating whether there is a way to prevent the younger child from following in his/her older sibling's footsteps rather than a criticism of their treatment of the older sibling. Nevertheless, some families did not want to think about history possibly repeating itself or saw the recommendation of treating the younger child as criticism and were not amenable to this study. Helping families to accept the design's premise is, therefore, already a therapeutic breakthrough. Although the design has implications for the study of a range of risk factors, not only ADHD, it also has clinical implications. Although family history is routine in psychiatric evaluations, detailed inquiry about younger or older siblings is rare. Settings that would routinely and systematically make such inquiries could provide research subjects at high risk for many complex psychosocial outcomes. Adolescent substance abuse treatment centers and child and adolescent clinics could immediately implement the assessment of siblings. Careful follow-up of these families could provide insight into the process by which a risk factor such as ADHD sometimes does and sometimes does not lead to SUD complications. Thus, the design has the potential to integrate research and clinical care under one setting.

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