

**Annual Report 2002: The Johnson and Johnson Center for Pediatric
Psychopathology at the Massachusetts General Hospital**

**Director: Joseph Biederman, MD
Co-Director: Stephen V. Faraone, PhD**

<i>Executive Summary</i>	<i>I</i>
Overview	1
Assessing the Efficacy and Safety of Medications for Child Psychopathology	1
Resolving Complex and Controversial Diagnostic Issues	2
Assessing the Severity and Chronicity of Child Psychopathology	3
Clarifying the Biological Basis of Childhood Psychopathology	3
Genetics	4
Neuroimaging	4
Disseminating Research Results and Educating Clinicians	4
<i>Details of Center Activities in 2002</i>	<i>5</i>
Creation of a Multidisciplinary Team	6
Data Collection Efforts Initiated in 2002	9
Treatment Studies	9
Comparative Effectiveness and Tolerability of RISPERDAL with SEROQUEL, GEODON, ZYPREXIA	9
REDACTED	9
REDACTED	9
REDACTED	9
RISPERDAL and CONCERTA for ADHD in Children and Adults with Bipolar Disorder	9
MR spectroscopy study of children before and after RISPERDAL	9
Development of driving simulator for adults with ADHD	9
Sleep apnea and ADHD in adults	9
Treatment of Psychiatric Comorbidity in Bipolar Disorder.	9
Pharmacokinetics and Drug-Drug Interactions.	10
Olanzapine plus Topiramate.	10
Initial Treatment Studies of Bipolar Depression.	10
Epidemiologic and Genetic Studies of Pediatric Psychopathology.	10
Genotyping Efforts and Genetic Databank Development	10
Phenotypic characterization of velo-cardio-facial (VFC) Syndrome	10
Studies of Temperamental Risk Factors for Pediatric Bipolar Disorder.	10
Longitudinal Family Study of Pediatric Bipolar Disorder.	11
Follow-Up of Preschoolers with Bipolar Disorder.	11
Children at High Risk for Bipolar Disorder	11
Neuropsychology and Neuroimaging of Pediatric Psychopathology	11
Magnetic Resonance Imaging of BPD+ADHD Adults	11
MR Spectroscopy of BPD children before and after treatment with RISPERDAL	11
Analyses of Archival Data Sets	11
Data Sets Available Through MGH	11
Clinic Data	11
Longitudinal Family Study of ADHD	12
Data Sets Available Through J&J	12
Double-Blind Trial of RISPERDAL in Children with Conduct Disorder and Mental Retardation	12

REDACTED	12
Other Data Sets	12
Bipolar Genetic Linkage Data.	12
Support of Junior Faculty to Develop Expertise in Pediatric Psychopathology Research	13
Communication With J&J Staff to Facilitate Collaborative Efforts	14
Initiation of Yearly Meetings of Experts in Bipolar Disorder	14
<i>Plans for the Future</i>	15
<i>Appendix A: Biographical Sketches of MGH Investigators</i>	17
<i>APPENDIX B: Presentations at National and International Meetings in 2002 By MGH Pediatric Psychopharmacology Research Program</i>	17
<i>APPENDIX C: Preparation of Manuscripts for Publication in 2002 By MGH Pediatric Psychopharmacology Research Program</i>	17
<i>References</i>	17

Executive Summary

Overview

The mission of the Center is to create a common ground for a strategic collaboration between Johnson & Johnson (J&J) and the Pediatric Psychopharmacology Research Program at the Massachusetts General Hospital (MGH). The Center provides an infrastructure for MGH researchers to collaborate with J&J researchers on comprehensive studies of pediatric psychopathology, including diagnostic, therapeutic, and neurobiologic studies. The formation of the Center has created a forum for multidisciplinary collaborative research in a number of key areas, with an initial focus on pediatric mood and disruptive behavior disorders.

An essential feature of the Center is its ability to conduct research satisfying three criteria: a) it will lead to findings that improve the psychiatric care of children; b) it will meet high levels of scientific quality and c) it will move forward the commercial goals of J&J. We strongly believe that the Center's systematic scientific inquiry will enhance the clinical and research foundation of child psychiatry and lead to the safer, more appropriate and more widespread use of medications in children. Considering that nearly all psychiatric medication use in children is off label, studies of safety and efficacy in children are essential for clinicians, parents and patients to feel comfortable using these medications in children. The Center is poised to test the effectiveness and safety of RISPERDAL, REDACTED and new products as they emerge from the pipeline.

Equally important to effective use of medications is the demonstration of the validity of disorders. Because parents, patients and clinicians are exposed to a media that frequently questions the validity of childhood disorders, genetic and brain imaging studies are needed to show the validity of these disorders as brain disorders that respond to medication. Epidemiologic studies are needed to show that childhood disorders are frequently chronic and severely debilitating. Without such data, many clinicians question the wisdom of aggressively treating children with medications, especially those like neuroleptics, which expose children to potentially serious adverse events. Epidemiologic studies also show the continuity of childhood and adult disorders. This provides an additional measure of validation for the childhood disorder and in some cases validates the disorder as a disorder of adulthood as we have seen for adult attention deficit hyperactivity disorder (ADHD).

Through the funding provided by J&J, we are creating a team of investigators focusing on the following issues.

Assessing the Efficacy and Safety of Medications for Child Psychopathology

We will generate and publish data on the efficacy and safety of medications for improving currently available treatment options for child psychopathology. This work is an essential precursor to the safe, appropriate and widespread use of medications given that most must be used off-label. Specific goals of this area of work include:

- Assessing the full range of symptoms treated by RISPERDAL by analyzing data from Janssen's study of RISPERDAL among conduct disorder/mentally retarded youth. This will allow us to extend Janssen's prior findings indicating efficacy for conduct disorder to mania, anxiety and other classes of psychopathology.
- Using MGH open-label studies to assess the differential effectiveness and safety of RISPERDAL and ZYPREXA in the treatment of pediatric bipolar disorder (BPD). For example, we have already shown that ZYPREXA leads to twice the weight gain as RISPERDAL.

- Using MGH open-label studies to demonstrate how combination pharmacotherapy can be used to treat complex cases. Examples include using RISPERDAL and CONCERTA to treat ADHD with BPD, REDACTED

REDACTED

Resolving Complex and Controversial Diagnostic Issues

Many children with psychopathology never receive medical treatment due to controversies in the media and debates among professionals about the validity of psychiatric diagnoses in children. Additional under-treatment occurs due to lack of mental health screening in primary care clinics. The Center seeks to address complex and controversial diagnostic issues through empirical research. This domain of work includes validating diagnostic methods, validating tools for screening and treatment monitoring and, if needed, creating new measures which will allow physicians to confidently screen for and diagnoses child psychopathology. Center investigators are now examining diagnostic and measurement issues for three disorders that have been particularly controversial: pediatric BPD, adult ADHD and pediatric psychosis. Specific goals of this area of work include:

- Analyzing databases at MGH to characterize pediatric BPD, adult ADHD and pediatric psychosis. This will help clinicians understand the nature of these disorders, which will facilitate their ability to diagnoses them in their practices.
- Developing and assessing the validity of screening tests for complex disorders such as comorbid ADHD, psychosis and pediatric BPD. Once appropriately validated, the use of these screening tests will alert physicians about disorders that exist which RISPERDAL and CONCERTA might treat. Currently, many children with psychosis and BPD and many ADHD adults are not identified as such so are not treated outside of specialty academic centers.
- Implementing training programs for screening tools in continuing medical education programs targeting pediatricians and general psychiatrists.
- Analyzing baseline data from Janssen funded studies to validate affective disorder subtype in the conduct disorder subpopulation. Further validation of this group will alert physicians to the existence of a large group of children who might benefit from treatment with RISPERDAL.
- Analyzing data bases at MGH to clarify the continuity between childhood and adult disorders. Showing how pediatric mania evolves into what some have called mixed or atypical mania in adulthood, will provide further support for the chronic use of

{Page}

RISPERDAL from childhood through adulthood. Such data will teach clinicians about how to identify these symptoms in adults.

- Using the classic criteria of Robins and Guze (1970) to validate diagnostic criteria for pediatric BPD, childhood psychosis and adult ADHD using studies of course, outcome, genetics, cognition and neuroimaging as described in the following sections.
- Using neuropsychological measures to accurately identify executive brain dysfunction and differentiate it from ADHD. Because executive brain dysfunction is seen in many ADHD children, there is some debate about whether it is a separate syndrome or another manifestation of ADHD. By clarifying this issue, we will demonstrate the need for clinicians to assess for executive brain dysfunction and consider potential medical treatments for this condition in their ADHD patients.
- REDACTED

Assessing the Severity and Chronicity of Child Psychopathology

We will study the natural course of pediatric psychopathology, the long-term incidence of the various dysfunctions and the long-term effects of pharmacologic and other interventions. This work validates childhood disorders by demonstrating how it evolves in adult manifestations of the same disorders. It shows clinicians that aggressive treatment is warranted because these disorders lead to substantial disability. By clarifying the chronicity of disorders, it further documents the necessity for the chronic treatment of some disorders by debunking myths which present childhood psychopathology as a normal phase of development. For example, in the past, ADHD was viewed as a remitting disorder and treatment was usually stopped during adolescence. Today, due to longitudinal studies the American Academy of Pediatrics now recommends treating ADHD as a chronic illness. Specific goals of this area of work include:

- Assessing the severity and chronicity of pediatric BPD using the same methods we have used for longitudinal studies of ADHD (Biederman et al., 1998b; Biederman et al., 2000).
- Characterizing the chronic, debilitating course of BPD to help people understand need for aggressive treatments such as RISPERDAL.
- Evaluating the effectiveness of medical and psychosocial treatments on long term outcomes in pediatric BPD using a naturalistic design.
- Evaluating the effect of RISPERDAL treatment on functioning in pediatric BPD in database studies and prospective short and long term studies.
- Assessing the disability associated with adult ADHD to help us understand the future of child ADHD and the need for chronic treatment. We are addressing this through a large longitudinal family study of ADHD and are also developing a day-long laboratory protocol to quantify the "real world" impairments associated with ADHD such as impaired driving skills and difficulty concentrating on work requiring sustained attention.

Clarifying the Biological Basis of Childhood Psychopathology

One of the main obstacles to the medical treatment of childhood disorders is the myth that they simply reflect problems of family and culture rather than dysfunctions of the brain. We will help dispel these myths using genetic and neuroimaging studies. These studies further validate childhood disorders as medical conditions and thereby give physicians more confidence in the use of medical treatments. By clarifying the causes of childhood disorders, these studies also lay

the ground work for the development of more efficacious treatments or the use of current treatments in a more effective manner. Specific goals of this area of work include:

Genetics

- Identifying genes that increase the susceptibility to child psychopathology with an initial emphasis on ADHD and BPD.
- Validating diagnostic criteria and assessing the validity of comorbidity using designs from genetic epidemiology.
- Creating a platform for collaboration between MGH and the J&J pharmacogenetics department by working with J&J to collect, DNA, safety data and efficacy data. The goal of this work is to discover genes which predict therapeutic response or adverse events during treatment with J&J medications.
- Collecting pharmacogenetic data in MGH studies of RISPERDAL, REDACTED REDACTED
- Studying children having a bipolar parent to develop rules for identifying pre-clinical cases. By accurately identifying children at risk for psychopathology, we will be able to develop early intervention and prevention treatment programs.

Neuroimaging

- Using magnetic resonance imaging to identify structural and functional patterns in the brain that characterize psychopathological subgroups, particularly controversial diagnoses such as pediatric BPD and adult ADHD.
- Initiating a prospective study of the efficacy and safety of RISPERDAL in pediatric BPD, including neuroimaging on a subset of patients.
- Using magnetic resonance spectroscopy to examine changes in NAA/CA, Choline, and other brain metabolites in response to RISPERDAL treatment.
- Using structural and functional magnetic resonance imaging in medication naïve patients to demonstrate that brain changes are associated with childhood disorders, not their treatment.

Disseminating Research Results and Educating Clinicians

To have an impact on clinical practice, research results from the Center must be disseminated through scientific publications, presentations and national and international meetings and continuing education programs. Our program of dissemination is as follows:

- Presenting findings and national meetings of the American Psychiatric Association, the American Academy of Pediatrics, the American Academy of Child and Adolescent Psychiatry, the American Psychological Association, Biological Psychiatry, NCDEU and the American College of Neuropsychopharmacology.
- Presenting findings at international meetings of the World Psychiatric Association, the World Congress of Psychiatric Genetics, the European College of Neuropsychopharmacology (ECNP) and the Collegium Internationale Neuro-Psychopharmacologicum (CINP).
- Developing and implementing a BPD continuing education program to teach pediatricians and psychiatrists how to screen for, diagnose and treat BPD

- Present continuing medical education programs at national and international professional meetings:
- Convening a yearly international conference for investigators studying pediatric BPD (this is possible through funding from Janssen and a grant from the National Institute of Mental Health to Dr. Biederman).
- Convening a yearly international conference for investigators studying the genetics of ADHD (this is possible through funding from the National Institute of Mental Health to Dr. Faraone).
- Preparing manuscripts for publication in psychiatric, pediatric and psychological journals.

Details of Center Activities in 2002

In 2002, we made progress in the following areas:

- At MGH, we identified a multidisciplinary team of psychiatrists, psychologists, psychiatric clinical nurse specialists, epidemiologists, and behavioral geneticists to participate in the Center
- We initiated several research projects
- We initiated data analyses of archival J&J and MGH data sets.
- We disseminated the results of our work and national and international meetings.
- We prepared initial manuscripts for publication.
- We supported junior faculty efforts to develop expertise in pediatric BPD.
- We developed and maintained a schedule of regular communication with J&J staff to facilitate collaborative efforts.
- We Initiated Yearly Meetings of Experts in Bipolar Disorder.

Creation of a Multidisciplinary Team

Table 1 lists the MGH investigators participating in the Center. These participants are each faculty members in the Harvard Medical School Department of Psychiatry at MGH. As Table 1 shows, they have experience using a wide range of methods and measurement tools. A comprehensive description of all the prior work in these areas of measurement is beyond the scope of this report, but an examination of the biographical sketches of the investigators (see Appendix A) shows the extent of their prior empirical work, most of which has used the methods and assessment measures to be used in the proposed Center.

Through this multidisciplinary faculty, the Center has access to the systematic assessments needed for screening, study recruitment and study implementation. Table 2 shows the domains of assessment expertise available to the Center. Most studies need structured interviews for psychiatric diagnostic assessments. Treatment protocols also require measurement in domains of functioning at baseline that might be predictive of subsequent treatment response as well as measures of psychopathology and functioning that will be sensitive to the clinically meaningful changes that will occur with treatment. The Center maintain assessment tools that allow for the assessment of functioning in multiple domains: psychiatric, psychosocial, neuropsychological, quality of life, and the utilization of health services.

Table 1: MGH Participants in Center Research

EXPERTISE	INVESTIGATOR
Psychosocial Treatment Outcome Designs	Stephen Faraone, PhD Ross Green, Ph.D Dina Hirschfeld, Ph.D.
Psychopharmacological Treatment Outcome Designs	Joseph Biederman, MD Tom Spencer, MD Tim Wilens, MD
Epidemiological Designs	Stephen Faraone PhD Eric Mick, Sc.D.
Molecular and Statistical Genetics	Stephen Faraone, PhD James Gusella, PhD Paul Van Eerdewegh, PhD
Psychiatric Assessment, Diagnosis and Treatment-Outcome	Joseph Biederman, MD Tom Spencer, MD Tim Wilens, MD Janet Wozniak, MD
Psychological and Psychosocial Assessment	Stephen Faraone, Ph.D. Ross Green, Ph.D Dina Hirschfeld, Ph.D.
Neuropsychological Assessment	Larry Seidman, PhD Alysa Doyle, Ph.D
Neuroimaging	Larry Seidman, PhD
Statistical Analysis	Stephen Faraone PhD Eric Mick, Sc.D.
Data Base Programming: Computer Hardware: Networking; Data Quality and Security	Eric Mick, Sc.D.
Biostatistics	Stephen Faraone PhD Eric Mick, Sc.D.

Table 2: Measurement Domains Available to the Center

	Type of Study		
	Diagnostic Studies	Treatment Studies	Etiology Studies
Psychiatric Symptoms			✓
Structured Diagnostic Psychiatric Interview	✓	✓	✓
Substance Use Assessments		✓	✓
Clinical Rating Scales	✓	✓	✓
Social Functioning	✓	✓	✓
Family Environment Scale		✓	✓
Expressed Emotion		✓	✓
Family Burden		✓	
Neuropsychological Functioning			
Health Services Utilization	✓	✓	

Because much of the under-treatment of psychiatric disorders in children is due to concerns about the accuracy and validity of diagnostic measures, the ability to validate measures of childhood psychopathology is an essential component of the Center. The availability and use of good measurement technologies leads to improved acceptance of research results by the FDA, physicians, patients, their parents and the general public.

Center investigators have completed many methodological studies that validate the use of these assessment tools in pediatric populations. Examples include:

- Showing that parent-based diagnoses of ADHD are predictive of teacher-based diagnoses (Biederman et al., 1993b; Biederman et al., 1990a). This work has facilitated drug development for ADHD, when teacher reports are lacking. This makes adolescent studies feasible and also provides reassurance to clinicians when they must diagnose children without information from teachers.
- Using clinical trials data to show that parent reports are sufficient for detecting efficacy in studies of long-acting medications for ADHD (Biederman et al., submit). This work provides reassurance to clinicians when they must titrate medications without feedback from teachers
- Demonstrating that structured interview diagnoses of child psychopathology show high reliability and diagnostic efficiency (Faraone et al., 1995). This type of work clarifies the objective nature of diagnosis, which helps clinicians understand the value of applying them in pediatric settings.
- Supporting the validity of adult ADHD diagnoses by showing that parental ADHD does not bias reports of ADHD in children (Faraone et al., in press), that symptom reports by ADHD adults are not influenced by the presence of ADHD in their children (Faraone et al., 1997) and that adult relatives of ADHD children have high rates of ADHD and that family study methods show adult ADHD to be a valid diagnosis (Faraone et al., 2000a). By demonstrating the validity of adult ADHD diagnoses, this and other work has led to a more widespread acceptance of the diagnosis, including acceptance by the FDA, which previously doubted its validity but has now given Lilly an adult ADHD indication for STRATTERA.
- Creating a method for assessing medication efficacy in a naturalistic setting by applying structured assessments to medical records (Biederman et al., 1999). This provides a simple method for assessing efficacy. As we have shown for the RISPERDAL treatment of bipolar disorder (Biederman et al., 1999), this method provides a quick assessment of whether a currently available medication is worth pursuing in a clinical trial.
- Using multiple definitions of remission to assess course and outcome (Biederman et al., 2000) and creating an assessment and analysis scheme for defining normalized functioning in children (Biederman et al., 1998b) we have been able to quantify the chronicity and severity of disorders and, thus, the need for chronic, aggressive medical treatment.
- Demonstrating the validity of the Social Adjustment Scale for Children and Adolescents (Biederman et al., 1993a) provides a useful tool for assessing the efficacy of medications in this "real world" domain of dysfunction affected by many psychiatric disorders.
- Creating new designs to clarify psychiatric comorbidity using the family study method has validated comorbid conditions and strengthened the rationale for treating them (Faraone et al., 1999).

- Showing that exclusive reliance on youth self-reports may identify a mild form of depression associated with limited morbidity and disability compared with that identified by parental reports (Braaten et al., 2001) and showing that the potential distortion of indirect interviews by depressed mothers may be stronger in community than in clinical settings and does not account for the increased risk for MD in referred adolescents with ADHD (Mick et al., 2000) This work will lead to better methods of identifying depression in children.
- Documenting substantial stability of Child Behavior Checklist (CBCL) scales over time for ADHD patients to support the informativeness of the CBCL as a useful measure of longitudinal course in clinical samples of youth with ADHD (Biederman et al., 2001b). This work provides further evidence that the CBCL is a useful tool for screening and monitoring the progression of disorders.
- Developing new methodologic approaches for prevention protocols (Faraone et al., 2002). This work will, in the long-term, lead to psychopharmacologic protocols aimed at the primary prevention of childhood psychiatric disorders

The Center also includes substantial expertise in data management and analysis, which allows it to provide methodological, statistical and data base management assistance to participating investigators. To facilitate study efficiency and data sharing the Center has implemented a common data analytic infrastructure. This infrastructure has enabled the design of shared databases for analytic efforts of data collected across various studies.

Eric Mick, ScD heads the Center's data management efforts. As an epidemiologist, he is highly experienced in the collection, editing and management of large complex data sets from psychiatric studies, including longitudinal and family studies. He and our data base developer, Ellie Remskar, are responsible for setting-up and maintaining the central data management system. To achieve the goals of central data management, he plans for the software and hardware needs of the central system and supervises the day to day work of the central data management staff. He also assures the integrity of data management for each Center project.

Stephen Faraone, Ph.D. heads the Center's data management efforts by coordinating group of two junior faculty and three masters level statisticians well versed in a variety of statistical techniques. This resource is available to participating investigators (i.e., developing and established scientists), clinicians planning to become investigators and students (including graduate students, interns, residents and fellows). The data analysis efforts at the Center also include the development of new methods to deal with new issues that arise in the Center's research program. Prior examples of methods development include:

- The use of analytic mathematics and simulations to choose among methods for analyzing autocorrelated binary data (Faraone and Dorfman, 1987);
- The development of a method to assess inter-observer agreement in the presence of autocorrelation (Faraone and Dorfman, 1988);
- Creation of a method to render radioreceptor assay results comparable between different neuroleptic medications (Young et al., 1989).
- The use of simulations to choose among methods of morbidity risk estimation (Faraone et al., 1994) and to assess the statistical power of linkage studies (Chen et al., 1992).
- The use of multidimensional scaling to clarify diagnostic confusability and reliability (Faraone et al., 1996).
- The use of mathematical genetic considerations to choose phenotypes for genetic analysis (Faraone et al., 2000b).

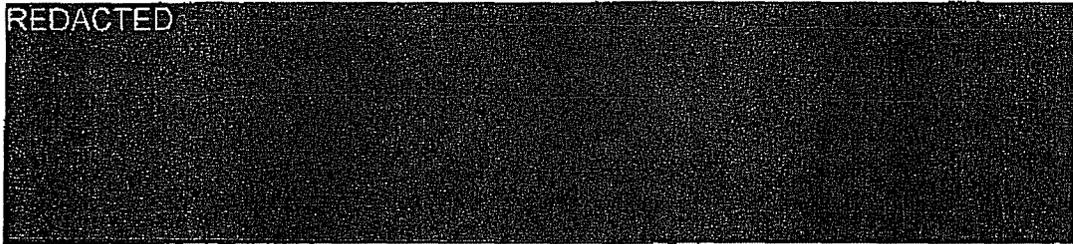
- The use of latent class methods to measure diagnostic accuracy in the absence of a gold standard (Faraone and Tsuang, 1994).
- An analytic demonstration of the effects of fixed-dose, clinical-dose and reduced-dose treatment designs on outcome measures (Faraone et al., 1992).
- The development of a receiver operating characteristic (ROC) based method to optimize the validity of psychiatric diagnoses (Faraone et al., 1993).
- The development of an ROC based method to comprehensively describe differences in efficacy between drug and placebo or between two drugs (Faraone et al., 2000c).
- Comprehensive reviews of ascertainment and statistical methods in psychiatric genetics (Faraone and Santangelo, 1992; Faraone et al., 1999; Faraone and Tsuang, 1995).

Data Collection Efforts Initiated in 2002

Treatment Studies

We will add descriptions of these.

Comparative Effectiveness and Tolerability of RISPERDAL with SEROQUEL, GEODON, ZYPREXIA



RISPERDAL and CONCERTA for ADHD in Children and Adults with Bipolar Disorder

MR spectroscopy study of children before and after RISPERDAL

Development of driving simulator for adults with ADHD

Sleep apnea and ADHD in adults

Treatment of Psychiatric Comorbidity in Bipolar Disorder.

Bipolar youth frequently present with one or more of the following comorbid disorders: ADHD, oppositional defiant disorder, pervasive developmental disorder, anxiety, and major depression. These disorders complicate treatment planning for two reasons. First, little is known about how to sequence the treatments for co-occurring conditions. In addition, the standard treatments for some comorbid conditions (e.g. stimulants for ADHD, SSRIs for depression) may exacerbate mania. Our plan is to develop open label trials targeted at these comorbid conditions to get an early signal regarding the effectiveness of these therapies. Those that look promising will be further developed by pursuing external funding for large scale clinical trials. We have currently initiated the following studies of comorbidity:

- Open-label study of RISPERDAL for pediatric BPD. This study serves as an ascertainment source for cases of BPD with ADHD, which can then be enrolled in a

study assessing the effectiveness of CONCERTA for ADHD in RISPERDAL treated BPD children.

- REDACTED

Pharmacokinetics and Drug-Drug Interactions.

Because many of the medications we are studying have not been used extensively in pediatric populations, it is essential that we collect pharmacokinetic data. Moreover, some of our protocols use more than one compound. Thus, a key component of our program is to evaluate potential drug-drug interactions associated with combined treatments using appropriate pharmacokinetic and pharmacodynamic protocols. Current pharmacokinetic studies are as follows:

- Pharmacokinetics of RISPERDAL in Pediatric ADHD
- REDACTED
- Pharmacokinetics of RISPERDAL and CONCERTA in Children with BPD and ADHD

Olanzapine plus Topiramate.

Topiramate has been used to offset weight gain associated with atypical neuroleptics in clinical practice but has not been systematically evaluated. Thus, the objective of this study is to evaluate the safety and effectiveness of added topiramate to minimize iatrogenic weight gain approaches to the treatment of BPD in children and adolescents.

Initial Treatment Studies of Bipolar Depression.

Since depression is a highly morbid state of bipolar disorder and since antidepressants can exacerbate manic symptoms, the evaluation of safe and efficacious treatments for bipolar depression remains uncertain. To this end, we initiated a clinical trial comparing the effectiveness of bupropion and paroxetine for the treatment of bipolar children with active symptoms of depression. These are potentially useful options to evaluate in this population since they have each been shown to have a low manicogenic risk in adults.

Epidemiologic and Genetic Studies of Pediatric Psychopathology.

Genotyping Efforts and Genetic Databank Development

We have been collecting blood samples from each member of the nuclear family of children with bipolar disorder. This blood is stored so that DNA may be extracted in the future in order to conduct linkage, association or pharmacogenetic analyses.

Phenotypic characterization of velo-cardio-facial (VFC) Syndrome

Since VCF has been associated with bipolar disorder in some studies, we are collecting digital photographs of children with bipolar disorder in order to test the hypothesis that hemizygous deletion of chromosome 22q11 may result in bipolar affective disorder. This finding may eventually lead towards the identification of candidate genes for early onset bipolar disorder.

Studies of Temperamental Risk Factors for Pediatric Bipolar Disorder.

Another major research interest of our group has been the study of temperament as a risk factor for subsequent psychopathology in at-risk children. We currently have a large program which has shown that behavioral inhibition is an early onset precursor of subsequent anxiety disorders

(Biederman et al., 2001a; Biederman et al., 1993c; Biederman et al., 1990b). If the new Center is funded, we plan to create a research program aimed at identifying temperamental risk factors for pediatric bipolar disorder. In particular, we intend to follow-up on some intriguing leads from our pilot studies, which suggest that behavioral disinhibition may be a very early onset risk factor for pediatric bipolar disorder.

Longitudinal Family Study of Pediatric Bipolar Disorder.

Longitudinal studies of pediatric bipolar disorder hold the promise of settling controversies that have plagued the field. If bipolar disorder is a valid diagnosis in children, signs of the disorder should remain evident at follow-up assessments. Equally important will be determining the course of comorbidity in pediatric bipolar disorder to see if they have a course and outcome that parallels that which has been seen for the comorbid disorder when it occurs in the absence of bipolar disorder. Dr. Wozniak collected 110 families ascertained via pediatric bipolar patients through her NIMH Career Development Award. With J&J funding, we have been able to initiate a follow-up study of this sample.

Follow-Up of Preschoolers with Bipolar Disorder.

In light of extensive media attention devoted to a recent pharmacoepidemiological analysis which asserted that large number of preschool children are inappropriately treated with pharmacotherapy and since children with bipolar disorder frequently present to clinics at very young ages with a very severe clinical picture, we are following preschoolers (age < 6 years) who meet criteria for bipolar disorder to systematically evaluate the longitudinal course of this disorder in this age group.

Children at High Risk for Bipolar Disorder

~~We will add descriptions of this.~~

Neuropsychology and Neuroimaging of Pediatric Psychopathology

Magnetic Resonance Imaging of BPD+ADHD Adults

~~We will add descriptions of this.~~

MR Spectroscopy of BPD children before and after treatment with RISPERDAL

Analyses of Archival Data Sets

Data Sets Available Through MGH

Clinic Data

For the past decade we have systematically collected data on consecutive admissions to our pediatric psychopharmacology clinic. As a result, we have extensive clinical data (e.g., structured interviews, rating scales, psychometric tests) on more than 2000 patients not selected for a specific disorder. We also have the capability of completing systematic chart reviews using the methodology developed by Biederman et al. (Biederman et al., 1998a; Biederman et al., 1999). Ongoing analyses of these data are as follows:

[Page]

- Clinical Features of Pediatric BPD
- Gender and Psychiatric Comorbidity in Adult ADHD
- Clinical Features of Children with Psychosis

Longitudinal Family Study of ADHD

Over the past twenty years, Drs. Biederman and Faraone have, with funding from NIMH, been following families of 140 ADHD boys, 140 ADHD girls and more than 200 gender and age matched control families from childhood to adulthood. Baseline and follow-up studies (which have also included family members) have provided a wealth of data about the course, outcome, clinical correlates and familial aggregation of ADHD. These data sets have allowed for the following analyses:

- Comorbid Anxiety Disorders Among Children with BPD
- Exposure to Parental Bipolar Disorder as a Risk Factor
- Follow-up Study of ADHD children with BPD

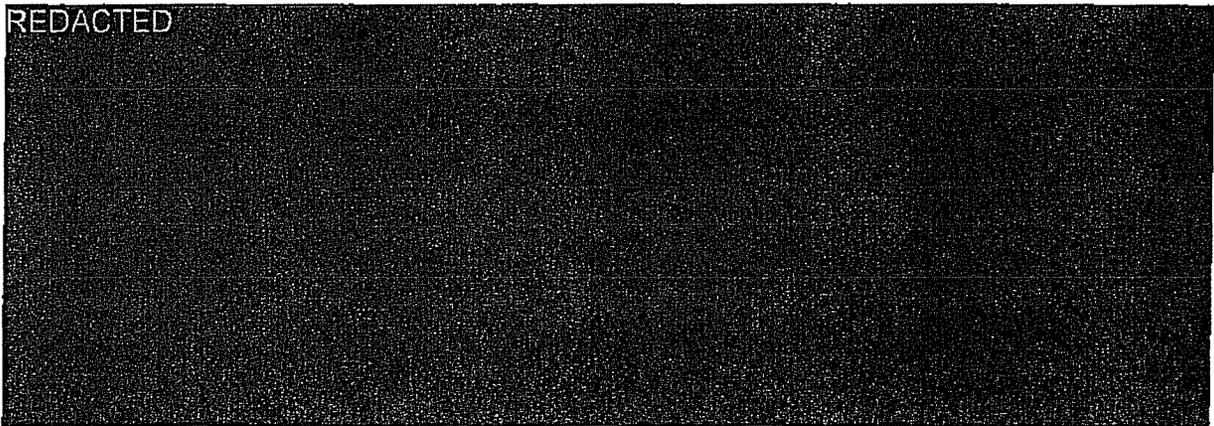
Data Sets Available Through J&J

Double-Blind Trial of RISPERDAL in Children with Conduct Disorder and Mental Retardation

This data set contains the results of Janssen's clinical trial of RISPERDAL for conduct disorder and mental retardation. It also includes outcome ratings on a wide variety of symptoms, which makes it useful for assessing the efficacy of RISPERDAL for other conditions in this population and for assessing psychometric features of the measures. Analyses completed to date are:

- Efficacy of RISPERDAL for manic symptoms
- Replication of Factor Analysis of BPD Symptoms

REDACTED



Other Data Sets

Bipolar Genetic Linkage Data.

We have access to the NIMH bipolar disorder genetic linkage data set, which is a public resource available through the NIMH Genetics Initiative Program. We are using this data set for the following:

- Linkage analysis of the age at onset of manic symptoms

- Factor analysis of manic symptoms
- Published Data

We have found meta-analysis to be very useful for clarifying issues in pediatric psychopathology. We have already applied this methodology to studying the DRD4 gene in ADHD (Faraone et al., 2001), the efficacy of ADHD medications (Faraone and Biederman, 2002; Faraone et al., 2002) and to studying the effects of stimulant medications on substance abuse in ADHD (Wilens et al., in press). We are currently using meta-analysis of published data as follows:

- Meta-analysis of multiple studies using CBCL to validate profiles
- Meta-analysis of the DAT gene in ADHD (through collaboration with the ADHD Genetics Network, S. Faraone (PI)).
- Meta-analysis of the DRD5 gene in ADHD (through collaboration with the ADHD Genetics Network, S. Faraone (PI)).

Support of Junior Faculty to Develop Expertise in Pediatric Psychopathology Research

Perhaps the most enduring impact of our Center will be the work of trainees and junior investigators whom we have attracted to the study of pediatric psychopathology. By doing so, we will create a new generation of investigators committed to studying the causes of and treatments for childhood psychopathology.

Table 3 describes the young investigators supported by our research program. The table shows that we have been creating a team of new investigators who have a wide range of expertise including psychopharmacology, psychosocial treatment, substance abuse, neuroimaging and pharmacology. Although each of these new investigators has a specific expertise, our approach to training requires that they study pediatric bipolar disorder within the broader context of childhood psychopathology. For example, we have not set up a bipolar disorder specialty clinic. Instead, clinicians are taught to diagnose bipolar disorder and all comorbid psychopathology. This makes it easier to recognize comorbidity and to devise research protocols aimed at understanding its causes or devising methods for its treatment.

Investigator	Speciality	Projects
Janet Wozniak, MD	Pediatric BPD	Clinical trials and longitudinal family study of BPD.
Ross Greene, PhD	Psychosocial Treatment	Clinical Trials of Psychosocial Therapies for Children with Bipolar Disorder.
Louise Cohen, PharmD	Pharmacokinetics	Developmental Pharmacokinetics of Psychotropic Drugs
Dina Hirshfeld, PhD	Anxiety Disorders	Temperament as a Risk Factor for Psychopathology
REDACTED		
Eric Mick, ScD	Methodology	Methods Development and Applications
Aude Henin, Ph.D.	Children at Risk	Children at Risk for Bipolar Disorder
Alysa Doyle, Ph.D.	Neuropsychology	Cognition and Genetics of ADHD
Dan Geller, MD	Obsessive Compulsive Disorder	Treatment and Epidemiologic Studies of OCD
Eve Valera, Ph.D	Neuroimaging	Structural and Functional MRI of ADHD

Our training program also encourages cross-fertilization among disciplines, a process that is facilitated by the fact that the Center Director, Dr. Biederman, is a psychiatrist, his Co-Director, Dr. Faraone, is a psychologist and the Scientific Coordinator, Dr. Mick, is an epidemiologist. On a practical, training level, cross-fertilization means that junior investigators must learn about

concepts and methods outside their main area of inquiry. Moreover, they must incorporate these into their research protocols.

Communication With J&J Staff to Facilitate Collaborative Efforts

We will add descriptions of this.

Initiation of Yearly Meetings of Experts in Bipolar Disorder

To address the controversy about pediatric bipolar disorder, we initiated a multi-year conference series which seeks to establish a forum for researchers and clinicians to improve dialogue and foster collaborative studies about children who present with extreme temper tantrums and dysregulated mood. Preceding roundtables on pediatric bipolar disorder had stressed the pressing need to advance the scientific knowledge of this severe mental disorder and had recognized the paralyzing effects of the ongoing controversy surrounding pediatric bipolar disorder and bipolar spectrum disorders. This controversy led to a vicious circle of diagnostic skepticism, void of scientific information, and therapeutic nihilism with its detrimental impact on patients and their families.

Fostering dialogue among scientists and clinicians is a key step to better defining the clinical and scientific questions and fostering necessary collaborative research critical to building a scientific foundation for the understanding and treatment of pediatric bipolar disorder. When collaborations are considered, they frequently face hurdles that cannot be easily surmounted. For example, clinical traditions at different centers often clash regarding diagnostic conceptualizations as well as over which clinical and research strategies are best suited to answering important research questions. Thus, the main goal of the conference series on pediatric bipolar disorder is to build consensus through a network of clinicians and investigators who are studying or are planning to study pediatric bipolar disorder. Sub-goals of these conferences are:

- To define the boundaries of the bipolar spectrum phenotype and determine if children who technically meet criteria for bipolar disorder actually have this disorder or are affected with another condition.
- To standardize data collection methods across different centers to facilitate pooling of diagnostic data.
- To facilitate joint submissions of large collaborative projects that will enable the study of a broad spectrum of scientific questions including genetic, imaging and therapeutic protocols.
- To create a mechanism for pooling samples so that potential findings from one group may be cross-validated on pooled data from remaining groups

The first meeting was held in March, 2002, through an unrestricted educational grant by Janssen Pharmaceuticals. The proceedings of the first meeting will be published in *Biological Psychiatry* (See www.mgh.harvard.edu/depts/pediatricpsych/bipolar_2002.htm to view the slide presentations). A list of the presentations follows:

- Phenotypes of Inpatient Children with Mania: Gabrielle Carlson, MD
- Convergence between Structured Interviews and Clinician Assessments of BPD: Janet Wozniak, M.D.
- High Risk Studies of Children at Risk for BPD: Kiki Chang, PhD.
- Dysphoric Conduct Disorder: The overlap between conduct disorder and BPD: Joseph Biederman, MD
- Proposed Cross Natural Study of Diagnosis of Pediatric Mania: Richard Harrington, MD

- Genetics of Pediatric Bipolar Disorder and Its Comorbidities: Steven Faraone, Ph.D.
- Magnetic Resonance Imaging Studies of Pediatric BPD: Jean Frazier, MD
- Combination Pharmacotherapy in Children and Adolescents with Bipolar Disorders: Robert Kovatch, MD
- Temperament and Mood DisordersóBehavioral Disinhibition: Dina Hirshfeld-Becker, Ph.D.
- Parent Advocacy Perspective: Martha Hellander
- Multifamily Psychoeducation Groups for Pediatric Bipolar Disorder: Mary Fristad, MD
- Defining Clinical Phenotypes of Juvenile Bipolar Disorder: Ellen Leibenluft, MD
- Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD): Andrew Nierenberg, MD
- Children and Adolescents with Bipolar Disorder: Methodological Issues: Boris Birmaher, MD
- Methodological Issues in Pediatric BPD: Eric Mick, Sc.D.
- Retrospective, unblinded chart review of pediatric BPD. Luis Rohde, MD
- BPD Among ADHD Children. Philip Hazell, MD

Plans for the Future

Table 4 presents our original timeline for research at the J&J Center for Psychopathology Research at MGH.

Table 4: Project Timeline for the J&J Center for Psychopathology Research at MGH						
	Yr 0	Yr 1	Yr 2	Yr 3	Yr 4	Yr 5
Treatment Research						
Efficacy of RISPERDAL for Pediatric BPD	X	XP	XP			
Pediatric BPD RISPERDAL PK Study		XP	XP			
Meridia for weight gain in Risp treated patients		XP	XP			
REDACTED						
PK study of stimulants and RISPERDAL		XP	XP			
Efficacy of adding Wellbutrin or Paxil for depression to RISPERDAL treated BPD patients		XP	XP			
PK study of Wellbutrin/Paxil and RISPERDAL		XP	XP			
Cabergoline for hyperprolactinemia in Risp treated patients		XP	XP			
Efficacy of galantamine for executive dysfunction in BPD			XP	XP		
Efficacy of RISPERDAL for BPD in PDD Children				XP	XP	
Efficacy of RISPERDAL for BPD in OCD Children				XP	XP	
Efficacy of Multimodal treatment of BPD using risperdone and cognitive behavior therapy				XX	XP	XP
Long term follow-up of Efficacy Studies to assess psychosocial outcome, cognitive outcome, symptomatic outcomes and substance use outcomes				XP	XP	XP
Etiologic Research						
Structural MRI of BPD adults with and without ADHD		XX	XP			
Structural MRI of BPD children with and without ADHD	XX			XX	XP	
Pharmacogenetic studies of BPD trials	XX	XX	XP	XP	XP	
Velo-Cardio Facial Syndrome and BPD			XX	XP		
Candidate gene studies of Pediatric BPD			XX	XP	XP	XP
Longitudinal Research						
Validation of affective-type conduct disorder with family study	XX	XX	XX	XP	XP	XP
Follow-up of BPD Children		XX	XX	XP	XP	XP
Follow-up of children at risk for BPD		XX	XX	XP	XP	XP
Analysis of Existing Data						
Efficacy of RISPERDAL for affective-type conduct disorder in Janssen clinical trial	XP	XP				
Use MGH follow-up and family study data to define and validate antisocial and non-antisocial subtypes of BPD	XP	XP				
Use MGH follow-up data to define risk factors and developmental trajectories of BPD			XP			
Use MGH follow-up and family study data to define CBCL screening rules for pediatricians			XP			
Use MGH follow-up and family study data to define executive dysfunction measure for galantamine study		XP				
Educational Initiatives						
Yearly Pediatric BPD Conference	X	X	X	X	X	X
Development of BPD CME Program	X	XX				
Implementation of BPD CME Program	X		XX	XX	XX	XX
BPD Programs at national and international professional meetings: NCDEU, AACAP, Biological Psychiatry, ACNP, APA, AAP, ECNP, CINP, WPA		XX	XX	XX	XX	XX

Appendix A: Biographical Sketches of MGH Investigators

APPENDIX B: Presentations at National and International Meetings in 2002 By MGH Pediatric Psychopharmacology Research Program

APPENDIX C: Preparation of Manuscripts for Publication in 2002 By MGH Pediatric Psychopharmacology Research Program

References

- Biederman J, Faraone S, Chen W (1993a), Social adjustment inventory for children and adolescents: Concurrent validity in ADHD children. *J Am Acad Child Adolesc Psychiatry* 32: 1059-1064
- Biederman J, Faraone S, Monuteaux M, Grossbard J (submit), How informative are parent reports of ADHD symptoms for assessing outcome in clinical trials? A pooled analysis of parents' and teachers' reports. *Pediatrics*
- Biederman J, Faraone SV, Milberger S, Doyle A (1993b), Diagnoses of attention deficit hyperactivity disorder from parent reports predict diagnoses based on teacher reports. *J Am Acad Child Adolesc Psychiatry* 32: 315-317
- Biederman J, Hirshfeld-Becker DR, Rosenbaum JF, Herot C, Friedman D, Snidman N, Kagan J, Faraone SV (2001a), Further Evidence of Association Between Behavioral Inhibition and Social Anxiety in Children. *American Journal of Psychiatry* 158: 1673-1679
- Biederman J, Keenan K, Faraone SV (1990a), Parent based diagnosis of attention deficit disorder predicts a diagnosis based on teacher report. *J Am Acad Child Adolesc Psychiatry* 29: 698-701
- Biederman J, Mick E, Bostic J, Prince J, Daly J, Wilens T, Spencer T, Garcia-Jetton J, Russell R, Wozniak J, Faraone S (1998a), The naturalistic course of pharmacologic treatment of children with manic-like symptoms: A systematic chart review. *J Clin Psychiatry* 59: 628-637
- Biederman J, Mick E, Faraone S (1998b), Normalized functioning in youths with persistent ADHD. *J Pediatrics* 133: 544-551
- Biederman J, Mick E, Faraone SV (2000), Age-dependent decline of symptoms of attention deficit hyperactivity disorder: Impact of remission definition and symptom type. *Am J Psychiatry* 157: 816-818
- Biederman J, Mick E, Prince J, Bostic JQ, Wilens TE, Spencer T, Wozniak J, Faraone SV (1999), Systematic chart review of the pharmacologic treatment of comorbid attention deficit hyperactivity disorder in youth with bipolar disorder. *J Child Adolesc Psychopharmacol* 9: 247-56
- Biederman J, Monuteaux MC, Greene RW, Braaten EB, Doyle AE, Faraone SV (2001b), Long-term stability of the Child Behavior Checklist in a clinical sample of youth with Attention Deficit Hyperactivity Disorder. *J Clin Child Psychol* 30: 492-502

- Biederman J, Rosenbaum JF, Bolduc-Murphy EA, Faraone SV, Chaloff J, Hirshfeld DR, Kagan J (1993c), A 3-year follow-up of children with and without behavioral inhibition. *Journal of American Academy of Child and Adolescent Psychiatry* 32: 814-21
- Biederman J, Rosenbaum JF, Hirshfeld DR, Faraone SV, Bolduc EA, Gersten M, Meminger SR, Kagan J, Snidman N, Reznick JS (1990b), Psychiatric correlates of behavioral inhibition in young children of parents with and without psychiatric disorders. *Arch Gen Psychiatry* 47: 21-6
- Braaten E, Biederman J, DiMauro A, Mick E, Monuteaux M, Muehl K, Faraone S (2001), Methodological complexities in the diagnosis of major depression in youth: An analysis of mother and youth self reports. *J Child Adolesc Psychopharmacol* 11: 395-407
- Chen WJ, Faraone SV, Tsuang MT (1992), Linkage studies of schizophrenia: A simulation study of statistical power. *Gen Epi* 9: 123-139
- Faraone S, Biederman J (2002), Efficacy of Adderall, for Attention-Deficit/Hyperactivity Disorder: A Meta-Analysis. *J Attent Disord* 6: 69-75
- Faraone S, Biederman J, Mick E (1997), Symptom reports by adults with attention deficit hyperactivity disorder: are they influenced by attention deficit hyperactivity disorder in their children? *Journal of Nervous and Mental Diseases* 185: 583-584
- Faraone S, Biederman J, Milberger S (1995), How reliable are maternal reports of their children's psychopathology?: One year recall of psychiatric diagnoses of ADHD children. *J Am Acad Child Adolesc Psychiatry* 34: 1001-1008
- Faraone S, Tsuang M (1994), Measuring diagnostic accuracy in the absence of a "gold standard". *Am J Psychiatry* 151: 650-657
- Faraone SV, Biederman J, Feighner JA, Monuteaux MC (2000a), Assessing symptoms of attention deficit hyperactivity disorder in children and adults: which is more valid? *J Consult Clin Psychol* 68: 830-42
- Faraone SV, Biederman J, Monuteaux MC (2000b), Toward guidelines for pedigree selection in genetic studies of attention deficit hyperactivity disorder. *Gen Epi* 18: 1-16
- Faraone SV, Biederman J, Roe CM (2002), Comparative efficacy of adderall and methylphenidate in attention-deficit/hyperactivity disorder: a meta-analysis. *J Clin Psychopharmacol* 22: 468-73
- Faraone SV, Biederman J, Spencer TJ, Wilens TE (2000c), The drug-placebo response curve: a new method for assessing drug effects in clinical trials. *J Clin Psychopharmacol* 20: 673-9
- Faraone SV, Biederman J, Sprich S, Buckminster S, Chen W, Tsuang M (1993), Efficiency of diagnostic criteria for attention deficit disorder: Toward an empirical approach to designing and validating diagnostic algorithms. *J Am Acad Child Adolesc Psychiatry* 32: 166-174
- Faraone SV, Blehar M, Pepple J, Moldin S, Norton J, Tsuang MT, Nurnberger JI, Malaspina D, Kaufmann CA, Reich T, Cloninger CR, DePaulo JR, Berg K, Gershon ES, Kirch DG, Tsuang MT (1996), Diagnostic accuracy and confusability analyses: An application to the diagnostic interview for genetic studies. *Psychol Med* 26: 401-410
- Faraone SV, Chen WJ, Tsuang MT (1994), Estimating the morbidity risk for diseases having a variable age at onset. *Psychiat Genet* 4: 135-142
- Faraone SV, Dorfman DD (1987), Robust alternatives for lag sequential analysis. *Psychol Bull* 101: 312-323
- Faraone SV, Dorfman DD (1988), Testing the significance of interobserver agreement measures in the presence of autocorrelation: The Jackknife procedure. *Journal of Psychopathology and Behavioral Assessment* 10: 39-47

Faraone SV, Doyle AE, Mick E, Biederman J (2001), Meta-analysis of the association between the 7-repeat allele of the dopamine d(4) receptor gene and attention deficit hyperactivity disorder. *Am J Psychiatry* 158: 1052-7.

Faraone SV, Monuteaux MC, Biederman J, Cohan SL, Mick E (in press), Does parental ADHD bias maternal reports of ADHD symptoms in children? *J Consult Clin Psychol*

Faraone SV, Santangelo S (1992), Methods in Genetic Epidemiology. *Research Designs and Methods in Psychiatry*. M. Fava and J. F. Rosenbaum. Amsterdam, The Netherlands, Elsevier: 93-118

Faraone SV, Simpson JC, Brown WA (1992), Mathematical models of complex dose-response relationships: Implications for experimental design in psychopharmacologic research. *Stat Med* 11: 685-702

Faraone SV, Tsuang D, Tsuang MT (1999), *Genetics and Mental Disorders: A Guide for Students, Clinicians, and Researchers*. New York, NY, Guilford

Faraone SV, Tsuang MT (1995), Methods in Psychiatric Genetics. *Textbook in Psychiatric Epidemiology*. M. Tohen, M. T. Tsuang and G. E. P. Zahner. New York, NY, John Wiley: 81-134

Mick E, Santangelo S, Wypij D, Biederman J (2000), Impact of maternal depression on ratings of comorbid depression in adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 39: 314-319

Robins E, Guze SB (1970), Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. *Am J Psychiatry* 126: 983-987

Wilens T, Faraone SV, Biederman J, Gunawardene S (in press), Does Stimulant Therapy of Attention Deficit Hyperactivity Disorder Beget Later Substance Abuse? A Meta-Analytic Review of the Literature. *Pediatrics*

Young AS, Faraone SV, Brown WA (1989), Correction of serum neuroleptic activity for blood-to-brain distribution: a method that may render radioreceptor assay results comparable between neuroleptics. *J Clin Psychopharmacol* 9: 361-3