

**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
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>	<i>15</i>
<i>Appendix A: Biographical Sketches of MGH Investigators</i>	<i>17</i>
<i>APPENDIX B: Presentations at National and International Meetings in 2002 By MGH Pediatric Psychopharmacology Research Program</i>	<i>17</i>
<i>APPENDIX C: Preparation of Manuscripts for Publication in 2002 By MGH Pediatric Psychopharmacology Research Program</i>	<i>17</i>
<i>References</i>	<i>17</i>

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

[Redacted text]

[Redacted text]


