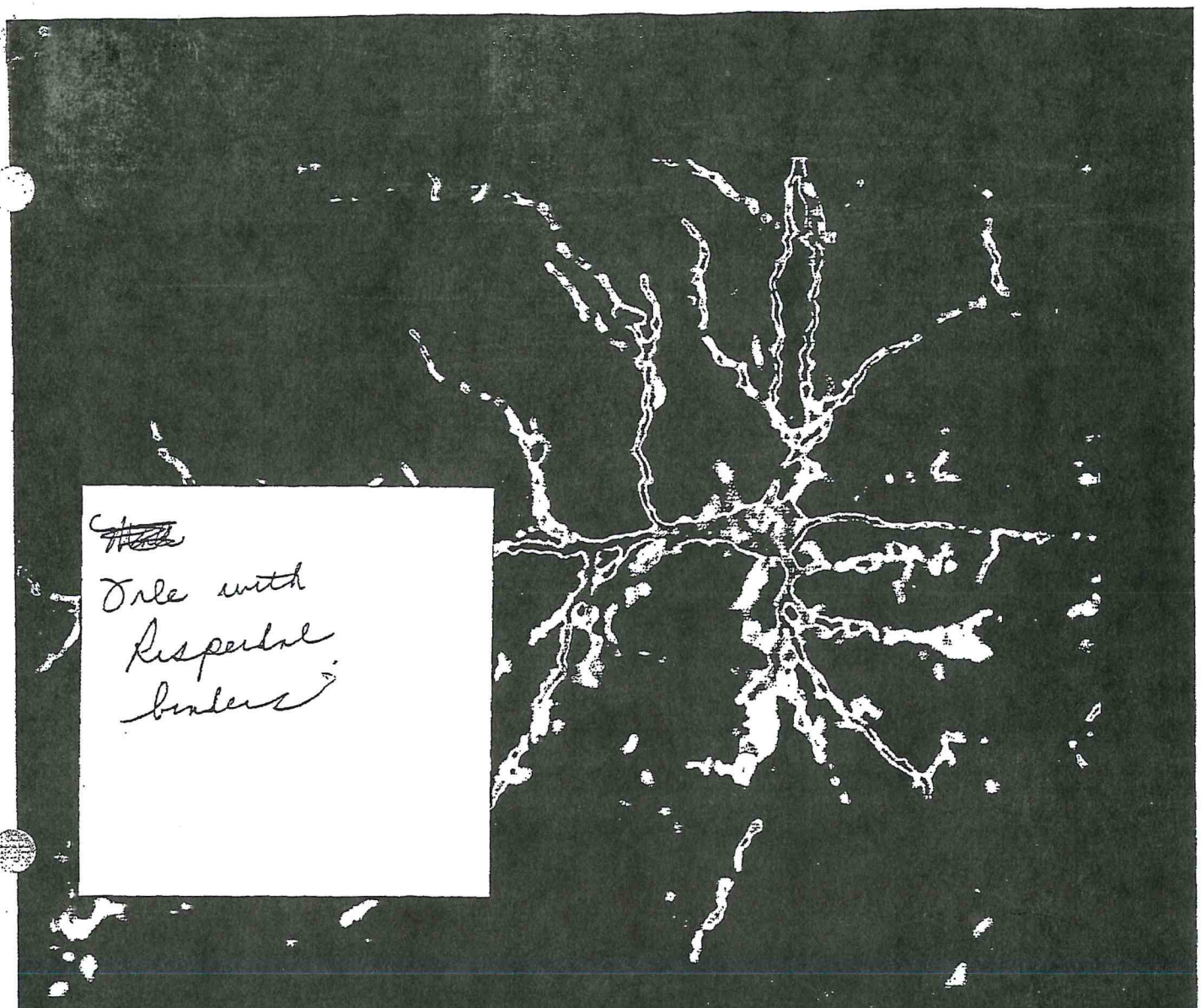

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CHILD & ADOLESCENT

REGIONAL ADVISORS MEETING

August 15–17, 2003

Los Angeles, California

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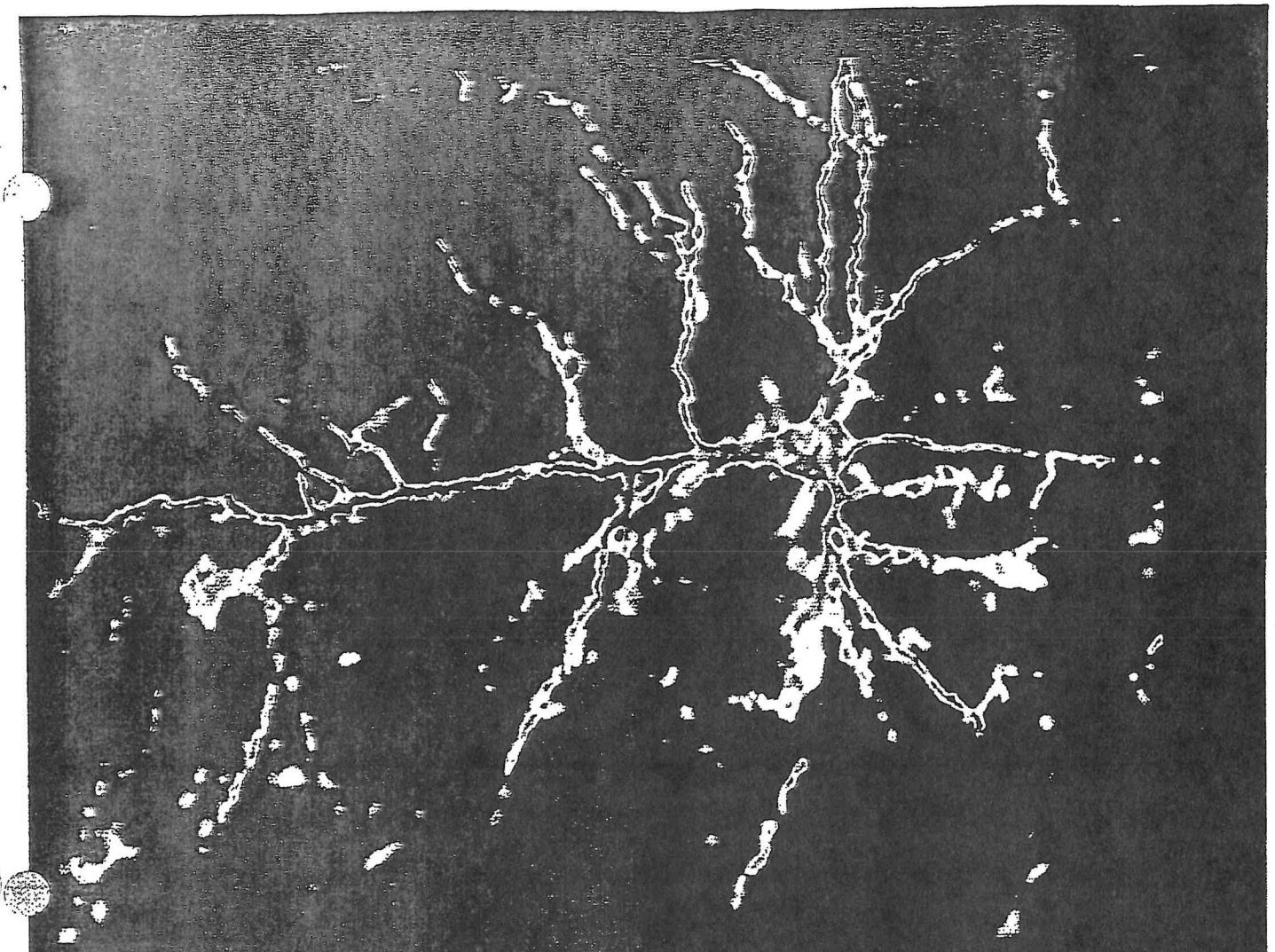

CHILD & ADOLESCENT

REGIONAL ADVISORS MEETING

August 15–17, 2003

Los Angeles, California

CHILD & ADOLESCENT
REGIONAL ADVISORS MEETING

JANSSEN PHARMACEUTICA PRODUCTS, L.P.

Welcome to **The Regent Beverly Wilshire** and the
Janssen Pharmaceutica Child and Adolescent Regional Advisors Meeting!

Upon your arrival to the hotel, please stop by the Janssen Registration Desk located in Le Petit Trianon on the Mezzanine Level in the Wilshire Wing to pick up your meeting materials. The Janssen Registration Desk will be open today, Friday, August 15, from 12:00 PM to 8:00 PM.

For your convenience, Janssen has prepaid bellman and housekeeping gratuities as well as parking charges, if applicable. However, please be advised that all incidentals such as honor bar charges, movie rentals, gift shop purchases, room service charges, or telephone calls will be at your own expense.

Tonight's Welcome Reception will begin at 7:00 PM in Le Grand Trianon located on the Mezzanine Level in the Wilshire Wing, followed by a Dinner Buffet.

Janssen Pharmaceutica provides the following group meals:

- Friday Night Welcome Reception and Dinner
- Breakfast, lunch and dinner on Saturday
- Breakfast and lunch on Sunday

PLEASE NOTE: Due to Janssen Healthcare Compliance Policy, guests will no longer be able to attend any meeting-related functions, including program-sponsored meals. We apologize for any inconvenience this may cause.

The Janssen Registration Staff will be available throughout the conference. Should the Registration Desk be closed, please call the front desk and ask for a member of the Janssen Registration Staff. In the event of an emergency, please call our 24-Hour Emergency Hotline number at (954) 868-1112.

Thank you for your participation.

We look forward to an educational and enjoyable weekend!

CHILD & ADOLESCENT
REGIONAL ADVISORS MEETING

JANSSEN PHARMACEUTICA PRODUCTS, L.P.

List of Attendees

Faculty

Gabrielle Carlson, MD	SUNY at Stonybrook
Peter Jensen, MD	Columbia University
Lawrence Scahill, MSN, PhD	The Yale School of Medicine

Northwest Region

Eileen Sullivan PharmD	
Richard Adler, MD	Bellevue, WA
Saleha Baig, MD	Las Vegas, NV
Shashi Bhatia, MD	Omaha, NE
Karen Black, MD	Salt Lake City, UT
Richard Crabbe, MD	Chehalis, WA
Kenneth Crumley, MD	Albuquerque, NM
Daniel Ferber, MD	Stevenson, WA
Jeffrey J. Hansen, MD	Vancouver, WA
Vilma Helmer, MD	Draper, UT
Stephen Huk, MD	Overland Park, KS
James Jarmuskewicz, MD	Bemidji, MN
Catherine Madden, MD	Wichita, KS
William Marchand, MD	Provo, UT
Benjamin Marte, MD	Moses Lake, WA
Michael Measom, MD	Salt Lake City, UT
Fred Michel, MD	Colorado Springs, CO
Charles Millhuff, DO	Topeka, KS
J. Ben Newman, PMHNP	Salem, OR
Kelly Palmer, DO	Pocatello, ID
Romelia Perez, MD	Seattle, WA
Ronald Rabin, MD	Denver, CO
Stephen Schilt, MD	Tacoma, WA

Nancy Solomon, MD	Kansas City, MO
William M. Sykes, MD	Denver, CO
James D. True, MD	Kansas City, MO
Joyce Vista-Wayne, MD	Ottumwa, IA

South Central Region

Richard Aiken, MD, PhD	Springfield, MO
David Calenzani, MD	Oklahoma City, OK
Rupa Chundu, MD	Phoenix, AZ
Tushar Desai, MD	San Marcus, TX
Kathy Goodwin, MSN, APN	McAllen, TX
James S. Harrold, Jr., MD	Shreveport, LA
Raju Indukuri, MD	Bedford, TX
Vernon Johnson, MD	Sherman, TX
Debra Katz, MD	Houston, TX
Murthy Mangipudi, MD	Corpus Christi, TX
Rita Pacheco-Gonzales, MD	Las Cruces, NM
Jhansi Raj, MD	Fort Worth, TX
Javier Ruiz-Nazario, MD	Spring, TX
Mark A. Sands, MD	Metairie, LA
Kishore Sunkara, MD	Fort Worth, TX
Gundlapalli Surya, MD	San Antonio, TEXAS
Daniel Tan, MD	Houston, TX
Letty G. Tan-Fermo, MD	Scottsdale, AZ
Samir Wahby, MD	Arlington, TX

West Region

Acelita Amparo, MD	Sacramento, CA
Scott Barshack, MD	Corte Madera, CA
Bernard Bierman, MD	Los Angeles, CA
Sai Chundu, MD	Corona, CA
Herbert Cruz, MD	Central Valley, CA
Richard Deamer, MD	Ventura, CA
Claude Friedmann, MD	Torrance , CA
Laurence Glasser, MD, MPH	San Diego, CA
Maria Goldstein, MD	Los Angeles, CA

Nageswara Rao Guntupalli, MD	Covina, CA
Christopher Heh, MD	Fullerton, CA
Joseph Johnson, MD	Santa Barbara, CA
Rajababu Kurre, MD	Corona, CA
Michael Levin, MD	San Ramon, CA
Janak K. Mehtani, MD	Sacramento, CA
Gurmeet Multani, MD	San Bernardino, CA
Okey Nwangburuka, MD	Redding, CA
Lynne Pappas, MD	Redding, CA
John K. Paul, MD	Sacramento, CA
Nicole Poliquin, MD	Pasadena, CA
Frank Rumore, MD	San Jose, CA
Sidney Russak, MD	Los Angeles, CA
Laurence Saben, MD	El Cajon, CA
Robb Saito, MD	Los Angeles, CA
Douglas Sears, MD	Encino, CA
Joseph Sison, MD	Sacramento, CA
Cindy Slominski, MD	Los Angeles, CA
Ihab Soliman, MD	Irvine, CA
Luis Velosa, MD	Visalia, CA
Daniel Vermilion, MD	Daly City, CA

Janssen Attendees

David Fabbri	Group Product Director, CNS
Joseph Lin	Product Director, CNS Marketing
Lynn McClure, PharmD	Manager, CNS Medical Services
Gahan Pandina, PhD	Assistant Director, CNS Medical Affairs
Gregory Panico	Director, Global Pharmaceutical Communications
Eileen L. Sullivan, PharmD	Medical Services, CNS

Child and Adolescent Regional Advisors Meeting
August 15 – 17, 2003
Regent Beverly Wilshire
Los Angeles, California

Meeting Evaluation Form - Day One

Thank you again for your participation in this program. We would greatly appreciate your responses to the following questions.

Your overall evaluation of the meeting- Day 1 (please circle rating):

	Excellent	Very Good	Good	Fair	Poor
Content:	5	4	3	2	1
Format:	5	4	3	2	1
Presenters:	5	4	3	2	1
Meeting Staff:	5	4	3	2	1

Please provide any additional comments/feedback on this topic:

_____
_____
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_____

Your overall evaluation of the presentation entitled "Treatment Recommendations for the Use of Antipsychotics for Aggressive Youth (TRAAY): Clinical Implications" by Peter Jensen, MD:

	Excellent	Very Good	Good	Fair	Poor
Content/Relevance:	5	4	3	2	1
Knowledge of Subject:	5	4	3	2	1
Presentation Skills:	5	4	3	2	1

Please provide any additional comments/feedback on this topic:

_____
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_____

Your overall evaluation of the presentation entitled "Challenges in the Diagnosis and Treatment of Bipolar Disorders in Children" by Gabrielle Carlson, MD:

	Excellent	Very Good	Good	Fair	Poor
Content/Relevance:	5	4	3	2	1
Knowledge of Subject:	5	4	3	2	1
Presentation Skills:	5	4	3	2	1

Please provide any additional comments/feedback on this topic:

_____
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_____

Your overall evaluation of the presentation entitled "New Developments in the Treatment of Pervasive Development Disorder/Autism" by Lawrence Scahill, MSN, PhD:

	Excellent	Very Good	Good	Fair	Poor
Content/Relevance:	5	4	3	2	1
Knowledge of Subject:	5	4	3	2	1
Presentation Skills:	5	4	3	2	1

Please provide any additional comments/feedback on this topic:

_____
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Your overall evaluation of the presentation entitled "A Review of Efficacy Data for Risperidone in the Child and Adolescent Population" by Gahan Pandina, PhD:

	Excellent	Very Good	Good	Fair	Poor
Content/Relevance:	5	4	3	2	1
Knowledge of Subject:	5	4	3	2	1
Presentation Skills:	5	4	3	2	1

Please provide any additional comments/feedback on this topic:

_____

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_____

Your overall evaluation of the Panel Discussion with Audience Q&A/Feedback by Peter Jensen, MD:

	Excellent	Very Good	Good	Fair	Poor
Content:	5	4	3	2	1
Format:	5	4	3	2	1
Moderator:	5	4	3	2	1
Panel:	5	4	3	2	1

Please provide any additional comments/feedback on this topic:

_____

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Your overall evaluation of the Interactive Case Study Session by Peter Jensen, MD:

	Excellent	Very Good	Good	Fair	Poor
Content:	5	4	3	2	1
Format:	5	4	3	2	1
Moderator:	5	4	3	2	1

Please provide any additional comments/feedback on this topic:

_____

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_____

What improvements, if any, would you recommend for future advisory meetings?

_____

_____

_____

Other than the formats used in this meeting, e.g., interactive case study, panel, didactic, what format would you recommend be incorporated into future meetings?

_____

_____

_____

What was your overall opinion of the Child and Adolescent Regional Advisors Meeting?

5 4 3 2 1
Favorable Unfavorable

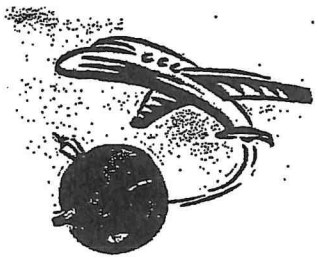
(Optional)

Name (please print) _____

City and State _____

JANSSEN PHARMACEUTICA PRODUCTS, L.P.

The Regent Beverly Wilshire
Beverly Hills, CA



Name: GREG PANICO

The recommended departure time to the airport is approximately 2 hours prior to your flight. Your departure will take place from the Hotel Driveway, Lobby Level.

DEPARTURE DATE:	17-AUG-03
HOTEL DEPARTURE TIME:	1:45 PM
FLIGHT INFORMATION:	CO1503
	3:40 PM

Please note that check out time from the hotel is at 12:00 PM. For any questions or flight changes, please see a representative at the Janssen Registration Desk.

If you have any changes to your itinerary after departing the hotel, please contact your airline directly or J&J Travel's 24-hour emergency hotline at 800-354-2400.

Thank you for participating in this meeting and have a safe trip!

SCHEDULE OF EVENTS

Janssen Pharmaceutica
Child & Adolescent Regional Advisors Meeting
August 15 – 17, 2003
The Regent Beverly Wilshire
Beverly Hills, California

FRIDAY, AUGUST 15, 2003

ALL DAY	**Registration** Le Petit Trianon
7:00 PM – 9:30 PM	**Reception & Dinner** Le Grand Trianon

SATURDAY, AUGUST 16, 2003

7:00 AM – 8:00 AM	**Breakfast** Wintergarden
8:00 AM – 10:00 AM	**General Session** The Ballroom
10:00 AM – 10:20 AM	**Break** Wintergarden
10:20 AM – 1:00 PM	**General Session (continued)** The Ballroom
1:00 PM – 2:00 PM	**Working Lunch** Wintergarden
2:00 PM – 5:00 PM	**Afternoon Group Activity** J. Paul Getty Museum Please meet at the Hotel Entrance at 2:00 PM for departure
7:00 PM – 10:00 PM	**Off-Site Dinner** Spago Please meet at the Hotel Entrance at 6:45 PM for departure

CONTINUED ON REVERSE SIDE

SUNDAY, AUGUST 17, 2003

7:00 AM – 8:00 AM	**Breakfast** Wintergarden
8:00 AM – 9:30 AM	**General Session** The Ballroom
9:30 AM – 12:00 PM	**Breakout Sessions**
	• **Breakout Group I** Northwest Region Champagne Room
	• **Breakout Group II** South Central Region Le Petit Trianon
	• **Breakout Group III** West Region Le Grand Trianon
12:00 PM – 1:00 PM	**Lunch** Wintergarden
1:00 PM	**Departures** Hotel Lobby

Question for the Faculty

Questions directed to: _____

Question: _____

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Name (optional): _____

CHILD & ADOLESCENT
REGIONAL ADVISORS MEETING

Los Angeles, California
August 15-17, 2003

Saturday, August 16

7:00am – 8:00am	Breakfast	*Wintergarden*
8:00am – 10:00am	**General Session**	*The Ballroom*
8:00am – 8:05am	**Welcome** *Joseph Lin, Product Director – Janssen CNS*	
8:05am – 8:10am	**Chairman's Welcome** *Peter S. Jensen, MD*	
8:10am – 8:45am	**Treatment Recommendations for the Use of Antipsychotics for Aggressive Youth (TRAAY): Clinical Implications** *Peter S. Jensen, MD* • Treatment options – a review of the evidence • Treatment algorithm	
8:45am – 9:30am	**Challenges in the Diagnosis and Treatment of Bipolar Disorders in Children** *Gabrielle Carlson, MD* • Comorbidities and shared symptoms across pediatric psychiatric disorders • Current treatment options for acute mania	
9:30am – 10:00am	**Panel Discussion with Audience Q&A/Feedback**	
10:00am – 10:20am	Break	*Wintergarden*
10:20am – 1:00pm	**General Session** *(continued)*	*The Ballroom*
10:20am – 10:55am	**New Developments in the Treatment of Pervasive Development Disorder/Autism** *Lawrence Scahill, MSN, PhD* → 203 785 2389 • Prevalence of PDD/autism • Issues in the treatment of autistic disorder • Review of the RUPP Autism clinical trial	
10:55am – 11:25am	**A Review of Efficacy Data for Risperidone in the Child and Adolescent Population** *Gahan J. Pandina, PhD* • Disruptive Behavior Disorders • Autism • Acute Mania	
11:25am – 11:55am	**Panel Discussion with Audience Q&A/Feedback**	
11:55am – 1:00pm	**Interactive Case Study Session** *Peter S. Jensen, MD* • Interactive patient case study series using Audience Response System	

1:00pm	**Closing Remarks**	
1:00pm – 2:00pm	Working Lunch	*Wintergarden*
2:00pm – 5:00pm	Afternoon Group Activities	
6:30pm – 9:00pm	Off-Site Dinner	*Spago*

Sunday, August 17

7:00am – 8:00am	Breakfast	*Wintergarden*
8:00am – 9:30am	**General Session**	*The Ballroom*
8:00am	**Good morning!** *Peter S. Jensen, MD*	
8:00am – 9:00am	**A Review of Safety & Tolerability Data in the Child and Adolescent Population** *Gahan J. Pandina, PhD* • Weight gain • Hyperglycemia/diabetes • Prolactin levels • Sexual maturation/growth • Movement disorders	
9:00am – 9:30am	**Safety & Tolerability Panel Discussion**	
9:30am – 12:00pm	**BREAKOUT SESSIONS**	
	Feedback Sessions Group 1 – *Northwest Region* Group 2 – *South Central Region* Group 3 – *West Region*	*Champagne Room* *Le Petit Trianon* *Le Grand Trianon*
12:00pm – 1:00pm	Lunch and Departures	*Wintergarden*

Faculty

4 pgs
Prof. St. Bridgette

Faculty

GABRIELLE A. CARLSON, MD

PROFESSOR OF PSYCHIATRY AND PEDIATRICS
DIRECTOR, CHILD AND ADOLESCENT PSYCHIATRY
STATE UNIVERSITY OF NEW YORK AT STONY BROOK

Gabrielle A. Carlson is Professor of Medicine and Pediatrics and Director of Child and Adolescent Psychiatry at the State University of New York at Stony Brook. She has specialized in childhood psychopathology and psychopharmacology with particular emphasis on adolescent depression and bipolar disorder. Her writings include more than 150 articles and book chapters; she is also the co-author of two books, Affective Disorders in Childhood and Adolescence and Psychiatric Disorders in Children and Adolescents.

A member of many scientific and professional associations, Dr. Carlson is a present or past member of the editorial boards of the *Journal of the American Academy of Child and Adolescent Psychiatry, American Journal of Psychiatry, Journal of Adolescent Disorders,* and *Journal of Child and Adolescent Psychopharmacology.* She has served on several professional committees including the APA Committee to Evaluate *DSM III* and the Child and Adolescent and Mood Disorders Work Groups for *DSM IV.* In addition, she has been an Examiner for the American Board of Psychiatry and Neurology for both Adult and Child Psychiatry and a member of the Scientific Advisory Board of the National Depressive and Manic Depressive Association.

Dr. Carlson has been named in both the *Best Doctors in America* and *Good Housekeeping's Best Mental Health Experts.* She received her MD from Cornell University Medical College at Ithaca, New York, before undergoing additional training at Washington University in St. Louis, Missouri, and the National Institutes of Health at Bethesda, Maryland. She completed a fellowship in Child and Adolescent Psychiatry at UCLA and taught there before moving on to Stony Brook. She is currently doing research on the relationship of behavior disorders and mood disorders as well as the effects of adolescent bipolar disorders on the patients' life in adulthood.

PETER S. JENSEN, MD

DIRECTOR, CENTER FOR THE ADVANCEMENT OF CHILDREN'S MENTAL HEALTH – PUTTING SCIENCE TO WORK
RUANE PROFESSOR OF CHILD PSYCHIATRY
COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS AND SURGEONS
NEW YORK, NEW YORK

Peter S. Jensen, MD, is Director of the Center for the Advancement of Children's Mental Health—Putting Science to Work and the Ruane Professor of Child Psychiatry at the Columbia University College of Physicians and Surgeons in New York. Before coming to Columbia University, he was the Associate Director of Child and Adolescent Research at the National Institute of Mental Health (NIMH) in Bethesda, Maryland.

Dr. Jensen's main areas of interest include the integration of research methods into clinical settings, effectiveness and dissemination research, and how to persuade medical practitioners and parents to adopt evidence-based mental health approaches in dealing with children who are suffering from mental disorders. He is a member of many professional organizations, has written scores of articles for scientific and clinical journals, is the co-editor of three books on children's mental health research, and serves on the editorial boards of a number of journals. His research, writing, and teaching have been recognized by a number of awards, including the Rieger (1990, 1996) and Lewis Awards (2000) of the American Academy of Child and Adolescent Psychiatry, and the McGavin (1996) and Ittelson Awards (1998) of the American Psychiatric Association. The National Alliance for the Mentally Ill honored him with its Exemplary Psychiatrist Award in 1999, while the American Academy of Child & Adolescent Psychiatry gave him its Oustanding Mentor Award in 2000.

Dr. Jensen received his MD degree in 1978 from the George Washington University Medical School in Washington, DC. He did his post-graduate training at the University of California, San Francisco, and at Letterman Army Medical Center. From there, he moved to the NIMH where he was lead investigator on the six-site NIMH and US Department of Education-funded Study of Multimodal Treatment of ADHD (the MTA Study) in addition to working on other multi-center studies.

GAHAN J. PANDINA, PHD

ASSISTANT DIRECTOR, CNS MEDICAL AFFAIRS
JANSSEN PHARMACEUTICA, INC.
TITUSVILLE, NEW JERSEY
ADJUNCT CLINICAL ASSISTANT PROFESSOR OF PSYCHIATRY
UMDNJ-ROBERT WOOD JOHNSON MEDICAL SCHOOL
PISCATAWAY, NEW JERSEY
VISITING PROFESSOR, CENTER OF ALCOHOL STUDIES
RUTGERS UNIVERSITY
NEW BRUNSWICK, NEW JERSEY

Gahan J. Pandina, PhD, is an Adjunct Clinical Professor of Psychiatry at UMDNJ-Robert Wood Johnson Medical School in Piscataway, New Jersey, a Visiting Professor in the Center of Alcohol Studies at Rutgers University in New Brunswick, New Jersey, and is an Assistant Director of CNS Medical Affairs for Janssen Pharmaceutica in Titusville, New Jersey.

Dr. Pandina is a member of the American Psychological Association, the International Neuropsychological Society, and is a founding associate member of the International College of Geriatric Psychoneuropharmacology. The author of a number of publications, he has a special interest in clinical research on the efficacy and outcomes of psychiatric treatments. In addition, he has been a co-investigator on a number of pharmaceutical clinical trials and research grants.

Dr. Pandina received his PhD in Clinical Psychology from Binghamton University in Binghamton, New York, and completed doctoral fellowships in both Neuropsychology and Child and Adolescent Neuropsychology at Robert Wood Johnson Medical School.

LAWRENCE SCAHILL, MSN, PHD

ASSOCIATE PROFESSOR, YALE UNIVERSITY SCHOOL OF MEDICINE & SCHOOL OF NURSING DIRECTOR OF THE CLINICAL TRIALS PROGRAM
YALE CHILD STUDY CENTER
NEW HAVEN, CONNECTICUT

Lawrence Scahill is Associate Professor of Nursing and Child Psychiatry at Yale University and Director of the Clinical Trials Program at the Yale Child Study Center in New Haven, Connecticut. In addition to his work in Tourette syndrome, Dr. Scahill coordinates the multisite Research Units on Pediatric Psychopharmacology Autism Network. Recent projects include: a study of guanfacine in the treatment of attention deficit hyperactivity disorder (ADHD) in children with tic disorders; a multisite study of risperidone in the treatment of children with autism; a multisite study of methylphenidate in children with pervasive developmental disorder and hyperactivity; and parent training in children with Tourette syndrome. Dr. Scahill serves on the Medical Advisory Board of the Tourette syndrome Association, is on the editorial board of several journals, and is the author of numerous articles on Tourette syndrome, ADHD, obsessive-compulsive disorder, and autism. Dr. Scahill earned a master's degree in child psychiatric nursing at the Yale School of Nursing and a doctorate in epidemiology from the Department of Public Health at Yale University.

Meeting Materials

CHILD & ADOLESCENT
REGIONAL ADVISORS MEETING

Welcome to Los Angeles

Joseph Lin
Product Director, CNS
Janssen Pharmaceutica Products, LP

JANSSEN

Bipolar
Schizophrenia
most common symptom: aggression
psychosis

Agenda

Saturday, August 16	
Welcome/Program Overview	Joseph Lin
The TRAAY Guidelines: Clinical Implications	Peter Jensen, MD
Bipolar Disorder in Children: Challenges in Diagnosis and Treatment	Gabrielle Carlson, MD
New Developments in the Treatment of Autistic Disorder	Lawrence Scahill, MSN, PhD
Clinical Data for RISPERDAL®: Efficacy	Gahan Pandina, PhD
Interactive Case Study	Peter Jensen, MD
Sunday, August 17	
Clinical Data for RISPERDAL®: Safety & Tolerability	Gahan Pandina, PhD
Small Group Breakout Sessions	

Meeting Objectives

For you:

To share your experiences, advice, and recommendations on current issues in child and adolescent psychiatry while gaining additional clinical knowledge from your peers and faculty

For us:

To apply your input and feedback to our clinical development plans and marketing strategies, so we can more effectively provide value to patients, physicians, and caregivers

Why You?

Highly recommended by the Janssen Management Team for your:

- Extensive clinical experience
- Willingness to provide candid feedback
- Thought leadership in your communities

Product Labeling

Throughout this advisory meeting, you will encounter information that discusses the use of Risperdal® that is outside of currently approved product labeling. This information is presented to you as advisors for Janssen Pharmaceutica and is not intended to promote or encourage the use of Risperdal® in these indications.

CHILD & ADOLESCENT

REGIONAL ADVISORS MEETING

Peter S. Jensen, MD

Director, Center for the Advancement of Children's Mental Health – Putting Science to Work

Ruane Professor of Child Psychiatry

Columbia University College of Physicians And Surgeons

New York, New York

CHILD & ADOLESCENT
REGIONAL ADVISORS MEETING

Treatment Recommendations for the Use of Antipsychotics for Aggressive Youth (TRAAY): Clinical Implications

Peter S. Jensen, MD
Center for the Advancement of Children's Mental Health
Columbia University

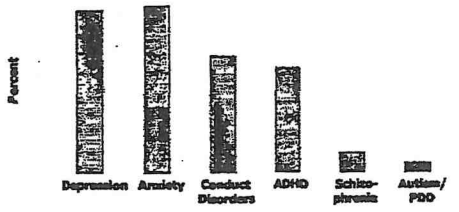
Mental Health of Children and Adolescents

- In the United States
  - 10% of children and adolescents suffer from mental illness severe enough to cause impairment
  - Less than 20% of these children receive needed treatment
- WHO predicts 50% rise in childhood neuropsychiatric disorders by 2020

WHO = World Health Organization.

Brief notes on the mental health of children and adolescents. [www.ninh.nih.gov/publicat/childnotes.cfm] Accessed 4/02.

Extent of Mental Disorders in US Children/Adolescents



ADHD = attention deficit/hyperactivity disorder; PDD = pervasive developmental disorders.

Sources: Office of the Surgeon General, and the National Institute of Mental Health, 1999.

Conduct Disorder in US Children/Adolescents

- Treatment
- Behavior therapy/psychotherapy: first-line treatment
- Medications to treat specific symptoms, eg, aggression
  - Lithium
  - Antipsychotic agents

Lynn D, King BH. Aggressive behavior. In: Kutcher S, ed. *Practical Child and Adolescent Psychopharmacology*. Cambridge, Eng: Cambridge University Press; 2002:305–327.

Labeling History and Current Uses: Typical Antipsychotics

- Chlorpromazine (Thorazine®), thioridazine (Mellaril®), and haloperidol (Haldol®)
- Severe behavior problems in children marked by combativeness and/or explosive hyperexcitable behavior
- Short-term treatment of hyperactive children with accompanying conduct disorders consisting of impulsive behavior, aggression, mood lability, and poor frustration tolerance

Haldol (package insert). Raritan, NJ: Ortho-McNeil Pharmaceutical, 2001.
Thorazine (package insert). Philadelphia, Pa: SmithKline Beecham Pharmaceuticals, 1999.
Mellaril (package insert). East Hanover, NJ: Novartis Pharmaceuticals Corporation, 2000.

Selected Studies of Disruptive Behavior Disorders With Aggression in Children/Adolescents

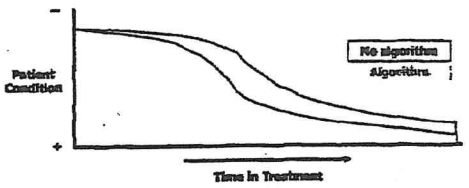
- Randomized studies
  - Aman, et al (2002)
  - Findling, et al (2000)
  - Turgay, et al (2002)
  - Snyder, et al (2002)
  - Buitelaar, et al (2001)
  - Van Bellinghen, De Troch (2001)
  - De Smedt, Van Bellinghen (1998)
- Nonrandomized studies
  - Findling, et al (2001)
  - Findling, et al (2000)
  - Simeon, et al (2002)

Evidence-Based Decision-Making

Science > Science + Opinion > Opinion

- Randomized, controlled clinical trials
- Epidemiologic studies, cohort studies, retrospective analyses, etc
- Case reports, expert opinion

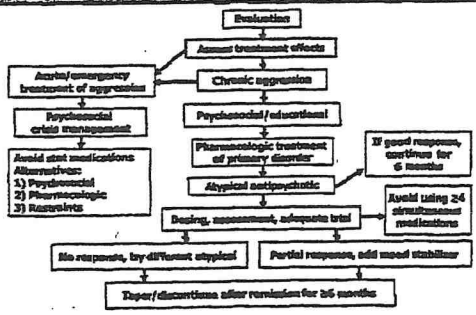
Potential Benefits of Algorithms: More Rapid and Thorough Response



Patient condition refers to combination of symptom severity and psychosocial functioning.
– = patient condition at initiation of treatment; + = improvement during course of treatment.

Rush AJ, et al. *J Clin Psychiatry*. 1998;59(suppl 20):73–84.

Algorithm for Treatment of Aggression in Children/Adolescents



Initial Evaluation Prior to Pharmacologic Treatment

- Comprehensive diagnostic interview with patient and parent/guardian
  - Contact prior treating physicians
  - Review treatment records
  - Identify other medications being taken
- Physical examination
- Appropriate laboratory studies

Premedication Laboratory Tests

- CBC, differential, hematocrit
- Urinalysis
- BUN
- Serum electrolytes
- Blood glucose
- Liver function tests: ALT, AST
  - Repeat once if elevated
  - Start drug if AST less than 2× normal

CBC = complete blood cell count; BUN = blood urea nitrogen; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Green WH. *Child and Adolescent Clinical Psychopharmacology*; 3rd ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2001.

Assess Treatment Effects and Outcomes

Use standardized symptom/behavior rating scales with proven reliability and validity to measure severity/frequency of target symptoms

- Prior to treatment
- At regular intervals throughout treatment
- During acute episodes
- When treatments are changed or discontinued

Chronic Versus Acute Aggression

- Chronic aggression is treated with a series of approaches
  - Treatment of primary disorder
    - Psychosocial/educational
    - Pharmacologic
  - Use of atypical antipsychotics
- Acute aggressive episodes are treated with crisis management

bipolar?
depression?
Treat primary disorder 1st.

Nonpharmacologic Treatment of Primary Disorder

- Initiate nonpharmacologic treatment
  - Behavioral therapy
  - Milieu/social therapy (family, school, friends, etc)
  - Educational Interventions
- Exact therapeutic approach will depend on diagnosis and individual circumstances

Use monotherapy to determine what's working
simplify treatment regimen...

Nonpharmacologic Treatment of Primary Disorder

- Assess patient response
- If good response, continue as needed for primary disorder

Pharmacologic Treatment of Primary Disorder

- Choose appropriate pharmacologic agent for primary disorder
  - Accurate diagnosis vital
  - Anticipate potential drug interactions
  - Evaluate potential impact of side effects on individual patient
- Use monotherapy whenever possible to simplify
  - Assessment of treatment response
  - Assessment of side effects
  - Medication regimen

Pharmacologic Treatment of Primary Disorder

- Dosage
  - Initial dose should be low
  - Titrate dosage carefully
- Assess efficacy
- Monitor side effects
- If good response, continue as warranted for primary disorder

Atypical Antipsychotic Agents

- First-line treatment for psychotic disorders in youth
  - Childhood-onset schizophrenia
  - First-episode schizophrenia
- Use an atypical antipsychotic (vs. a typical antipsychotic) for aggressive symptoms*
- Aggressive symptoms often require simultaneous use of antipsychotics with first-line treatments for primary conditions

*Atypical antipsychotic therapy in children/adolescents represents off-label prescribing.

Atypical Antipsychotic Agents

- Dosing strategies should:
  - Be conservative—"start low, go slow, taper slowly"
  - Minimize use of emergency drug treatment (prn or stat)
- Assess response and side effects on routine and systematic basis
- Use atypical antipsychotic agent at adequate dose for appropriate period before making changes

Evaluating Antipsychotic Therapy

- When using atypical antipsychotic as first-line treatment for aggression:
  - If no response, try a second atypical agent
  - If a partial response, consider adding a mood stabilizer

Monitoring During Treatment With Antipsychotic Agents

- Vital signs and weight
- Thorough review of systems
- Targeted physical exam, including assessing
  - Extrapyramidal symptoms
  - Cardiac function
  - Potential prolactin-associated phenomena (gynecomastia, galactorrhea, amenorrhea)
- Ongoing monitoring of liver function and glucose metabolism

prolactin assoc phenomena
gynecomastia

Monitoring Hematologic Parameters During Clozapine Use

- Platelets
  - Repeat count in 1 week if 25% reduction
  - Discontinue if platelets <100,000
- WBC and ANC
  - If ANC reduced <25%, repeat count in 1 week
  - Discontinue if ANC <1,000

WBC = white blood cell; ANC = absolute neutrophil count

Avoiding Polypharmacy

- Avoid using multiple medications simultaneously whenever possible
- Reevaluate regimen of patient who does not experience decreased aggression while receiving multiple medications
- Consider tapering/discontinuing one or more medications if patient is on ≥4 medications without clear benefit

taper

Tapering/Discontinuing Medications

- Consider tapering atypical antipsychotic medications in patients showing remission of aggressive symptoms for 6 months or longer
- If tapering of dose is well tolerated, discontinue the medication

consider stopping meds after srx months

⅓ of pts did well on placebo after 6 mos of treatment.

Chronic Versus Acute Aggression

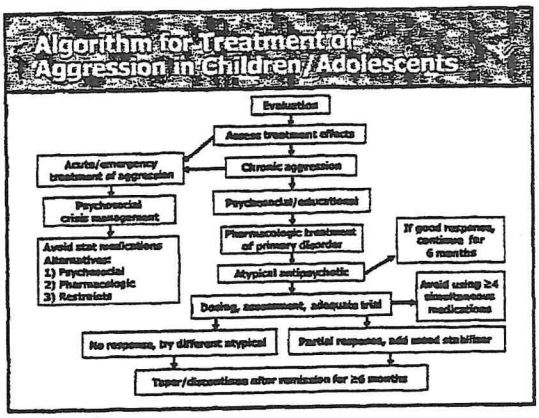
- Chronic aggression is treated with a series of approaches
  - Treatment of underlying condition
    - Psychosocial/educational
    - Pharmacologic
  - Use of atypical antipsychotics
- Acute aggressive episodes are treated with crisis management techniques

Acute or Emergency Treatment of Aggression

- Treatment alternatives
- Psychosocial crisis-intervention strategies
- Pharmacologic intervention
- If all else fails, use of physical and mechanical restraints and locked seclusion

Acute or Emergency Treatment of Aggression: Pharmacologic Intervention

- When behavioral strategies fail to control agitated/aggressive behavior:
  - Employ emergency (stat or prn) use of medications
  - Avoid intramuscular and use oral medications, if possible
  - Avoid frequent "stat" use of medications
- Pharmacologic management should correspond to risk for potential injury



CHILD & ADOLESCENT
REGIONAL ADVISORS MEETING

Challenges in the Diagnosis and Treatment of Bipolar Disorders in Children

Gabrielle A. Carlson, MD
Professor of Psychiatry and Pediatrics
Director, Child and Adolescent Psychiatry
State University of New York at Stony Brook

Where We've Been

- **Manic-Depressive Illness—1968**
  - Euphoria/irritability concurrent
  - Depression is a separate episode
  - Psychosis may occur in either, but only within the context of mood congruence
  - Both phases are needed (i.e. there is a time when you are one or the other, and a time you are neither)
  - Relatively rare disorder but not some extreme of a distribution curve

Evolution of Manic Depressive Disorder

- **Changes in manic depression/bipolar disorder have occurred in:**
  - **Definition of episode**
    - Specific duration of "distinct period"
    - "Mixed," BPII, rapid cycling
  - **Handling the content of psychosis**
    - Degree of mood congruence
  - **Handling the concept of secondary mania**
    - CNS pathology
    - Substance/medication relationships

15min episodes - rapid cycling
bipolar + bipolar II
secondary mania

Epidemiology

- 1/250 16-year old high school students had a lifetime manic and depressive episode (0.06%)[1]
- 0.95% of 1700 youth (n=18) ages 14-18 "bipolar"
  - 0.1% (n=2) had lifetime mania
  - 0.6% had depression with hypomania
  - 0.3% had cyclothymia[2]
- 1-year incidence was 0.13%; annual incidence over follow-up 0.08% (only 1 of the hypomanic patients had progressed to mania)
- 5.7% experienced at least 1 week of elated, expansive or irritable mood (none became manic over the next 4 years)

[1]Carlson and Kashani, 1988.
[2]Lewinsohn et al., 1995; 2000.

About 1 o/o of teenagers have bipolar disorder

0.1 o/o had acute manic episode

rest had symptoms

more developed depression + anxious depression

Differences Between Child and Adult Bipolar Disorder

Clear Mood Episodes	Absent	Present	Present
Comorbidity	> 90%	~ 50%	~ 20%
DBD Disorder	Very often	Some-times	Never
Substance Abuse	n/a	Often	Rare
Euphoric Mania	Rare	Some-times	Often
Psychomotor Retarded Dep.	Rare	Yes	Yes

DBD - destructive behavior disorder

Differences Between Child and Adult Bipolar Disorder

Confusion with schizophrenia	Rare ?mdi	Often	Rare
Switch from MDD	Yes	Yes	Rare
Family History mood disorder	++++	++++	++
Uncomplicated Bipolar	Rare	Common	Common
Rate of chronicity	High	5%–10%	c. 5%
Lithium response	Poor	+/–	Common

Pediatric Bipolar Disorder

- **Easily Misdiagnosed**
  - Severe ADHD
  - Conduct Disorder
  - "BAD CHILD"
  - Schizophrenia
  - Oppositional Defiant Disorder

odd
oppositional defiance disorder

Diagnostic Challenges of BPD

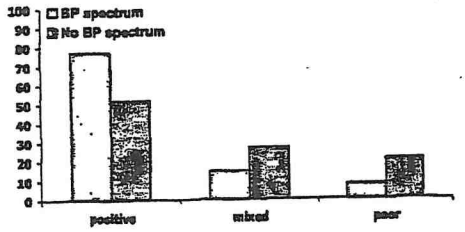
- Children With Treatment-Resistant Depression May Have BPD
- 60% of BPD Adults Report First Symptoms in Childhood or Adolescence
- Delay in Diagnosis in Adults Averages 8 Years
- Most Adults See 3 Physicians Prior to Correct Diagnosis

Confound #1 – Switching, cycling, disinhibition

- Prospective inpatient study at Stony Brook (Carlson and Mick):
  - Drug-induced disinhibition occurs in children
  - Rates are low when systematically observed ~ 8%
  - NO DIAGNOSTIC SIGNIFICANCE
- Rebound occurs in 10%–30% of children 9% had to stop because of it
  - NO DIAGNOSTIC SIGNIFICANCE
- MTA trial: no short-term differences in stimulant response between children with manic symptoms (defined either on the DISC or on the CBCL profile) and without

(Studies in JCAP, in press fall, 2003)

Childhood MPH Response in MBD Adults With BP Spectrum Disorders



Carlson et al. 1999.

stimulant response predicts stim response only

Confound #2— Symptom Sharing

Mania	MDD	ADHD	ODD	Anxiety
Elated mood				
Irritability	67%	Low frustration tolerance	Touchy/ Easily annoyed	Irritability
Hyperactivity agitation	Agitation	Hyperactivity		Restlessness agitation
Distractibility	Poor conc.	Distractibility		Difficulty in concentration
Flight of ideas		Communication disorders		
Grandiosity				
Poor judgment		Impulsivity		
Reduced sleep	Insomnia	Trouble settling wakes early		Initial insomnia

mania: elated mood
grandiosity

Confound #3— Manic Symptoms

- 5%–10% of general population of adolescents
- 9%–22% of child/adolescent outpatients
- 58% of psychiatrically hospitalized children
  - Hospitalized longer, more hyperactive, aggressive and learning disabled, but respond similarly to stimulants as non "manic" hospitalized ADHD children
- Like psychotic symptoms, manic symptoms complicate a number of disorders without necessarily being diagnostically specific

Conditions With Manic Symptoms/Emotional Lability

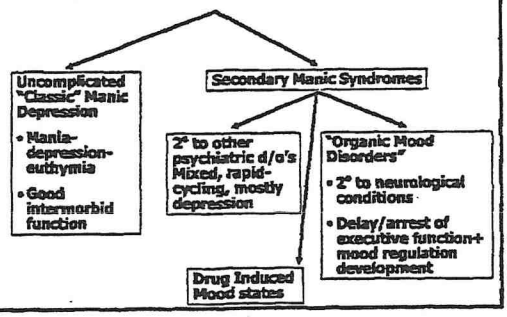
- "Organic" etiologies (e.g. closed head injury, frontal lobe syndromes)
- PDD NOS (MCDD/borderline disorder)
- Not quite schizophrenia (multi-dimensionally impaired, schizotypal personality disorder)
- ADHD ("MBD" i.e. ADHD with LDs and "soft signs")
- "Borderline Personality Disorder"

kids who don't meet criteria

Implications—Manic Symptoms

- It is unclear what children who fall in these gray areas "have" but whatever it is, it is difficult to treat
- When you get a family history of bipolar disorder—get a very good history about the family member
- One suggestion is to divide mania into primary and secondary

Bipolar Disorder



emotion regulation delay

Confound #4—Measurement

- Developmentally sensitive measures needed
  - e.g. the Young Mania Rating Scale (Y-MRS) scores are higher in younger children and higher in boys
- Besides hyperactivity/inattention, need cross-sectional/other-observer ratings of:
  - Mood elevation
  - Irritability—number and intensity of blow-ups
  - Psychosis
  - Thought disorder

Other Measures Needed

- A child mental status is imperative
  - Needed to assess pervasive developmental disorder
  - Language disorder and thought disorder
  - Psychotic symptoms
- Measures of comorbidities needed
- Measures of what episodes are and how long they last are needed

2 hrs needed

Possible Rating Scales

- Interview scales
  - Brief Psychiatric Rating Scale (BPRS)
  - Young-Mania Rating Scale (Y-MRS)
  - Children's Atypical Development Scale
- Parent/Teacher/Child Rating scales
  - Child/Adolescent Symptom Inventory (Gadow and Sprafkin, 1997)
  - Childhood Behavioral Check List (CBCL)
  - Conners Rating Scales

Treatment Wrinkle #1—Samples

- Most data in adults has been gathered on patients with acute mania, usually hospitalized acute mania
- Studies in youth have been in acute mania, and were discontinuation studies (lithium), open and/or add-on studies (DVP)
- Other studies (lithium, DVP, CBZ) have included outpatient manic, hypomanic and BP,NOS cases

Wrinkle #2

- "Mania" in children is:
  - Chronic
  - Heterogeneous
  - Developmentally complicated
  - Not easily modified without medication
- Unfortunately, medication efficacy is not robust (50% improvement in 50% of adults)
- Short-term serious risks (liver, blood and electrolyte aberrations, weight gain)
- Possible long-term risks (polycystic ovary disease, diabetes, consequences of prolactin elevation and decreased estrogen, renal insufficiency, thyroid disease)

Immediate Goals for Acute Mania/Hypomania Treatment

- Discontinue antidepressants/stimulants
- Ensure full sleep with medication
- Reduce external social/sensory stimulation
- Reduce escalation with immediate acting medication (olanzapine is the most rapid acting approved medication in adults)
- Start and titrate mood stabilizer

FDA Approval for Drugs in the Treatment of Adults With Acute Mania

Lithium*	X	
Valproate	X	
Olanzapine	X	(wr)
Clozapine		X
Risperidone		X (wr)
Quetiapine		X (wr)
Carbamazepine		X
Oxcarbazepine		X
Topiramate		X
Aripiprazole		X (wr)

*also approved for prophylaxis.

Suggested Algorithm for Acute Mania

Euphoric	Mixed Dysphoric	Psychotic	Rapid Cycling
Lithium Valproate Olanzapine Carbamazepine	Lithium Valproate Olanzapine Carbamazepine	Valproate or Lithium + Atypical Antipsychotic or Typical Antipsychotic	Valproate Valproate + Carbamazepine

If no response in 4 weeks at therapeutic levels, the next step is basically a choice between adding either another mood stabilizer (evidence of synergism) or an A-AP; if that doesn't work after 3 weeks, do whatever you didn't do. If that doesn't work, reconsider diagnosis; consider diagnostic hospitalization.

Somatic Treatments in Acute Mania

	Data score adults	Data score "youth"	Efficacy score (A)	Safety score (A)
lithium	A	B	B	B
DVP	A	C	B	B
CBZ	B	C	B	B
T-Aps	B	C	B	B
clozapine	B	C	B	B
risperidone	B	C	B	B
olanzapine	B	C	B	B
benzodiazepines	D	C	B	B
oxcarbazepine	B	C	B	B
lamotrigine	C	C	B	B
topiramate	B	C	B	B
ECT	C	C	B	B

Source: Keck et al., JAD 12, 2000; modified by Carlson, 2002.

Mood Stabilizers in Youth-BP Disorder

- **Lithium**—discontinuation studies; anecdotal; literature reviews; open studies; one double-blind trial
- **Carbamazepine**—literature reviews, case reports; open trial
- **Valproate**—open studies; literature reviews; discontinuation study
- **Neuroleptics** (typical and atypical)—anecdotal or open trials

Lithium

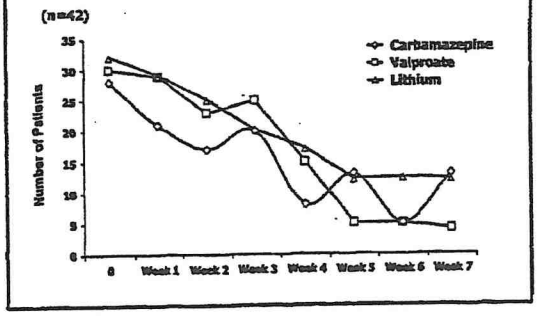
- Best studied and without industry hype
- For classic manic depressives (M-D-E; + family history bipolar; euphoria/grandiosity), most efficacious
- Works synergistically with valproate
- Decreases recurrences
- Reduces depression
- Decreases suicide
- The problem is most children and teens do not seem to have this kind of manic-depression

Divalproex Dosage

- Initiation
  - Acute:
    - 10–15 mg/lb/day
    - Increase by c. 5 mg/lb every 1–2 days (i.e. acute mania needs aggressive dosing)
  - Subacute:
    - 5–10mg/lb/day
    - Increase by c. 5 mg/lb every 4–7 days
    - Go slow doesn't mean take forever
  - Dose until effective or adverse events; decrease or divide dose if adverse events
  - Target: 50–150 mcg/ml
- Extended release diminishes peaks and valleys but not yet tested in psychiatric patients

use moderately aggressively...

Patient Retention in Open Trial of Mood Stabilizers in BP I and II 6-18 Year Olds



Irritability items from the ABC Checklist

- Injures self
- *Aggressive to other patients and staff*
- Screams inappropriately
- *Temper tantrums*
- *Irritable ("grizzly" or "whiny")*
- Yells at inappropriate times
- *Depressed mood*
- *Demands must be met immediately*
- *Cries over minor annoyances or hurts*
- *Mood changes quickly*
- Cries and screams inappropriately
- *Stamps feet while banging objects or slamming doors*
- *Deliberately hurts himself/herself*
- Does physical violence to self
- *Throws temper tantrums when doesn't get own way*

Aman et al., 1985.

acute impulsive aggression

Primary Efficacy Parameter N-CBRF Conduct Problem Subscale

- *Argues with parents, teacher, or other adults*
- Cruelty or meanness to others
- Defiant, challenges adult authority
- Knowingly destroys property
- Disobedient
- Doesn't feel guilty after misbehaving
- *Explosive, easily angered*
- *Gets in physical fights*
- Physically attacks people
- Runs away from adults, teachers or other authority figures
- Stubborn
- *Talks back to teachers, parents or other adults*
- *Temper tantrums*
- Threatens people
- Violates rules
- Argues with other people or peers

Treatments for Mania and Aggression

Lithium	X	X
Valproate	X	X
Carbamazepine	X	X
Stimulants	X	A few case reports but not routinely
Neuroleptics	X	X
Atypical neuroleptics	X	X
Antidepressants	X	During the depressive phase
Anxiolytics		
Buspirone	X	
Benzodiazepines		X
B-blockers	X	
Clonidine		
Calcium channel blockers		X
ECT		X

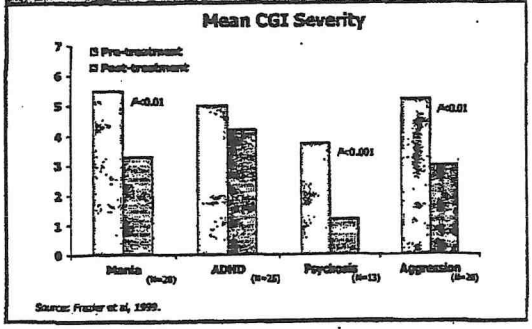
Risperidone Clinical Efficacy

Disruptive Behavior Disorders (CD, ODD, DBD-NOS)	Aman et al. (2002)[1]	NCBRF – Conduct Prob.	-46.2**	-18.0
	Snyder et al. (2002)[2]	NCBRF – Conduct Prob.	-47.3**	-20.9
	Turgay et al. (2002; Snyder et al. LT ext.)[3]	NCBRF – Conduct Prob.	-7.2% over Snyder et al. endpoint	N/A
Autism/ PDD	RUPP Autism Gp. (2002)[4]	ABC – Irritability	-56.9**	-14.1
	Shea et al. (2002)[5]	ABC – Irritability	-58.1*	-30

*P<0.01 v. PBO, **P<0.001 v. PBO.

[1]Aman et al. (2002), *Am J Psychiatry, 159*, 1337-1346. [2]Snyder et al. (2002). *JAACAP, 41:9*, 1026-1036. [3]Turgay, et al. (2002), *Pediatrics; 110 (3)*, pp:e34. [4]Shea et al. (2002), Poster presented at the AACAP annual mtg., San Francisco; October. [5]RUPP Autism Network (2002), *N Engl J Med, 347(5)*, 314-321.

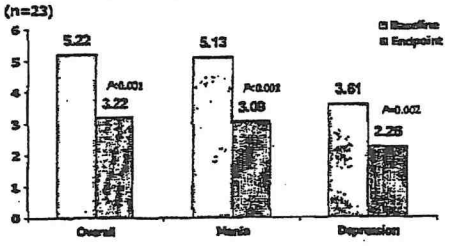
Treatment in Juvenile Mania: Response Pre- and Post-Risperidone



Source: Frazier et al, 1999.

Open Trial of Olanzapine in Juvenile Bipolar Disorder

(n=23)



There were significant improvements in Clinical Global Inventory Bipolar Severity scores, not only overall, but also in both the mania and depression subscores, following olanzapine treatment.

Source: Frazier et al, 2001.

Pediatric Bipolar Disorder Quetiapine as Adjunctive Treatment

- 30 Manic Youth (12 to 18 Years) on Depakote (20 mg/kg/day) randomized at outset to placebo and quetiapine (250 - 450 mg/day) in 6 Week Double-Blind Trial
- 1 withdrew from Depakote + Pbo; 7 withdrew from Depakote + quetiapine; i.e. 22 completers
- YMRS dropped from 30 to 15 with Depakote; 34-c. 10 with combo ($p<0.01$). No difference in CDRS, PANSS or CGI

DelBello et al, 2002

Treatment at 4-Year Follow-up: SCPP

Mood stabilizer use —most of follow-up	39.1%	26.7%
Never used	17.4%	20.0%
Intermittent med use	13.0%	31.0%
No med use most of follow-up	45.4%	41.4%

compliance issue

MOA –

Risperdal:

Serotonin and Dopamine
not sure what transmitter
Systems are regulated downstream.
why don't we use antiepileptics?

How do you define aggression disorder.
Reluctance by FDA to define and approve
indication.

Risperidone in Tourette's.

DSM: anger spectrum disorders.
Intermittent Explosive Disorder

Break out group

antipsychotic - 37.8 million in 2002,
12.9%

Risp: 11.3 million in 2002
most widely prescribed.
51% - Risp /

perception is that zyprexa is more widely used than it is.
cont Rx vs NRx

liquid form + MTab

2, 3 4 – Risperdal
consultation liaison specialty
GI symptoms

[redacted]

speaker training

[redacted]

Acute mania
4 Q 02

Dementia

Autism

Hard to diff ADHD + bipolar in young patients
PCPs tend not to initiate prescriptions

Challenges in monitoring efficacy and side effects

Dosing: Add Dx 1.8 mg/day
Conduct / ADHD / 1.6 mg/day
Bipolar / 1.5 mg/day
Schiz / 3.0 day

Indic in 21 other countries for disruptive behavior disorder

specificity in terms of diagnosis

30 ml oral
0.5 mg tablet
0.25 mg tablet
IR consta - Pending appvl

microspheres suspended in an aqueous solution
don't get PK peaks and troughs

Risp (2) M-Tab - 0.5 mg (melt)

$1 more per pill

1.0 mg
2.0 mg
.25?

numerical difference; not statistically significant.

Shld change be updated?
seemed to be consensus to inform of label change.

low freq of events in sm # of trials
Numeric ↑ in CVA in risp group → over 85, prev history of stroke, nonverbal.

CHILD & ADOLESCENT
REGIONAL ADVISORY MEETING

New Developments in the Treatment of Pervasive Development Disorder/Autism

Lawrence Scahill, MSN, PhD
Associate Professor of Nursing and
Child Psychiatry
Yale Child Study Center
Yale University, School of Nursing
New Haven, Connecticut

autism + related:
prevalence:

40-60 per 10,000.

Autism: 20 people per 10,000.

Emerging Uses of Atypicals in Pediatric Populations

- Psychosis
- Autism and related disorders*
  - Aggression
  - Tantrums
- Mental retardation
  - Impulse control problems
- Tourette syndrome
  - Tics
- Bipolar disorder

Brief Background: Autism Defined

- Chronic, disabling condition of early childhood onset
- Part of a spectrum of pervasive developmental disorders characterized by:
  - Impaired social interaction
  - Delayed and deviant language
  - Restricted interests
  - Repetitive behavior
- Often complicated by serious behavior problems (tantrums, aggression and/or self-injurious behavior)

Hope for children w/autism. Treatment must start early.
Keep these children calm.
Help them w/ ADLs and differentiate between acceptable and unacceptable behaviors.

Social reciprocity issue -- some advances that come from early treatment

Need for good screening measure in autism.
Case vignettes for diagnostic criteria
collaborate with advocacy groups
clarify safety data / risk in this population
take leadership to train physicians in rural areas to treat people with autism

Spraker dinners -
Pediatricians trained by protocol -
ruling out
age
dose
what to worry about
when to refer
control behavior
length of episode; frequency

Autism Spectrum: Prevalence

Disorder	Prevalence
• Autism	20 per 10,000
• Asperger's	1 per 10,000*
• PDD-NOS	20 to 40 per 10,000
➔ total	40 to 60 per 10,000

*Based on minimal data.

Medications Used in the Treatment of Autism and Related Disorders

- Haloperidol*
- Fenfluramine
- Clonidine
- Naltrexone
- Propranolol
- Clomipramine
- SSRIs
- Stimulants
- Secretin*
- Amantadine

* Best studied.

Atypical Antipsychotics in Children With PDD

Drug	N	Dose/Day	Design	Target	Benefit
Risperidone	223	0.5 to 6.0	open, controlled	aggression, tantrums, self-injury	++
Clozapine	4	200 to 400	open	aggression, hyperactivity	-
Quetiapine	6	100 to 350	open	aggression	-
Olanzapine	16	8 to 40	open	aggression, agitation, psychosis	-+/-
Ziprasidone	19	10 to 120	open	aggression, stereotypies	+/-

Atypical Antipsychotics: Adverse Effects

	Weight Gain	Serious Effects
Risperidone	Yes (6 lb in 8 weeks)	(1) liver failure ? ↑ prolactin
Quetiapine	Yes	(1) seizure
Olanzapine	Yes (9 lb in 6 weeks)	? ↑ triglyceride ? diabetes
Ziprasidone	No	? ↑ QTc

case
rapid weight gain
+ fatty infiltration

Research Units in Pediatric Psychopharmacology (RUPP)

- Autism Network
  - Indiana University
  - Kennedy-Krieger (Johns Hopkins)
  - Ohio State University
  - U California at Los Angeles
  - Yale University (Coordinating Center)

Sponsor: NIMH

Janssen: Drug and Matching placebo

Data Management: Nathan Kline Institute

Research Units in Pediatric Psychopharmacology (RUPP)

- Principal Investigators
  - Michael Aman
  - Jim McCracken
  - Chris McDougle
  - Larry Scahill
  - Elaine Tierney
  - Ben Vitiello

CHILD & ADOLESCENT
REGIONAL ADVISORS MEETING

RUPP Autism Network: Risperidone Protocol I

8-Week, Double-Blind,
Placebo-Controlled, Randomized Trial

Risperidone in Children and Adolescents With Autism: Hypothesis

- Risperidone will be superior to placebo for
  - Aggressive behavior
  - Agitation
  - Tantrums (eg, in response to change)
  - Self-injurious behavior

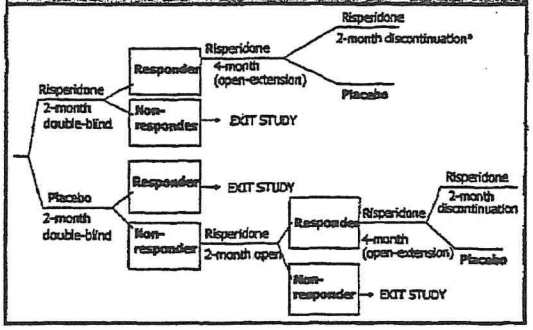
RUPP Autism Network. *N Engl J Med.* 2002;347:314-321.

Not treatment of autism per se.

Risperidone in Children & Adolescents with Autism

- Inclusion criteria
  - Autism
  - Age 5 to 17
  - Irritability subscale score > 18
  - CGI-severity > 4
  - Mental age > 18 months
  - Medication free
    (14 to 28 days depending on drug)
    (except anticonvulsants)

Study Design



Risperidone in Children and Adolescents With Autism: Outcomes

- Primary outcomes
  - ABC Irritability scale (15-item parent-rated measure containing aggression, SIB, tantrums)
  - CGI-Improvement (clinician-rated)

clinical global impressions

RUPP Autism Network. *N Engl J Med.* 2002;347:314-321.

Risperidone in Children and Adolescents With Autism: Results

- Subjects (N = 101)
  - 82 males, 19 females
  - Risperidone (n = 49), placebo (n = 52)
  - Mean age = 8.8 y (range, 5-17 y)
  - No significant differences across groups at baseline

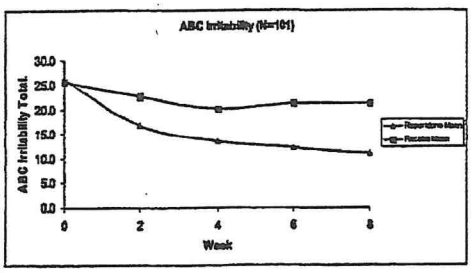
RUPP Autism Network. *N Engl J Med.* 2002;347:314-321.

ABC Irritability Scores at Baseline and Endpoint by Treatment Group

	Risperidone		Placebo	
ABC Scale	Baseline Mean (SD)	Endpoint Mean (SD)	Baseline Mean (SD)	Endpoint Mean (SD)
Irritability	26.2 (7.9)	11.3 (7.4)	25.5 (6.6)	21.9 (9.5)

P<.0001

Risperidone in Autism: Irritability Scale

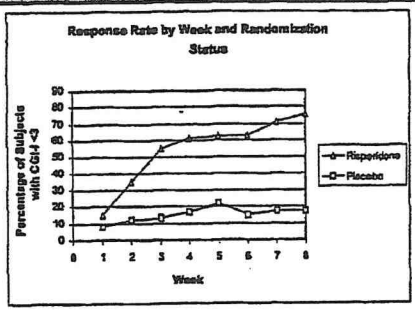


Baseline & endpoint ABC scores by group

	—Risperidone—		—Placebo—		
ABC Scale	Baseline Mean (SD)	Endpoint Mean (SD)	Baseline Mean (SD)	Endpoint Mean (SD)	P
Irritability	26.2 (7.9)	11.3 (7.4)	25.5 (6.6)	21.9 (9.5)	<.0001
Social Withdrawal	16.4 (8.2)	8.9 (6.4)	16.1 (8.7)	12.0 (8.3)	<.05*
Stereotypy	10.6 (4.9)	5.8 (4.6)	9.0 (4.4)	7.3 (4.8)	<.0001
Hyper-activity	31.8 (9.6)	17.0 (9.7)	32.3 (8.5)	27.6 (10.6)	<.0001
Inapprop. Speech	4.8 (4.1)	3.0 (3.1)	6.5 (3.6)	5.9 (3.8)	NS

*After adjusting for multiple comparisons not significant

Clinical Global Impressions: Improvement



RUPP Autism Study: Adverse Events

Adverse event	Risperidone n=49 n (%)	Placebo* n=52 n (%)	P value†
Increased appetite			
Mild	24 (49)	15 (29)	0.05
Moderate	12 (25)	2 (4)	0.01
Tiredness	29 (59)	14 (27)	0.002
Drowsiness	24 (49)	6 (12)	<0.001
Drooling	13 (27)	3 (6)	0.01
Tremor	7 (14)	1 (2)	0.05
Weight gain in kg	2.7 ± 2.9	0.8 ± 2.2	<0.01

*One child withdrew from trial at baseline and thus was not included in AE analysis.
†Other AEs reported, but were considered not statistically significant (Pall.1).

RUPP Autism Network. *N Engl J Med.* 2002;347:314-321.

Atypical Antipsychotics in PDD: Conclusions

- Atypical antipsychotics are being used for a range of problems in children with PDD
- Best studied in risperidone
  - Effective for serious behavioral problems at relatively low doses
  - Positive effects are stable over time
  - Does not have marked effects on core sx of PDD
  - Although reduced risk of EPS, weight gain is a concern
- Future studies
  - Efficacy and safety of other drugs in this class
  - Combined effects of medication and behavior therapy

$\frac{1}{3}$ of children when switched to placebo did not relapse...

CHILD & ADOLESCENT
REGIONAL ADVISORS' MEETING

A Review of Efficacy Data for Risperidone in the Child and Adolescent Population

Gahan J. Pandina, PhD
Associate Director, CNS Clinical Development
Janssen Pharmaceutica Products, LP

Common Symptoms in Pediatric Psychiatric Disorders: Diagnostic Overlap

Diagnosis	Aggression	Mood Instability	Irritability	Anxiety	Psychosis	Hyperactivity	Impulsivity
ADHD	+++	++	+++	++		+++	+++
CD	+++	++	+++	+		++	+++
ODD	+++	++	+++	+		++	+++
Schizophrenia	+++	++	++	++	+++	++	+++
Bipolar Disorder	+++	+++	+++	+	+	++	+++
GAD	++	++	++	+++		+	+
PTSD	++	++	++	+++		++	++
PDD/Autism	+++	++	++	+++		++	++

Outline – Efficacy Data

I. Disruptive Behavior Disorders

II. Newly Emerging Data in Pediatric Bipolar Disorder

III. Newly Emerging Data in Autism/PDD

CHILD & ADOLESCENT
REGIONAL ADVISORS MEETING

Disruptive Behavior Disorders

Overview of Studies in Disruptive Behavior Disorder

Author Study #	N	Age	Design	Publication
Findling	28	6-14	Randomized, DB, PC, 10 week	(2000) JAACAP 39(4):509-516
Aman US 93	118	5-12	Randomized, DB, PC, 6 week, multi-center	(2002) Am J Psychiatry 159:1-10
Findling US 97	107	5-12	Open-label, 48 wk extension to Aman	Submitted
Snyder CAN 19	110	5-12	Randomized, DB, PC, 6 week. IQ = 36-84	(2002) JAACAP 41(9):1026-1036
Turgay CAN 20	77	5-12	Open-label, 48 wk extension to Snyder	(2002) Pediatrics 110(3):1-12
Croonenbergh INT 41	504	5-14	Open-label, multi-center, international	Submitted
Reitaner	38	12-15	Rand., DB, PC, 6 wk, hospitalized	(2001) J Clin Psychiatry 62:239-245

Total n=874

Study Outcomes: Risperdal effective and well tolerated in DBD
Long-term (1 year) safety and efficacy demonstrated

RIS vs Placebo: US and Canadian Short-Term Studies

- **US 93 and CAN 19** (borderline, mod IQ impairment)
  - Six-week, double-blind, placebo-controlled inpatient comparison (n=118 [US]; n=110 [Canadian])
  - DSM-IV Conduct Disorder, Oppositional Defiant Disorder, Disruptive Behavior Disorder, Borderline Intellectual Functioning/Mental Retardation (IQ 35 to 84)
  - Rating of ≥24 on the Nisonger Child Behavior Rating Form
  - Prominent symptoms of aggression, impulsivity, stereotypical and self-injurious behaviors

Aman MG, et al. *Am J Psychiatry*. 2002; 159: 1-10 .Snyder R, et al. *JAACAP*. 2002; 41:9, 1026-1036

About 1,000 pts studied in D.B.D.

my behaviorally disturbed children

RIS vs Placebo: US and Canadian Long-Term Studies

- **US 97, CAN 20 and INT 41**
  - All subjects eligible in the short-term double-blind phase (US 93 and CAN 19) were also eligible to receive Risperdal in the long-term open label phase for up to 48 weeks
  - A fifth study, INT 41, was a 48-week open label safety study in the same population (ages 5-15)

Turgay A, et al. *Pediatrics.* 2002;110(3):1-12

Patient Characteristics (US Study)

Sex, N (%) Female Male	13 (21%) 50 (79%)	8 (15%) 47 (85%)
Age in years Mean ± SD[1]	8.1 ± 2.3	8.7 ± 2.1
Intelligence Quotient* Mean ± SD	86±16	76±12
DSM - IV, axis I, N (%) Axis I* Axis I* + ADHD[2] Conduct Disorder (CD) CD + ADHD	13 (21%) 21 (33%) 12 (19%) 14 (22%)	12 (22%) 17 (31%) 9 (16%) 12 (22%)
DSM - IV, axis II, N (%) Borderline Intellectual Disability Mild Mental Retardation Moderate Mental Retardation	28 (44%) 22 (35%) 13 (21%)	32 (58%) 16 (29%) 7 (13%)

[1]SD: Standard deviation
[2]Axis II including subjects with Oppositional Defiant Disorder or Schizotypal Disorder not otherwise specified.
[2]ADHD: Attention Deficit/Hyperactivity Disorder.
* Perd.04 vs. placebo

Aman MG, et al. *Am J Psychiatry.* 2002;159:1-10

borderline mental / intellectual ability

Pediatric Study Populations

Number of subjects by protocol and treatment

Double Blind		Open Label			
Protocol	Treatment	Protocol	Treatment	All Subjects	ITT
CAN-19	RIS	CAN-20	RIS	43	41
CAN-19	PBO	CAN-20	RIS	39	39
CAN-19	RIS	INT-41	RIS	10	10
CAN-19	PBO	INT-41	RIS	13	13
USA-93	RIS	USA-97	RIS	55	48
USA-93	PBO	USA-97	RIS	59	57
		INT-41	RIS	481	457
				700	665

Aman et al, Am J Psychiatry 2002;159:1337-1346
Snyder et al, J Am Acad Child Adolesc Psychiatry 2002;41:1026-1036
Turgay et al, Pediatrics 2002;110:e34
Data on file: Janssen Pharmaceutica Products, LP

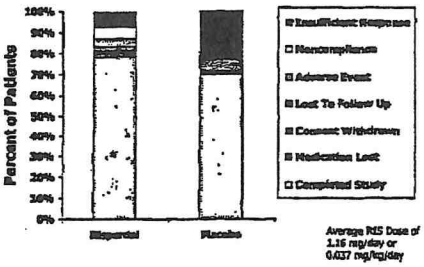
Dosing

Short-term		Long-term	
US 93 Aman AJP 2002	1.16 mg/d (0.037 mg/kg/d)	US 97 Findling submitted	1.5 mg/d (0.04mg/kg/d)
CAN 19 Synder JAACAP 2002	0.98 mg/d (0.033 mg/kg/d)	CAN 20 Turgay Ped 2002	1.38 mg/d (0.041 mg/kg/d)
		INT-41 Croonenberghs	1.59 mg/d (0.02 mg/kg/d)

Titration: Short-term Studies
- RIS oral solution: 0.02 mg/kg/day to 0.06 mg/kg/day
- Once daily dose given in AM
- Initial dose/Day 1: 0.01 mg/kg
- Day 2: 0.01 mg/kg
- Day 3: 0.02 mg/kg
- Adjusted weekly as clinically needed

Aman MG, et al. *Am J Psychiatry*. 2002; 159: 1-10
Snyder R, et al. *JAACAP*. 2002; 41:9, 1026-1036.

Patient Disposition (US Study)



Average RIS Dose of 1.16 mg/day or 0.037 mg/kg/day

Aman MG, et al. *Am J Psychiatry*. 2002; 159: 1-10

insufficient response in placebo group

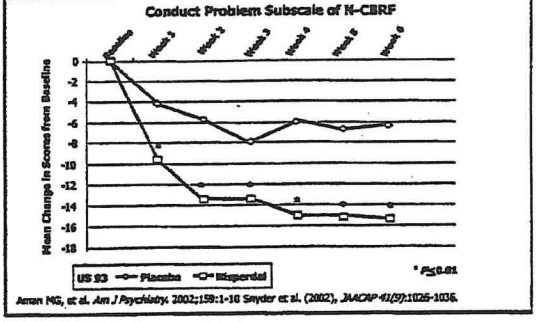
Primary Efficacy Parameter N-CBRF Conduct Problem Subscale

13 of 16 items have counterpart from CD or ODD symptoms in DSM-IV:

- Argues with parents, teacher, or other adults
- Cruelty or meanness to others
- Defiant, challenges adult authority
- Knowingly destroys property
- Disobedient
- Doesn't feel guilty after misbehaving*
- Explosive, easily angered
- Gets in physical fights
- Physically attacks people
- Runs away from adults, teachers or other authority figures
- Stubborn*
- Talks back to teachers, parents or other adults
- Temper tantrums
- Threatens people
- Violates rules
- Argues with other people or peers*

*not in DSM-IV criterion

EFFICACY: Behavioral Symptoms



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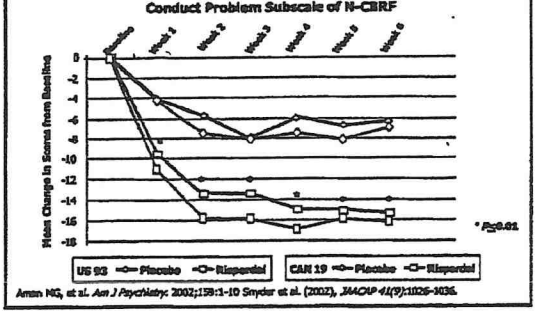
EFFICACY: Behavioral Symptoms



Aman MG, et al. *Am J Psychiatry*. 2002;159:1-10 Snyder et al. (2002), *JAACAP 41(9):1026-1036.*

symptoms dropped 50% in treatment group

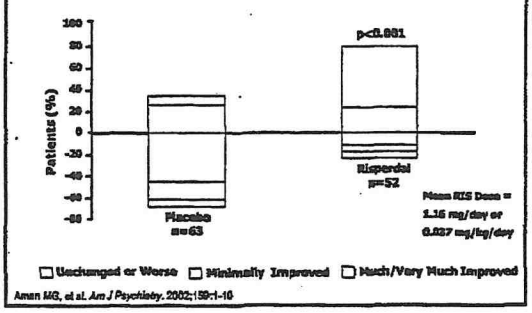
EFFICACY: NCBRF-Conduct Percent Change

Conduct Problem Subscale of N-CBRF

US 93	Baseline	Endpoint	% Change
Placebo	34.5	28.3	-17.97
RISPERDAL®	32.9	17.7	-46.20

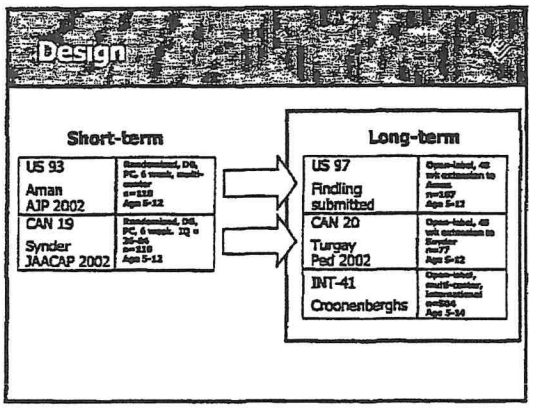
CAN 19	Baseline	Endpoint	% Change
Placebo	32.6	25.8	-20.9
RISPERDAL®	33.4	17.6	-47.6

EFFICACY Clinical Global Impression – Change

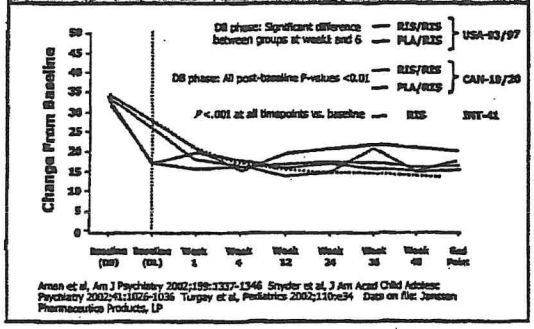


Aman MG, et al. *Am J Psychiatry*. 2002;159:1-10

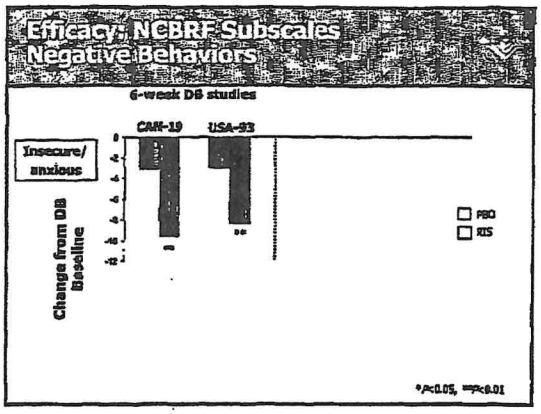
Design

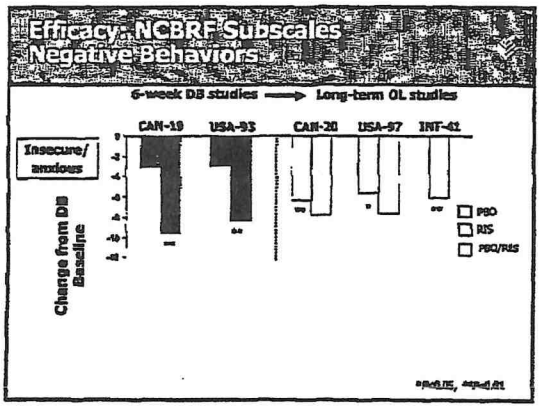


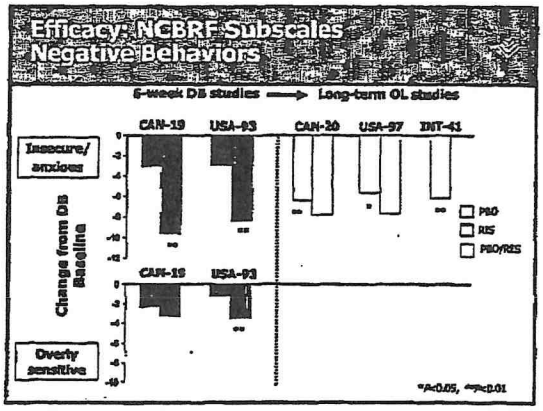
Primary Efficacy Measure: NCBRF Conduct Problems Subscale

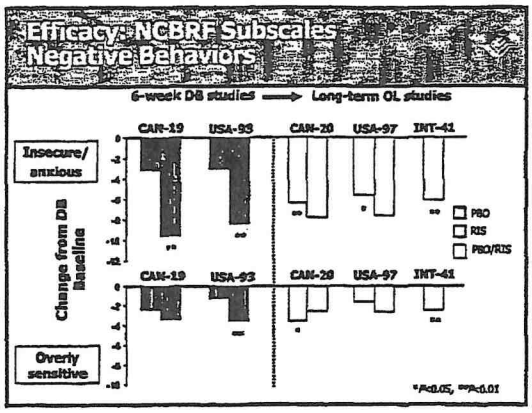


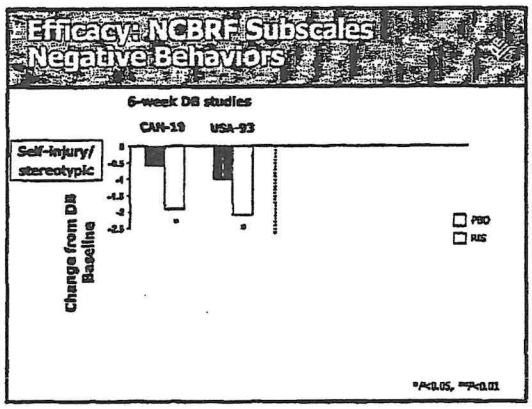
Aman et al, Am J Psychiatry 2002;159:1337-1346 Snyder et al, J Am Acad Child Adolesc Psychiatry 2002;41:1026-1036 Turgay et al, Pediatrics 2002;110:e34 Data on file: Janssen Pharmaceutica Products, LP

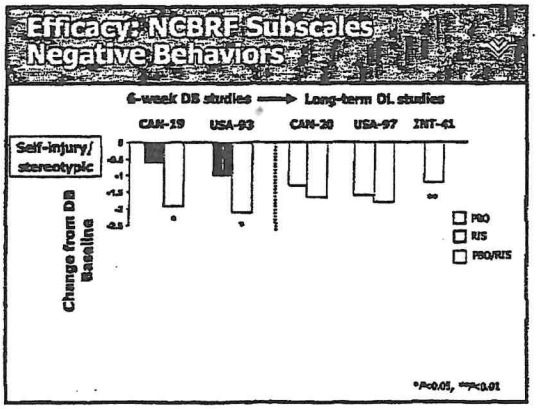


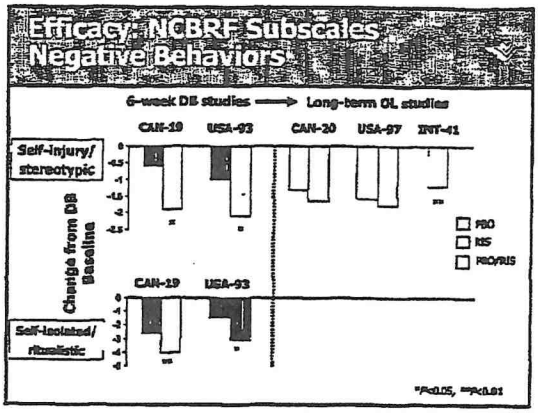


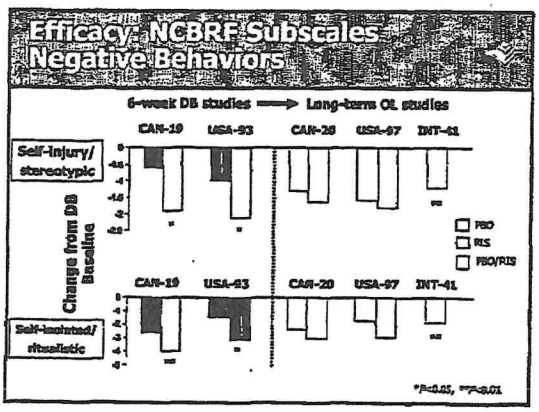









Efficacy: NCBRF Subscales
Negative Behaviors
6-week DB studies
Long-term OL studies
CAN-19
USA-93
CAN-20
USA-97
INT-41
Self-injury/ stereotypic
Change from DB Baseline
PBO
RIS
PBO/RIS
Self-isolated/ ritualistic
*P<0.05, **P<0.01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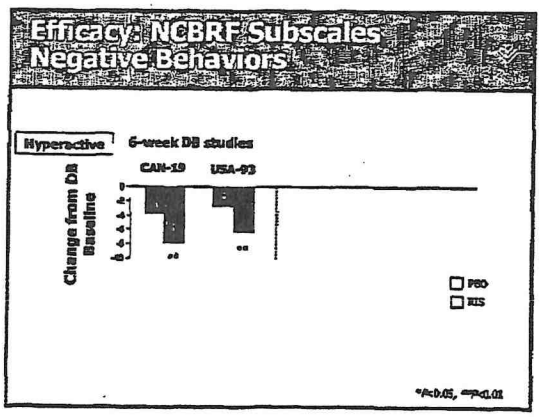
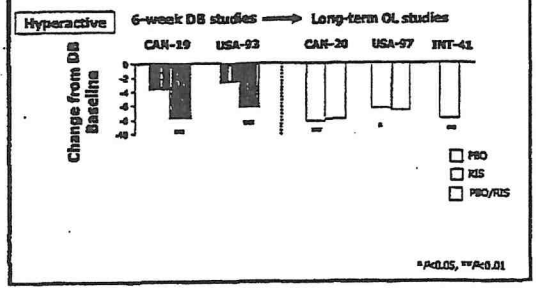
*P<0.05, **P<0.01

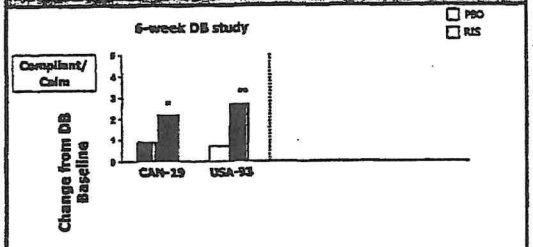

Efficacy: NCBRF Subscales
Negative Behaviors
Hyperactive
6-week DB studies
CAN-19
USA-93
Change from DB Baseline
PBO
RIS
*P<0.05, **P<0.01

Efficacy: NCBRF Subscales Negative Behaviors



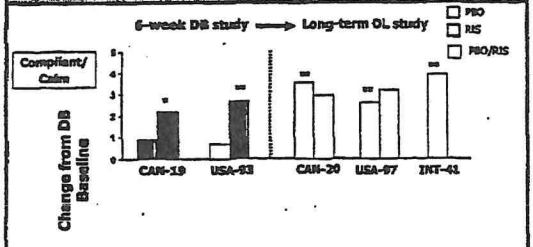
*P<0.05, **P<0.01

Efficacy: NCBRF Subscales Prosocial Behaviors



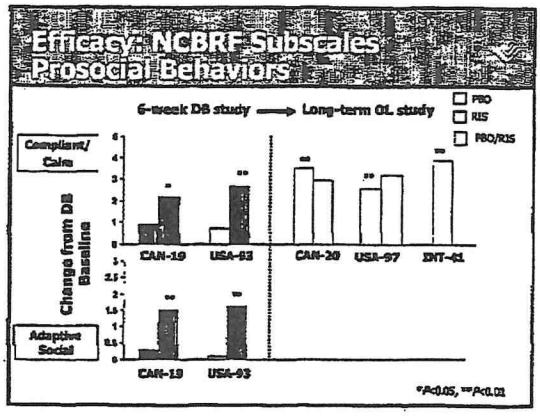
*P<0.05, **P<0.01

Efficacy: NCBRF Subscales Prosocial Behaviors

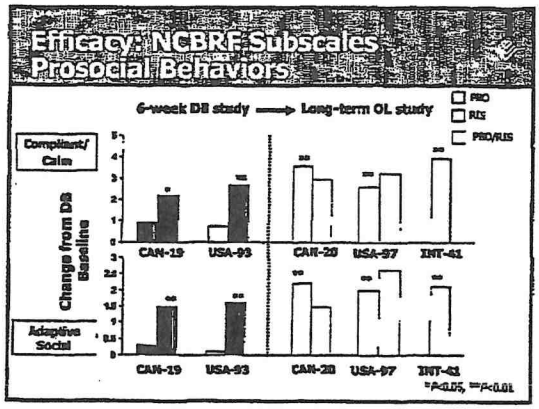


*P<0.05, **P<0.01

Efficacy: NCBRF Subscales Prosocial Behaviors



Efficacy: NCBRF Subscales Prosocial Behaviors



CHILD & ADOLESCENT
REGIONAL ADVISORS MEETING

Do these results hold true for adolescents with more severe conduct problems?

Other Short-Term: Risperdal in Hospitalized Adolescents with Aggression

- Randomized, double blind, placebo-controlled n=38 in hospitalized adolescents with aggression
- 2 week baseline, 6 week treatment, and 2 week post-study washout
- Initial dose 0.5 mg BID with titration to clinical response
- Fixed dose maintained for 4 weeks

Buitelaar JK, et al. J Clin Psychiatry 2001;62:239-248.

Aggression / mania

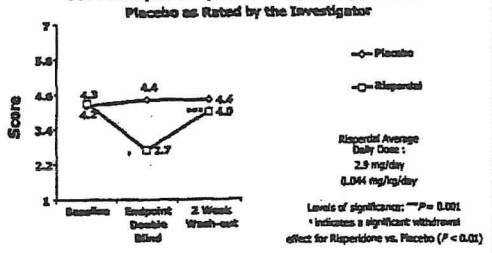
Patient Characteristics

Variable	Risperdal (N=19)	Placebo (N=19)	P Value[b]
Age, Y, mean ± SD	14.0 ± 1.5	13.7 ± 2.0	NS
Sex, M:F	17:2	16:3	NS
WISC-R IQ, mean ± SD Full Scale	76.0 ± 9.9	73.3 ± 10.1	NS
Principal Diagnosis, N			
Conduct Disorder	14	16	NS
Oppositional Defiant Disorder	4	2	NS
Disruptive Behavior Disorder NOS	1	1	NS
Comorbid Diagnosis, N			
ADHD	14	12	NS
Anxiety Disorder	8	3	NS
GAF Score, mean ± SD (Range, 30 – 70)	52.8 ± 9.6	52.9 ± 10.5	NS

[a]Abbreviations: ADHD = attention deficit/hyperactivity disorder, GAF = Global Assessment of Functioning, NS = not significant, WISC-R = Wechsler Intelligence Scale for Children – Revised.
[b]Wilcoxon 2 - sample test or chi-square test, as appropriate.
Buitelaar JK, et al. J Clin Psychiatry 2001;62:239-248.

Results: CGI-Severity

CGI-Severity Scores (mean and SD) for Risperdal and Placebo as Rated by the Investigator



Levels of significance: **P = 0.001
* indicates a significant withdrawal effect for Risperidone vs. Placebo ($P < 0.01$)

Buitelaar JK, et al. J Clin Psychiatry 2001;62:239-248.

Summary

- Efficacy demonstrated in:
  - Disruptive Behavior Disorder
  - Pediatric Bipolar Disorder
- Safety.....To be discussed tomorrow!

CHILD & ADOLESCENT
REGIONAL ADVISORS MEETING

A Review of Safety & Tolerability Data for Risperidone

Gahan J. Pandina, PhD
Associate Director, CNS Clinical Development
Janssen Pharmaceutica Products, LP

Efficacy Highlights: Disruptive Behavior Disorder

Author Study #	N	Age	Design	Publication
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Aman US 92	118	5-12	Randomized, DB, PC, 6 week, multi-center	(2002) Am J Psychiatry 159:1-18
Findling US 97	107	5-12	Open-label, 48 wk extension to Aman	Submitted
Snyder CAN 10	110	5-12	Randomized, DB, PC, 6 week. IQ = 36-84	(2002) JAACAP 41(8):1026-1036
Turgay CAN 20	77	5-12	Open-label, 48 wk extension to Snyder	(2002) Pediatrics 110(3):e1-12
Croonenberghs INT 46	504	5-14	Open-label, multi-center, international	Submitted
Reinhardt	38	12-15	Rand., DB, PC, 6 wk, hospitalized	(2001) J Clin Psychiatry 62:239-248

Total n=974

Study Outcomes: Risperdal effective and well tolerated in DBD
Long-term (1 year) safety and efficacy demonstrated

Efficacy Highlights: Pediatric Bipolar Disorder & Autism

Study	N	Age	Design
Pediatric Bipolar Disorder	30	6-17	Open-label, 8 week
Autism/PDD	80	5-12	Randomized, DB, PC, 8 week, multi-center

Outline

- Weight changes
- Hyperglycemia/Diabetes
- Prolactin
  - Normalization (Findling study)
  - Sexual maturation/growth
- Movement Disorders
- Cardiovascular

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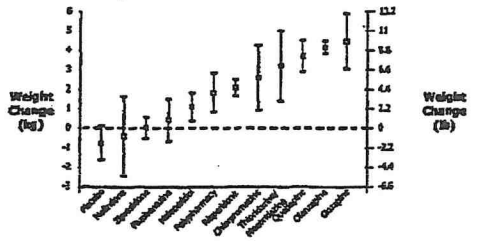
Weight Changes

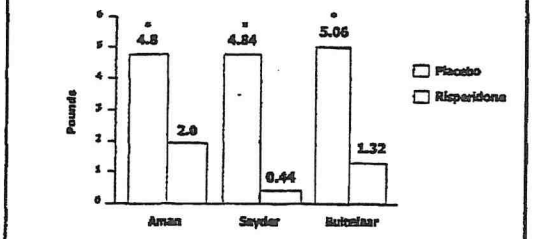
Antipsychotics: Meta-Analysis of weight change at 10 weeks



Allison DB et al. Am J Psychiatry. 1999;156:1686-1696.

Mean weight increase (pounds) from baseline to endpoint: 6-week trials

Short-term disruptive behavior studies

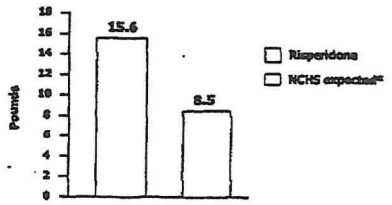


*$P < 0.01$ vs. placebo

Aman MG, et al. *Am J Psychiatry* 2002; 159: 1-10
Snyder R, et al. *JAACAP* 2002; 41:9, 1026-1036.
Butcher JK, et al. J Clin Psychiatry 2001;62:239-248

Mean weight increase (pounds) from baseline to endpoint: 48-week trial

Long-term disruptive behavior study

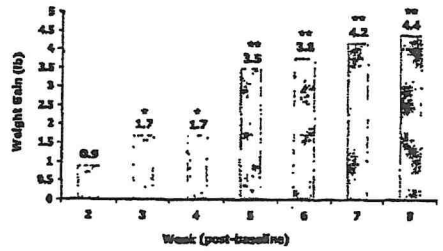


* National Center of Health Statistics: 8.5 lbs (3.85 kg) is expected wt increase over 1 yr in a child of same age and baseline wt

Turgay A et al. Pediatrics 2002; 110(3)1-12

median gain 4.4 lbs

Weight Gain in Open-Label Study of Risperidone in Pediatric Bipolar Disorder



*P<0.01, **P<0.001, versus baseline

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Hyperglycemia/Diabetes and Atypical Antipsychotics

Case reports: Summary

Clozapine	1990	332	92*
Olanzapine	1996	118	20*
Quetiapine	1997	2	1
Risperidone	1994	3	1

*25 deaths
* 2 deaths

PubMed Literature Search: 01/01/1994 - 01/06/2002

Summary of Epidemiologic Studies

Cohort Study	Results
Gianfrancesco (2002)	RIS = untreated
	OLA > untreated
Gregg	RIS = untreated
	OLA > untreated
Caro	OLA > RIS
Meisen	OLA > RIS
Sharma	OLA > RIS
Covenant (PCS)	RIS > HAL
	THOR, HAL, QUE, OLAZ, RIS > untreated
Covenant (GPRD)	OLA = untreated
	RIS > untreated
Koro	OLA > untreated
	OLA > CONV
Gianfrancesco (2003)	RIS, QUE = untreated
	OLA > untreated
Sernyak	RIS = CONV
	OLA, QUE > CONV

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Prolactin

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Prolactin elevation with dopamine D_2 antagonists

- Hyperprolactinemia is a well-recognized effect of all dopamine antagonists
- Class labeling for all antipsychotics, including olanzapine, quetiapine, and risperidone*
- Clinical significance of hyperprolactinemia is unknown for most patients
- As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration

Sources:
*Zyprexa [package insert]. Indianapolis, Ind: Eli Lilly and Company; 1999.
Seroquel [package insert]. Wilmington, Del: Astra-Zeneca Pharmaceuticals; 1997.

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Normalization of Prolactin Levels in Children After Long-term Treatment With Risperidone

R.L. Findling; V. Kusumakar; D. Daneman; C. Binder; G. De Smedt

Methods

- Study Design
  - Data from 5 trials were analyzed: two 6-week, double-blind, placebo-controlled trials; three 48-week, open-label, extension trials (2 of these were follow-ups on the double-blind trials)
- Patient Selection
  - Aged 5–15 years
  - IQ 36–84
  - DSM-IV Axis I diagnosis of CD, ODD, or DBD-NOS, with or without ADHD
  - Total rating ≥24 on the Conduct Problem subscale of the N-CBRF
  - Vineland Adaptive Behavior Scale score <85
- Treatment
  - Risperidone 0.02–0.06 mg/kg/day as an oral solution

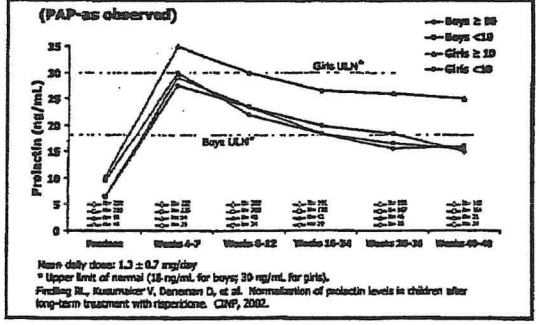
Findling RL, Kusumaker V, Daneman D, et al. Normalization of prolactin levels in children after long-term treatment with risperidone. CINP, 2002.

Subject Characteristics

Characteristic	Primary Analysis Population (PAP) N=592
Age, years • Mean ± SE • Median (range)	9.9 ± 2.5 9.9 (5.1 - 15)
Gender, n (%) • Male • Female	489 (82.6%) 103 (17.4%)
Race, n (%) • Black • White • Other	57 (9.6) 475 (80.2) 60 (10.2)
Weight, kg, mean ± SE	35.3 ± 13.4
Height, cm, mean ± SE	137.8 ± 15.9
IQ, mean ± SD	65.1 ± 13.3

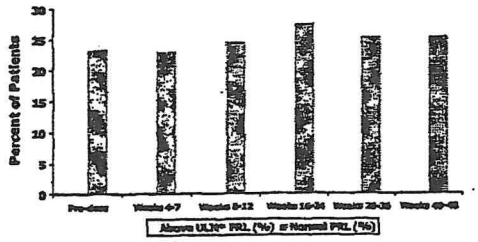
Findling RL, Kusumaker V, Daneman D, et al. Normalization of prolactin levels in children after long-term treatment with risperidone. CINP, 2002.

Mean Prolactin Observations by Gender and Age Group



Mean daily dose: 1.3 ± 0.7 mg/day
* Upper limit of normal (18 ng/mL for boys; 30 ng/mL for girls).
Findling RL, Kusumaker V, Daneman D, et al. Normalization of prolactin levels in children after long-term treatment with risperidone. CINP, 2002.

Percent of Patients with EPS by Prolactin (PRL) Levels



* Upper limit of normal (16 ng/mL for boys; 30 ng/mL for girls).

Findling RL, Kusumaker V, Demeraan D, et al. Normalization of prolactin levels in children after long-term treatment with risperidone. CINP, 2002.

Risk of EPS ↑ as dose ↑.

Clinical Outcomes Potentially Related to Prolactin

Prolactin-related adverse events reported in children/adolescents

Study	Risperidone	Placebo
Short-term		
- Aman	0	0
- Buitelaar	0	0
- Snyder	0	0
Long-term		
- Findling (2000)	0	open-label
- Turgay	0	open-label
- Findling (2001)	10 (mild-moderate gynecomastia) 1 (galactorrhea) 1 (amenorrhea)* 1 (menorrhagia)	open-label

* Amenorrhea resolved with treatment. All reported cases remitted spontaneously

Aman MG, et al. *Am J Psychiatry.* 2002;159:1337-1346.; Findling RL, Aman MG, De Smedt G et al. ACNP, 2000.; Turgay A, et al. *Pediatrics.* 110 (3) pp:e34.; Buitelaar JK, et al. J Clin Psychiatry 2001;62:239-248.; Snyder et al. (2002), *JAACAP, 41:5,* 1026-1036. ; Findling RL, Fegert JM, De Smedt G. ACNP, 2001.

Conclusion

- Mean serum prolactin levels began to decrease after 8 weeks of risperidone therapy, despite a modest, early increase, and were within normal limits although above baseline values at the end of 1 year of treatment
- There was no association between prolactin levels and side effects hypothetically attributable to prolactin

Findling RL, Kusumaker V, Demeraan D, et al. Normalization of prolactin levels in children after long-term treatment with risperidone. CINP, 2002.

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Sexual Maturation, Growth and Correlation with Prolactin

Growth and Sexual Maturation Analysis Populations

- Growth population:
  - Patients who had received treatment with risperidone for 12 months and had both baseline and 12-month height measurements
- Sexual maturation population
  - Girls ≥9 years and boys ≥10 years who had received treatment with risperidone for 12 months and had both baseline and 12-month Tanner staging

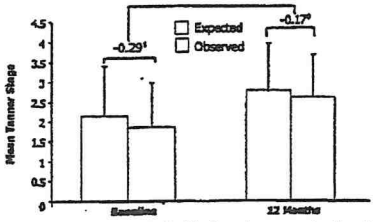
Dunbar K et al. Poster presented at the 49th Meeting of the American Academy of Child and Adolescent Psychiatry; 2002; San Francisco, CA.

Tanner Staging–Patient Demographics and Baseline Characteristics

Characteristic	Growth Population (n = 230)	Sexual Maturation Population (n = 222)
Age ± SD, years	10.2 ± 2.4	11.9 ± 1.4
Gender, M/F, %	84.0/16.0	79.7/20.3
Ethnic Origin, %		
Caucasian	87.1	88.3
Black	5.4	4.5
Hispanic	0.6	0.9
Oriental	0.3	0.0
Other	6.6	6.3
Mean IQ ratio ± SD	83.0 ± 12.9	81.0 ± 14.4
Mean height ± SD (cm)	139.4 ± 15.5	148.2 ± 12.4
Mean weight ± SD (kg)	35.3 ± 12.6	41.3 ± 12.5
Mean BMI ± SD (kg/m²)	17.6 ± 3.3	18.4 ± 3.5
Tanner Stage, %		
1	71.4	51.8
2	14.3	23.9
3	7.4	12.2
4	5.7	9.5
5	1.1	2.7

Observed vs. Expected Tanner Stage for Boys (≥10 years) and Girls (≥9 years)

Deviation from expected maturation at year 1 was 0.12 ± 0.77[1]; N=222



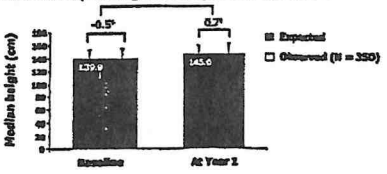
[1]Deviation from expected maturation at year 1 = Deviation from reference mean at predose – Deviation from reference mean at year 1. [2]Deviation from reference mean

Dunbar K et al. Poster presented at the 49th Meeting of the American Academy of Child and Adolescent Psychiatry; 2002; San Francisco, CA.

Observed vs. Population Median Height from Growth Chart

ITT Population; NHANES III National Health & Nutrition Examination Survey

Deviation from expected growth at year 1 was 1.2 ± 2.8[1]

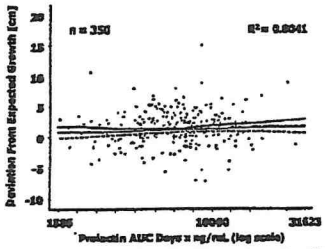


[1]Deviation from expected maturation at year 1 = Deviation from reference mean at predose – Deviation from reference mean at year 1. [2]Deviation from reference mean.
Reference population extracted from growth charts (NHANES III).

Dunbar K et al. Poster presented at the 49th Meeting of the American Academy of Child and Adolescent Psychiatry; 2002; San Francisco, CA.

Deviation from Expected Growth vs. Prolactin at Year 1

PRL AUC was used to reflect total risperidone duration over 1 year



Dunbar K et al. Poster presented at the 49th Meeting of the American Academy of Child and Adolescent Psychiatry; 2002; San Francisco, CA.

Prolactin and Development: Conclusions

- Prolactin levels rise predictably but decrease to near-normal limits across age
- Clinical symptoms potentially related to prolactin occur at low frequency and are not correlated with prolactin levels
- Growth and sexual maturation appear to progress normally at one year during risperidone treatment
- Temporary rise in prolactin not correlated with deviation from expected growth

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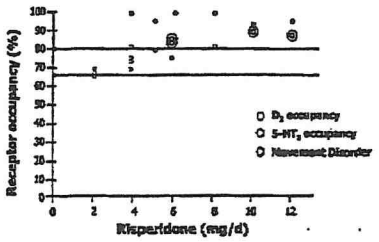
REGIONAL ADVISORS MEETING

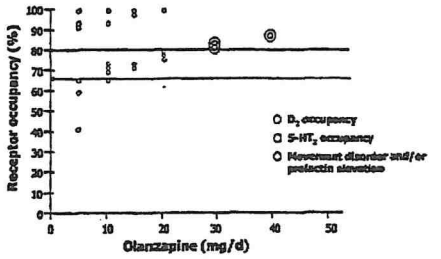
Movement Disorders

PET scan study: Risperidone 5-HT$_2$ and D$_2$ occupancy



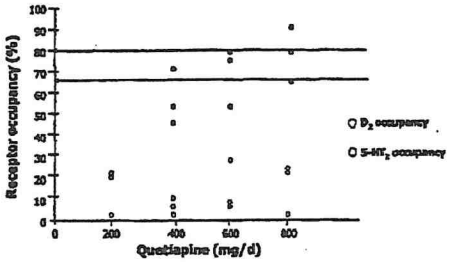
Kapur, et al. Am J Psychiatry 2000;157:514-20
Kapur, et al. Am J Psychiatry 1999;156:286-93

PET scan study: Olanzapine 5-HT_2 and D_2 occupancy



Kapur, et al. Am J Psychiatry 2000;157:514-20
Kapur, et al. Am J Psychiatry 1999;156:286-93

PET scan study: Quetiapine 5-HT_2 and D_2 occupancy



Kapur, et al. Am J Psychiatry 2000;157:514-20
Kapur, et al. Am J Psychiatry 1999;156:286-93

Risperidone Clinical Trials Incidence of Movement Disorders

Short- and long-term trials

Study	n	Risperidone	Placebo
Short-term			
Aman (2002)	118	2	0
Snyder (2002)	110	7 0 (TD)	3 1 (TD)
Long-term			
Findling (2000)	107	17 (16%)	Open-label
Findling (2001)	319	71 (22.3%) 2 ("TD-like" resolved after discontinuation)	Open-label
Turgay (2002)	77	20 (26%)	Open-label

Aman MG, et al. *Amer J Psychiatry*. 2002;159:1337-1346.
Snyder R, et al. *J Am Acad Child Psychiatry*. 2002;41:1076-1083.
Findling RL, et al. AOP. 2000.
Findling RL, et al. AOP. 2001.
Turgay A, et al. *Pediatrics*. 2002;110.

Measured changes in ESRS: 6 week trial in children

Mean Change at Endpoint	**1.0**	**1.3**	
Total ESRS	-0.6	0.0	0.36
Parkinsonism/dystonia	-0.5	-0.1	0.48
Bucco-linguo-masticatory	0.0	0.1	0.16
	1.16 mg/day		

Footnote: Lower scores imply improved conditions

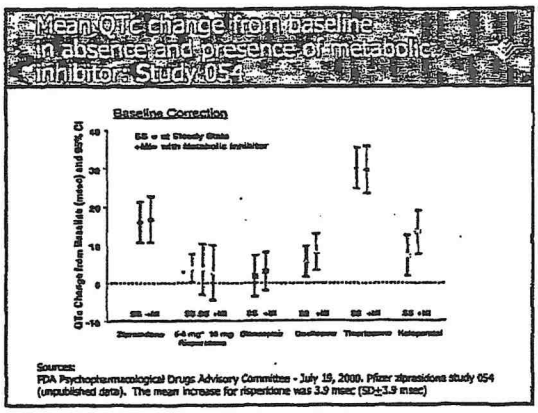
Aman MG, et al. *Amer J Psychiatry*. 2002;159:1337-1346.

CHILD & ADOLESCENT
PSYCHOPHARMACOLOGY DIRECTIONAL ADVISORS MEETING

Cardiovascular Safety

QTc interval

- Corrected QT interval
  - Adjusted for heart rate
    - ex: Bazett or baseline correction
- Normal values
  - Men: QTc < 420 msec
  - Women: QTc < 430 msec
- Consequence of prolonged QTc interval
  - Ventricular arrhythmias
    - e.g. Torsades de Pointes, ventricular fibrillation
  - Sudden cardiac death



Dose limiting issue in Autism: tiredness
liquid Risperdal given PRN works quickly
pharmacokinetics are such that you do fine giving 2x/day or even 1 x 1. day,

NO rel bet dosage + weight gain from data in meta-analysis

prolactin - issue of bone density

treatment of lab values when there are no clinical symptoms?

Further Readings

FURTHER READINGS

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Notes

Notes

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