Food and Drug Administration
Center for Drug Evaluation and Research

SUMMARY MINUTES OF THE CDER PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE AND THE FDA PEDIATRIC ADVISORY COMMITTEE

September 13-14, 2004

Members Present (Voting)
Wayne Goodman M.D. (Chair)
Jean Bronstein, R.N., M.S.
James McGough, M.D.
Lauren Marangell, M.D.
Delbert Robinson, M.D.
Bruce Pollock, M.D., Ph.D.
Barbara Wells, Pharm.D.
Daniel Pine, M.D.

FDA Participants
Robert Temple, M.D.
Russell Katz, M.D.
Thomas Laughren, M.D.
M. Dianne Murphy, M.D.
Anne Trontell, M.D., M.P.H.

Executive Secretary
Anuja M. Patel, M.P.H.

Consultants to the Psychopharmacologic Drugs Advisory Committee (Voting)
Matthew Rudorfer, M.D.
Irene Ortiz, M.D.
Tana Grady-Weliky, M.D.
Richard Malone, M.D.
Cynthia Pfeffer, M.D.
Gail Griffith, B.A., M.A. (Patient Representative)

Psychopharmacologic Drugs Advisory Committee Member (Non-voting)
Philip Wang, M.D., M.P.H., Dr. P.H.

Psychopharmacologic Drugs Advisory Committee Industry Representative (Non-voting)
Dilip Mehta, M.D., Ph.D.

Pediatric Advisory Committee Member (Voting)
Joan Chesney, M.D.
Robert Nelson, M.D., Ph.D.,
Thomas Newman, M.D., .M.P.H.,
Victor Santana, M.D.
Judith O'Fallon, Ph.D.
Michael Fant, M.D., Ph.D.
Deborah Dokken, M.P.A. (Patient-Family Representative)

Pediatric Advisory Committee Consultants (Voting)
Charles Irwin, Jr., M.D. (CDER SGE)
James Perrin, M.D. (CDER SGE),
Laurel Leslie, M.D., FAAP (CDER SGE)
Robert Gibbons, Ph.D. (CDER SGE)
Norman Fost, M.D., M.P.H. (CBER SGE)
Steven Ebert, Pharm.D. (Consumer Representative for AIDAC)

Pediatric Advisory Committee Member (Patient Health Organization Representative - Non-voting)
Richard Gorman, M.D., FAAP

Guest Pediatric Advisory Committee Industry Representative (Non-voting)
Samuel Maldonado, M.D., M.P.H. (AIDAC Industry Representative)

Guest Speakers (Non-voting)
Kelly Posner, Ph.D.
John March, M.D., M.P.H.

Guests (Non-voting)
Barbara Stanley, Ph.D.
Madelyn Gould, Ph.D., M.P.H.

These summary minutes for the September 13-14, 2004, meeting of the Psychopharmacologic Drugs Advisory Committee and the Pediatric Drugs Advisory Committee were approved on September 29, 2004.

I certify that I attended the September 13-14, 2004, meeting of the Psychopharmacologic Drugs Advisory Committee and the Pediatric Advisory Committee meeting and that these minutes accurately reflect what transpired.

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Anuja M. Patel, M.P.H.
Executive Secretary

Wayne K. Goodman, M.D.
Chair

Open Public Hearing Speakers:

- Kenneth Duckworth - National Alliance for the Mentally Ill
- Julie Totten - Families for Depression Awareness
- Ronnie Wilkins - American College of Neuropsychopharmacology
- Ann Blake Tracy & Marion Goff - International Coalition for Drug Awareness
- Andrew Chmilewsky
- Susan Furlough
- Lisa van Syckel
- Raul Lagurre
- Gloria Pope - Depression and Bipolar Support Alliance
- Andy Vickery
- Vera Sharav - Alliance for Human Research Protection
- Jennifer Tierney
- Alan Salerian
- Sara Bostock
- David Fassler - American Psychiatric Association
- Tom Woodward
- Sheila McDonald - The Child & Adolescent Bipolar Foundation
- John Walkup
- Mark Taylor & Donna Taylor
- Kim Witczak
- Karen Barth Menzies
- Lawrence Greenhill - American Academy of Child & Adolescent Psychiatry
- Lawrence Diller
- Reese Butler - Kristin Brooks Hope Center
- Suzanne Vogel-Scibilia
- Mary Ellen Winter
- Beverly Hatcher
- David Shaffer
- Mark Miller - International Coalition for Drug Awareness
- Donald Farber
- Allan Routhier
- Sharon McBride
- Peter Breggin
- Bruce Orr
- Jerry Reed - Suicide Prevention Action Network, USA
- Chris Coffin
- Alice Erber
- Leigh Webb
- Chester Witzcak
- Nancy Parker
- Richard Schneeberg
- David Risinger
- David Healy
- Cynthia Wainscott - National Mental Health Association
- Deborah Gruder
- Mary Guardino - Freedom from Fear
- Terri Williams
- Laurie Yorke

- Robert Fritz
- Stuart Varon
- Julie Zito
- Adelaide Robb
- Steve Rebarber
- Christopher Kratochvil
- Eric Swan
- Patty Weathers – Ablechild
- Celeste Steubing
- Robert Mann - American Foundation for Suicide Prevention
- Lawrence Brain
- Mark Shapiro
- Mathy Milling Downing
- Peter Kahn
- Eileen McGinn

FDA Presentations:

Overview of Issue	M. Dianne Murphy, M.D. Director, Office of Pediatric Therapeutics, Office of the Commissioner Russell Katz, M.D. Director, Division of Neuropharmacological Drug Products (DNDP), CDER, FDA
Regulatory History and Background	Thomas Laughren, M.D. Team Leader, DNDP, CDER, FDA
Recent Observational Studies of Antidepressants (ADs) and Suicidal Behavior	Diane Wysowski, Ph.D. Epidemiologist, Division of Drug Risk Evaluation, Office of Drug Safety (ODS), CDER, FDA
Brief Report on TADS Trial	John March, M.D., M.P.H. Duke University
Characteristics of Pediatric Antidepressant Trials	Greg Dubitsky, M.D. Medical Officer, DNDP, CDER, FDA
Classification of Suicidality Events	Kelly Posner, Ph.D. Columbia University
OCTAP Appraisal of Columbia Classification Methodology	Solomon Iyasu, M.D., M.P.H. Team Leader, Office of Counter-Terrorism and Pediatric Drug Development (OCTAP), CDER, FDA
Results of the Analysis of Suicidality in Pediatric Trials of Newer Antidepressants	Tarek Hammad, M.D., Ph.D., M.Sc., M.S. Senior Medical Reviewer, DNDP, CDER, FDA
Comparison between Original ODS and Current DNDP Analyses of Pediatric Suicidality Data Sets	Andrew Mosholder, M.D., M.P.H. Epidemiologist, Division of Drug Risk Evaluation, ODS, CDER, FDA

Sponsor Presentations:

Citalopram and Escitalopram Pediatric Safety Data	Forest Laboratories Incorporated
Sertraline Use in Pediatric Population: A Risk Benefit Discussion	Pfizer Incorporated
Antidepressant Use in Pediatrics	Wyeth Pharmaceuticals

Questions to the Committee:

1. **Please comment on our approach to classification of the possible cases of suicidality (suicidal thinking and/or behaviors) and our analyses of the resulting data from the 23+1 pediatric trials involving 9 antidepressant drugs.**

Given the caveat that the data set was inherently limited (e.g., not intended to evaluate suicide as an endpoint, non-uniform ascertainment of suicide information, relatively small number of events, etc.) the reclassification enhanced the confidence the committee had in the data compared to last February. The overall consensus of the committee was that the classification of the cases of suicidality (suicidal thinking and/or behaviors) was reliable and valid. The use of independent suicide experts, training and blinding of source materials made it a rigorous process. Excellent inter-rater reliability was demonstrated through agreement in classification between the Columbia and FDA teams in a sub-sample of the cases. The Committee was impressed by the quantity and quality of the work the Agency accomplished in a short time in analyzing the re-classified data.

The committee advised the agency to address the issues of violent behavior and aggression in future data collection. The committee further suggested that the agency investigate whether suicidality outcome was related to lack of response, other somatic adverse events, or dose changes. The committee urged use of reliable and valid measures of suicidality and possible antecedent behavioral toxicity in prospective fashion in future clinical trials.

Please see transcript for details.

2. **Do the suicidality data from these trials support the conclusion that any or all of these drugs increase the risk of suicidality in pediatric patients?**

Prior to voting, the Committee engaged in discussion regarding this question. The Committee felt that there was a lack of clarity in the word “suicidality” therefore they redefined “suicidality” as the “suicidal ideation, attempts and preparatory actions” as indicated in Outcome 3. Additionally, the Committee clarified that the “trials” in this question refer to the 23+1 pediatric trials as stated in question 1 where the “+1” corresponds to the TADS trial.

Since there were no completed suicides in any of the 23+1 trials, the answer is limited to the data presented from these trials.

Yes= 25 No= 1 Abstain= 1

Please see transcript for details.

3. **If the answer to the previous question is yes, to which of these 9 drugs does this increased risk of suicidality apply?**
   - **Please discuss, for example, whether the increased risk applies to all antidepressants, only certain classes of antidepressants, or only certain antidepressants.**

The Committee revised the question above into a statement to read:
"The data in aggregate indicate an increased risk of suicidality, as previously defined, in pediatric patients. Although there is variability in the results, we are unable to conclude that any single antidepressant agent is free of risk at this time. Do you agree?"

The Committee was unanimously in agreement with the statement above.

Yes= 27 No= 0 Abstain= 0

Please see transcript for details.

4. **If there is a class suicidality risk that is limited to certain drugs in this class, how should this information be reflected in the labeling of each of the products?**
   - **What, if any, additional regulatory actions should the Agency take?**

The Committee revised the question above to state:
"Does the Committee support a "black box" warning for all antidepressants for pediatric use?"

Yes= 15 No= 8 Abstain= 0

There were a total of 23 votes. Four voting members were absent at the time of the vote. A consensus was reached by the committee that a med-guide for patients was needed and any warning should be extended to all antidepressants for all pediatric uses not just depression. The committee members expressed the need for additional warnings as congruent with their vote on question #3 but there were various opinions on what form this warning should assume. Those voting against a "black box" warning felt that this option might be too alarming and that bold lettering or similar means would be a more measured response to communicate the possible risk. An advantage cited for the "black box" is that it might deter marketing through direct to consumer ads.

Please see transcript for details.

5. **Please discuss what additional research is needed to further delineate the risks and benefits of these drugs in pediatric patients with psychiatric illness.**

The Committee made several suggestions to the Agency including more efficacy data and more safety data focusing on suicidality. The committee encouraged future long-term trials including placebo and fluoxetine as controls. The Committee advised the Agency to include additional information on the prior history of patients (e.g. personal and family history of bipolar disorder). The committee strongly felt a need to ensure that prescribers know how to use antidepressant drugs safely and effectively with greater attention to medication induced side effects (e.g. possible signs of behavioral toxicity as reflected by an activation syndrome), risk factors (e.g. history of bipolar disorder, co morbid anxiety disorder, etc.), age-appropriate dosing, possible pharmacokinetic factors, and need for close monitoring. The Committee advised the Agency that children with major depressive mood disorder (MDD) be further studied by the National Institutes of Health; such research should aim at better understanding the natural history and longitudinal course of the disorder, and the risks of no treatment as well as those associated with pharmacological and non-pharmacological interventions.

Please see transcript for details.

Following the discussion session, the meeting adjourned at approximately 5:00 PM.