Food and Drug Administration
Center for Drug Evaluation and Research

SUMMARY MINUTES OF THE PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE MEETING AND THE PEDIATRIC SUBCOMMITTEE OF THE ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

February 2, 2004

Members Present (Voting)
Matthew Rudorfer, M.D. (Chair)
Tana Grady-Weliky, M.D.
Irene Ortiz, M.D.
Richard Malone, M.D.
Andrew Leon, Ph.D.
Philip Wang, M.D., M.P.H., Dr. PH
Wayne Goodman, M.D.
James McGough, M.D.
Jean Bronstein, R.N., M.S. (Consumer Representative)

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

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

Consultants to the Psychopharmocologic Drugs Advisory Committee (Voting)
Gail Griffith, B.A., M.A. (Patient Representative)
Cynthia Pfeffer, M.D.

Psychopharmacologic Drugs Advisory Committee Consultant (non-voting):
Daniel Pine, M.D.
David Shaffer, M.D.

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

Pediatric Subcommittee Consultant Members of the Anti-Infective Advisory Committee (voting):
Joan Chesney, M.D.
Robert Nelson, M.D. Ph.D.
Victor Santana, M.D.
David Danford, M.D.
Robert Fink, M.D.
Mark Hudak, M.D.
Susan Fuchs, M.D.
Richard Gorman, M.D., FAAP
Norman Fost, M.D., M.P.H. (CBER Consultant)

AIDAC Members of the Pediatric Subcommittee of the Anti-Infective Advisory Committee (voting):
Mary Glode, M.D.
Judith O'Fallon, Ph.D.
Steven Ebert, Pharm.D. (Consumer Representative)

Pediatric Subcommittee of the Anti-Infective Advisory Committee Consultants (voting):
Charles Irwin, Jr., M.D.
James Perrin, M.D.
Laurel Leslie, M.D., FAAP
Elizabeth Andrews, Ph.D.

Pediatric Subcommittee of the Anti-Infective Advisory Committee Acting Industry Representative (non-voting):
Samuel Maldonado, M.D., M.P.H.

Cardio-Renal AC Members Absent:
None

Guest Speaker (non-voting):
Kelly Posner, Ph.D

These summary minutes for the February 2, 2004, meeting of the Psychopharmacologic Drugs Advisory Committee and the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee were approved on March 4, 2004.

I certify that I attended the February 2, 2004, meeting of the Psychopharmacologic Drugs Advisory Committee and the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee meeting and that these minutes accurately reflect what transpired.

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

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Matthew Rudorfer, M.D.
Chair

On February 2, 2004, the Psychopharmacologic Drugs Advisory Committee and the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee met in open session at the Holiday Inn, at

8120 Wisconsin Avenue, in Bethesda, Maryland. The Committees discussed reports of the occurrence of suicidality (both suicidal ideation and suicide attempts) in clinical trials for various anti-depressant drugs in pediatric patients with major depressive disorder (MDD). The Committees also considered optimal approach to the analysis of data from these trials, as well as further research needs to address these issues.

Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA and written statements submitted by the public. The meeting was called to order by Matthew Rudorfer, M.D. (Committee Chair); the Conflict of Interest Statement was read into the record by Anuja M. Patel, M.P.H. (Executive Secretary). There were approximately 450 persons in attendance. There were approximately 54 speakers for the Open Public Hearing session.

Open Public Hearing Speakers:

- David Antonuccio, Ph.D. and Irving Kirsch, Ph.D.
- Lisa VanSyckel
- Anne Blake Tracy, Ph.D.
- Mark Miller
- Jay and Corey Baadsgaard
- Joyce Storey
- Jennifer and Jame Tierney
- Donna Taylor
- Shannon Baker
- Dawn Rider and Vincent Boehm , A.S.P.I.R.E
- Sara Bostock
- Vera Sharav, The Alliance for Human Research Protection
- Cynthia Brockman
- Rosie Meysenburg
- Rachel Adler and Sheila McDonald, Child and Adolescent Bipolar Foundation
- Andy Vickery
- Pepper Draper
- Donald Marks, M.D., Ph.D.
- Leah Harris M.A.
- Donald Farber, Esq., Law Office of Donald J. Farber
- Lorraine, Robert, and Jonathan Slater
- Paul Domb and Matthew Piepenburg
- Terri Williams
- Glenn McIntoch
- Delnora Duprey
- Tod and Eileen Shivak
- Suzanne Vogel-Scibilia, M.D., The National Alliance of the Mentally Ill
- Dennis Winter
- Steve Cole
- Allan Routhier
- Daniel Safer, M.D.
- Julie Magno Zito, Ph.D., UMD School of Pharmacy
- Joseph Glenmullen, M.D.
- Linda Cheslek
- Jeff Avery
- Harry Skigis
- Sharon McBride
- David Fassler, M.D. American Psychiatric Association
- Lawrence Diller, M.D.
- Thomas Moore, M.D.
- Pamela Wild
- Karen Menzies
- Amy Coburn
- Gary Cheslek, M.D.

- Joe Pittman
- Richard Mack
- Gloria and Noah Wright
- Marion Goff
- Sherri Walton, Mental Health Association of Arizona
- Peter Breggin, M.D.
- Robert Fritz
- Lawrence Greenhill, M.D., American Academy of Child & Adolescent Psychiatry
- Tom Woodward

FDA Presentations:

Overview of Issues	Russell Katz, M.D. Director, Division of Neuropharmacological Drug Products, FDA
Pediatric Drug Development	Dianne Murphy, M.D. Director, Office of Counter-Terrorism and Drug Development, FDA
Pediatric Depression and Its Treatment	Cynthia Pfeffer, M.D. Weill Medical College of Cornell University
Suicide and Related Problems in Adolescents	David Shaffer, F.R.C.P. (Lond), F.R.C. Psych Columbia University
Pediatric and adolescent Antidepressant Drug Use in the U.S.	Gianna C. Rigoni, Pharm.D., M.S. Epidemiologist, Office of Drug Safety, FDA
One Year Post-Exclusivity Mandated Adverse Event Review for Paroxetine and Citalopram	Solomon Iyasu, M.D., M.P.H Lead Medical Officer, Division of Pediatrics Drug Development, FDA
Office of Drug Safety Data Resources for the Study of Suicidal Events	Andrew Mosholder, M.D., M.P.H. Epidemiologist, Office of Drug Safety, FDA
Regulatory History on Antidepressants and Suicidality and Update on Current Plans for Analysis of Pediatric Suicidality Data	Thomas Laughren, M.D. Team Leader, Division of Neuropharmacological Drug Products, FDA
Suicidality Classification Project	Kelly Posner, Ph.D. Columbia University
Plans for Analysis of Patient Level Data for Pediatric Studies	Tarek Hammad, M.D., Ph.D., M.Sc., M.S. Safety Reviewer, Division of Neuropharmacological Drug Products, FDA

Questions to the Committee:

Topics Directly Pertinent to Continuing Evaluation of Data from Pediatric Controlled Trials:

1. Possible Failure to Fully Capture All Events of Potential Interest with Regard to Suicidality

The first step in the process of evaluation for suicidality was to find events of potential interest. GSK (Glaxo Smith Kline) had developed an algorithm for searching for events possibly representing suicidality in their database, and FDA proposed a variation of this to other sponsors. However, this was admittedly a compromise. It is conceivable that certain cases of interest might have been missed by the search methods employed. The only fail safe approach to identifying all possible events of interest would be to have experts blindly evaluate every case report form for the more than 4000 patients who participated in these trials. Since that is not feasible, FDA welcomes advice from the committee on possible modifications to the search strategies used for identifying cases that might have been missed. Additional searches at this point would further delay the analyses of these data, and this needs to be taken into consideration. However, if the committees feel there are serious deficiencies in the search methods employed, it would be helpful to hear about alternative approaches.

The overall consensus of the Committees was that the FDA should proceed with the planned re-analysis of the data once a team of mental health experts at Columbia University and elsewhere have reclassified the cases. The re-analysis, however, may not yield accurate results. The Committees' concern in this respect reflected impressions that the data had been collected during the medication trials in a fashion that would not easily allow the generation of an accurate estimate of adverse behavioral reactions associated with suicidal behavior or ideation. Despite these concerns, the statisticians on the Committees felt that the methodological concepts learned from the re-analyses will be valuable. The Committees encouraged the Agency to go back and examine data on adverse effects in individual study participants for signs of what has been labeled the "stimulation" or "activation" syndrome. These terms have been used to refer to a constellation of behaviors, including agitation, restlessness, hyperactivity, and disinhibition. In severe cases, probably representing a very small percentage of treated patients, the clinical picture may resemble frank akathisia, accompanied by considerable subjective distress. Treatment-emergent mood lability, irritability, or hostility should also be noted. The Committees encouraged study of these and related phenomena. In particular, the Committees inquired about whether the presence of these behaviors may be associated with drug levels or with suicidal ideation, suicidal behavior, or impulsive acts, and the response of such behaviors to drug discontinuation or dosage change (either decrease or increase). Although not necessarily available in the planned data re-analysis, the Committees recommended the use of clearer inclusion/exclusion criteria, the collection of additional data including drug concentrations for pharmacokinetic analysis, and more established endpoints in future antidepressant clinical trials in children and adolescents. With respect to study entry criteria and endpoints, the Committees encouraged an evaluation of study quality. This could be accomplished partially by examining the degree to which cross-site reliability was established in each individual study for the rating of criteria and endpoints. In addition, the Committee felt that off-label prescription including dispensing of antidepressant medication samples, by non-psychiatrists is problematic. Therefore, improved labeling information, highlighting potential side effects of greatest concern, was suggested by the Committee.

In conceptualizing future plans for re-analysis of data on adverse behavioral reactions, some discussion focused on defining the boundaries of events that should be considered indicative of suicidal behavior. Committee members recognized the need to define these boundaries more precisely than in the reviewed studies and offered some guidelines. In particular, some Committee members recommended that

"cutting" should not be considered a symptom of suicidal behavior.

The Chair summarized the consensus of the committee stating that although individual members had reservations about the limitations of the existing database, the Committee endorses the continuation of the re-classification of data with some additional measures as mentioned above. The Committee advised the FDA to attempt to recreate the process of identifying cases of suicide-related events and look for multiple different types of definitions that may be subsumed under "stimulation (or activation) syndrome." This would necessarily require keeping definition(s) as broad as possible.

2. Approaches to Classifying Events into Meaningful Categories for the Purpose of Further Analysis

As noted, an important next step is to decide on categories into which events of interest might be classified, along with operational definitions for such classifications. The approach used by sponsors thus far has been to classify cases first into a crude category of "possibly suicide-related," and then a further sub-grouping of that broader group into a "suicide attempt" class. Since we are just now beginning to address this question with our outside experts, we would welcome any advice the committees might have on how to classify these events for the purpose of further analysis.

The consensus of the Committees was that a level of certainty and variability in analysis be included in the reclassification of data. The Committees were concerned that the general quality of the data, as they were originally collected, was relatively low. This complicates any effort of reclassification. Efforts at re-creating the methodology used at various sites of the different trials are important for understanding the specific information that was actually gathered in each data set. The Committees encouraged the identification of treatment-emergent agitation and related behaviors as potentially relevant mediators of self-harm ideation or actions.

3. Patient Level Data Analysis

Since we are in the preliminary stages of designing an appropriate analysis of patient level data, this would be an opportune time to get feedback on how to approach this analysis. In addition, you have seen our list of potential covariates for inclusion in this analysis, and we would welcome any thoughts you might have on this list. If we have left out important covariates, please let us know, since this would be the time to try to gather any additional information that you feel might be helpful in trying to understand these data.

As noted, the Committees did have suggestions for additional covariates that might be collected from these databases to assist in designing an appropriate analysis plan. Individual committee members provided multiple suggestions to approaches to identifying covariates, and mentioned the potential value of evaluating observed events in relation to time of dosing or other intervention changes. Committee members expressed an interest in seeing data from various patient-level variables. These included a broader array of adverse effect variables, related to the broader "stimulation/activation" syndrome described above, as well as potential patient-level data that may have moderated therapeutic or adverse effects delineated in the available studies. Committee members inquired specifically about data on co-morbid psychopathology, such as anxiety or disruptive behavior disorders, adverse environmental events, and family history or other variables that may relate to the risk for bipolar disorder. In sum, the Committee felt that extending the analysis of patient level data beyond the focus specifically on suicidality related or mediating variables would be of value. These would include family history of mood and other mental disorders, pretreatment pre-morbid conditions such as hypomanic/manic symptoms or akathisia, careful delineation of the diagnosis where possible, e.g. unipolar vs. bipolar depression vs. schizophrenia

spectrum, comorbidities (other mental and physical disorders, substance use), administration of other medications. As noted, particular attention to the presence of signs and symptoms of treatment-emergent agitation and activation is recommended, to include time to development and severity of such behaviors both pre- and post- treatment in both patients on medication and control group members.

Topics of Future Interest

4. Ascertainment for Suicidality

As we reviewed the descriptive information for the events identified by sponsors as possibly suggestive of suicidality, it became apparent that ascertainment for emergence of suicidality was not optimal. The case descriptions were frequently sparse and lacking the kind of detail that would ordinarily be useful in assessing whether or not the events might legitimately be considered to represent suicidality. Of course, these studies were not designed with that goal in mind. Indeed, patients who were judged to be suicidal at screening were excluded. Nor did we emphasize such assessment for suicidality in our Written Requests for these pediatric programs. Furthermore, there is, of course, no fix for this problem with regard to these studies. However, one of our outside experts will address the issue of how one might develop guidance for more adequate assessment for emergent suicidality in future studies. We would welcome any advice from the committees on the development of such guidance.

The Committee's consensus was that the review of the available data pointed to the pressing need for more research on this topic in new samples of children and adolescents studied in randomized controlled trials. In such future studies, the Committee noted the importance of including children on various other medications while gathering high-quality data on adverse events. The Committee also recognized the importance of including placebos in such trials, in order to sort out the disease from the treatment and to evaluate the data accurately. Particular focus on behavioral toxicity early in treatment, including various forms of dysphoric activation, as noted above, is recommended for more definitive assessment in future clinical trials to try to capture instances of treatment-emergent difficulties that might precede or occur in association with frank suicidality. Pressing methodological issues for future clinical trials include the desirability of standardizing assessment instruments to capture suicidality or antecedent adverse effects of interest and permit better analysis across sites and across trials. Such measures should include self-assessment instruments for use by patients and their parents/guardians.

5. Future Approaches to Trying to Address the Question of What Benefits These Drugs Might Have in Pediatric MDD

Due to time constraints the Committee did not discuss this item completely. The Committee was mixed on the idea of drug-discontinuation designs. Some Committee members clearly recognized the potential superior statistical power in this design, given results from studies using this design in adults. Other Committee members noted that this design does not address key questions concerning the safety and efficacy of delivering antidepressants as opposed to other treatments for a child or adolescent presenting for the first time with symptoms of an untreated major depressive disorder. To the extent that this question remains central, it may be important to utilize various research designs beyond a randomized withdrawal design.

In answering these questions please keep in mind that the FDA does not regulate the practice of medicine, but is responsible for providing information on the safety and efficacy of the products it regulates. As a reminder, the FDA issued a Public Health Advisory on October 27, 2003, which stated:

"FDA emphasizes that these drugs must be used with caution. Prescribers are reminded of the following statement present in all antidepressant labeling:

Suicide: The possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Drug X should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose".

The Committee discussed the need to consider revising this statement, in light of recent data. As noted, there was a consensus of the Committee that labeling include a more prominent warning of the risk of behavioral toxicity, particularly dysphoric agitation/activation, early in the course of antidepressant treatment. It was also noted that the last statement in the existing warning cited above, emphasizing the risk of medication overdose, is a legacy of the tricyclic antidepressant era, and is no longer appropriate, as drug overdose per se as a means of suicide is not a concern with the SSRIs and other newer antidepressants. Similarly, a bolded warning in all current Selective Serotonin Reuptake Inhibitor (SSRI) labeling regarding the necessity to avoid a potentially fatal drug-drug interaction with monoamine oxidase (MAO) inhibitor antidepressants, while true, may well not reflect current medical practice, which entails only rare use of MAO inhibitors. Consideration to replacement of these outdated warnings with labeling more representative of modern medical practice and concern is recommended.

6. **A public meeting is planned in late summer to discuss the results of further analyses of the controlled trials. Until that time, should the FDA provide additional advice to practicing physicians regarding the use of these drugs?**

- **If your answer is yes, please provide specific information on what that advice should be.**

The Committee advised the FDA to issue a warning in the interim to the physicians and the public on the potential side effects of the SSRIs and other newer antidepressants. The Committee advised the FDA to inform the public and health care workers including pediatricians and family practitioners of the level of concern regarding possible harm to a minority of children on antidepressants and the signs associated with the side effects. Specifically, the Committee felt that the necessity of close follow-up, with monitoring for emergent adverse effects, during the first weeks of treatment of children and adolescents with antidepressants should be stated explicitly. Parents or other responsible adults should be informed of the signs and symptoms of the "activation syndrome" and of the urgency of having the child seen by physician should such behaviors emerge, especially early in the treatment course.

The Committee advised the FDA to inform the public and health care workers, including pediatricians and family practitioners, that the data on the efficacy of SSRIs for pediatric major depression is less compelling than Committee members had recognized prior to recent events discussed by the Committee. The Committee is concerned that health care workers are unaware of the fact that the strong majority of randomized controlled trials of SSRIs do not demonstrate superiority over placebo in the treatment of major depression in children and adolescents. The Committee felt that it was important for the FDA to communicate this fact as it bears on the risk-benefit ratio for the use of SSRIs in pediatric major depression.

7. **Should FDA involve other professional organizations in the community? If so, how should FDA involve these organizations? What messages should these organizations provide?**

   The Committee felt that the Agency should involve all health care organizations whose membership includes physicians and other medical personnel who might prescribe or be asked questions about antidepressant use in children and adolescents. Such health care professionals would include

pediatricians, child and adult psychiatrists and psychologists, internists, family practitioners, emergency room, intensive care, and rehabilitation physicians, nurse practitioners, pharmacists, and physicians' assistants. Other professionals who work with young people, including teachers and social workers, should also be included. Examples of such professional organizations cited by Committee members include medical organizations such as the American Academy of Pediatrics (AAP) and the American Association of Family Practitioners (AAFP), and similar organizations representing the other health care professions. Professional publications, e.g. Pediatric News, while heightening awareness of the prevalence of depression and risk of suicide, may play a role in informing health care workers and family members of the relative benefits and risks, including possible side effects, of antidepressant drugs.

These organizations and the Agency should provide information to health care providers through a variety of sources, including newsletters and the Internet, as well as face-to-face meetings and panel discussions.

In addition, the organizations should also inform and educate parents so that when they make collaborative decisions with their child's physician they are fully informed and understand completely the serious potential risks of the drug. The adults responsible for the young person being treated with antidepressants should be aware of the small but real risk of an "activation syndrome" developing in their children and informed of the need to be vigilant about this concern and to immediately contact the prescribing health care professional should any behavioral toxicity emerge during treatment.

Following the discussion session, the meeting adjourned at approximately 6:15 PM.