RISPERDAL® CHILD AND ADOLESCENT PSYCHIATRY NATIONAL ADVISORY BOARD MEETING

MEETING REPORT

Prepared for Janssen Pharmaceutica Products, L.P.

Meeting Date: November 15, 2002
Location: The Palace Hotel, New York City
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Risperdal® Child and Adolescent Psychiatry National Advisory Board Meeting
November 15, 2002 ♦ New York, NY

EXECUTIVE SUMMARY

Attendees

Attendees included key opinion leaders in child and adolescent psychiatry (see **List of Advisors**) and Janssen Pharmaceutica personnel (see **Janssen Attendees**).

Meeting Objectives

- Solicit feedback on:
  - the re-analyses of the effects of risperidone on weight-gain, prolactin, and growth and development (Tanner stage) data from the disruptive behaviors disorders (DBD) dataset
  - additional re-analyses of the DBD dataset assessing the effect of risperidone on affective symptoms
  - the re-analysis of risperidone in the treatment of children with autistic disorder and other pervasive developmental disorders (PDD)
- Determine the optimal approach to crafting messages and disseminating the data

Subanalysis of Weight Gain

- Data from the disruptive behavior disorder studies were reanalyzed in an attempt to answer the following questions: how much weight is gained? who gains the most weight? what factors affect weight gain? Weight gain data were presented by age, gender, baseline weight, risperidone dose and treatment duration, country, clinical factors, and comorbidity with ADHD and use of PSTIMs
- Key discussion points and conclusions:
  - weight gain associated with risperidone treatment was approximately 10% greater than what would normally be expected (based on CDC growth charts)
  - weight gain associated with risperidone treatment appears to plateau at 6 months
  - children who are already heavy appear to be at the greatest risk of weight gain
  - few patients increase more than 1 percentile category in weight
- Next steps include a further analysis of:
  - the apparent 6-month plateau in weight gain using random, mixed-model, and logistic regression
  - the correlation between absolute risperidone dose and absolute weight gain
  - outliers (those with excessive weight gain and those who lost weight)
  - the shift in percentile weight in patients on PSTIMs versus those not on PSTIMs
  - the relationship between weight gain and improvement in symptoms

Subanalysis of Prolactin

- The following data were presented: change in prolactin (PRL) levels over time and the relationship between PRL and age and gender; comparison of the results in children with prolactin levels below versus above 50 ng/mL; data on the relationship between PRL and side effects hypothetically attributable to prolactin (SHAP), motor effects, clinical response, comorbid ADHD and PSTIM
- Key discussion points and conclusions:
  - there appears to be no relationship between PRL and SHAP, Tanner stage, or motor effects
  - PRL levels appear to peak at 4 to 7 weeks and decline steadily thereafter to within ULN
  - the available data suggest that routine monitoring of PRL levels is not necessary
  - clinicians should be informed that endocrine symptoms may occur as part of normal development
- Next steps include the following:
  - redefine SHAP to be as inclusive as possible; include all boys with gynecomastia
  - examine the correlation between investigator-rated EPS and ESRS score; further clarify the relationship between peak PRL level and onset of motor effects and SHAP
  - contact the editor of the target journal and ask to have an expert write a commentary discussing the importance of PRL and putting the data into a clinical context
  - publish a review article based on the PRL information presented by Dr Reyes-Harde at the June advisory board meeting

Long-term Risperidone Treatment and Growth and Development

- The results of the Tanner stage analysis and data on the relationship between prolactin and Tanner were presented

- Key discussion points and conclusions:
  - there is no effect of risperidone treatment on sexual maturity and development
- Next steps include a further analysis of:
  - the relationship between change in Tanner stage and change in weight, PRL, ADHD, and IQ

Efficacy and Safety of Risperidone in the Treatment of Children With Autistic Disorder and Other Pervasive Developmental Disorders (PDD)

- Results of a study assessing the safety and efficacy of risperidone oral solution in the treatment of behavioral symptoms in children with PDD, including autism, were presented. Assessments included change from baseline (risperidone versus placebo) in ABC subscale, NCBRF, and CGI-C scores
- Key discussion points and conclusions:
  - risperidone oral solution is efficacious and well tolerated in this patient population

Risperidone and Affective Symptoms in Children With Disruptive Behavior Disorders

- Results of a subanalysis of RIS-93 on the effects of risperidone on affective symptoms were presented. Items from the NCBRF were selected and categorized as "mania" and "depression" factors.
- Key discussion points and conclusions:
  - selected mania and depression factors do not measure true bipolar disorder (BPD) but reflect symptom profiles that are typical of BPD
- Next steps include the following:
  - examine each item that was not included in the analysis to see if they have any effect
  - re-label the candidate factors as "possible mood-spectrum symptoms"

Risperdal® Child and Adolescent Psychiatry National Advisory Board Meeting November 15, 2002 ♦ New York, NY

MEETING SUMMARY

Overview

On November 15, 2002, Janssen Pharmaceutica hosted a national advisory board meeting for child and adolescent psychiatrists. The meeting was held at The Palace Hotel, New York, NY. The primary objectives of the meeting were as follows:

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- Solicit feedback on the re-analyses of the effects of risperidone on weight-gain, prolactin, and growth and development (Tanner stage) data from the disruptive behaviors disorders (DBD) dataset
- Determine the optimal approach to crafting messages and disseminating the data
- Solicit feedback on additional re-analyses of the DBD dataset assessing the effect of risperidone on affective symptoms
- Solicit feedback on re-analysis of risperidone in the treatment of children with autistic disorder and other pervasive developmental disorders (PDD)

Overall Impressions

The meeting was very well received. The discussions were focused on interpretation of the re-analyses data from the risperidone in DBD dataset and recommendations for further analyses.

The weight data elicited a substantial amount of discussion. Clearly, this is an area that the advisors recognize as important and one that requires attention. They did not appear overly concerned about weight gain in general but were more interested in identifying those patients who were at greatest risk of gaining weight. They appeared to gain a level of comfort with the weight-gain issue, particularly since it appears to plateau eventually and is not what they would consider morbid. Identifying if and when weight gain plateaus was a major discussion point. The advisors suggested several re-analyses, the most important of which were a mixed-model regression analysis, a random-regression analysis, and an analysis of absolute weight gain versus absolute risperidone dose. The advisors commented that in some patients (eg, those on PSTIMs) weight gain may actually be desirable. There were no specific comments or recommendations regarding publication of these data, but the advisors agreed that the data are important for physicians.

In general, the advisors viewed the prolactin data very favorably, particularly since no other company has data on prolactin in such a large population and over such a long period. One key message that emerged is that there is no need to routinely monitor prolactin level. They agreed that these data are important for clinicians, but noted the difficulty of communicating the data effectively. The discussion focused on SHAP and motor effects. The advisors mentioned that the data are too complicated for the field. They emphasized that the data must be presented within a clinical context for them to be meaningful to physicians and suggested publishing them along with an editorial or commentary by a recognized expert (eg, Dr Rapoport). They also suggested publishing a review article outlining the difficulties in measuring and interpreting prolactin data; the article can be based on Dr Reyes-Harde's presentation at the June advisory board meeting.

There was minimal discussion and few recommendations from the advisors on Carin Binder's and Dr Mick's presentations; although both of these presentations were well received.

The advisors thanked Janssen for sharing the data with them in such an open forum and allowing them to have a candid discussion about the results. They also thanked Janssen for their efforts in following

through on their previous recommendations for re-analyses and for inviting them to participate in the advisory board.

Next steps include:

- Review the advisors' recommendations for further analyses
  - Determine which of the analyses are possible
  - Prioritize the recommendations for re-analyses
- Publish the prolactin data
- Decide how to disseminate the weight-gain data

AGENDA

8:00 – 8:15 AM	Welcome and Introductions *Joseph Lin*
8:15 – 8:20 AM	Overview of Today's Presentations *Gahan Pandina, PhD*
8:20 – 9:15 AM	Subgroup Analysis: Weight Gain I *Michael Aman, PhD*
9:15 – 9:30 AM	BREAK
9:30 – 10:15 AM	Subgroup Analysis: Weight Gain II *Michael Aman, PhD*
10:15 – 11:00 AM	Subgroup Analysis: Prolactin I *Carin Binder, MBA*
11:00 – 11:15 AM	BREAK
11:15 – 12:15 PM	Subgroup Analysis: Prolactin II *Gahan Pandina, PhD*
12:15 – 1:15 PM	LUNCH
1:15 – 2:00 PM	Subgroup Analysis: Growth and Development *Gahan Pandina, PhD*
2:00 – 2:30 PM	Subgroup Analysis: Affective Symptoms *Eric Mick, ScD*
2:30 – 3:00 PM	Risperidone in Pervasive Developmental Disorders *Carin Binder, MBA*
3:00 – 3:15 PM	Break
3:15 – 4:00 PM	Discussion/Future Directions *Group*
4:00 PM	ADJOURN

Welcome and Introductions
Joseph Lin

Joseph Lin opened the meeting by welcoming the advisors. He then introduced Dr Gahan Pandina who briefly reviewed the meeting objectives and the re-analyses that were requested at the June 2002 advisory board meeting.

Subanalysis of Weight Gain
Michael Aman, MD

Dr Aman's presentation focused on the results of recent analyses of the effect of risperidone on weight, including how much weight is gained, who gains the most weight, and what factors affect weight gain. He presented data on weight gain by age, gender, baseline weight, risperidone dose and treatment duration, country, clinical factors, and comorbidity with ADHD and use of PSTIMs.

There was a substantial amount of discussion concerning the time course and extent of weight gain and identifying those children who are at the highest risk of accelerated weight gain (ie, weight gain above what would be expected based on CDC growth curves). As stated by several advisors, knowing which patients are likely to gain weight and how much weight they are likely to gain would afford physicians a measure of comfort in 1) deciding whether to continue therapy, and 2) counseling patients and their parents/guardians about weight gain. There was some concern about using percent change from baseline instead of absolute weight gain. For the analyses on change in weight percentile, weight was divided into the following percentile categories:

- <5th percentile
- 5th to 25th percentile
- 25th to 50th percentile
- 50th to 75th percentile
- 75th to 95th percentile
- >95th percentile

The advisors summarized the weight-gain data as follows:

- How much weight is gained?
  - There is a persistent pattern suggesting that weight gain is twice the normal value based on CDC growth charts
  - Children on risperidone should expect to gain, on average, an additional 10% (absolute) over expected weight gain
  - Few patients increase more than 1 percentile category in weight
- When does weight gain occur?
  - Most weight gain appears to occur during the first 6 months of therapy, beyond which weight gain plateaus; this apparent plateau needs to be examined in greater detail
- Who is at risk for weight gain?
  - Children who are already heavy appear to be at the greatest risk of weight gain
  - Social factors and family history of obesity probably account for some of the variability in weight gain, but these data are not in the current database

The data on risperidone dose was discussed briefly. The primary concern of the advisors was that weight-adjusted dose was used as opposed to absolute dose; using weight-adjusted dose confounds the statistical model because weight is included in both variables. The advisors summarized the weight-gain data as follows:

- Although there appears to be no relationship between risperidone dose and weight gain, no definitive statements regarding risperidone dose and weight gain can be made
- These data are nonetheless re-assuring for physicians, particularly when treating heavier children

The weight by country data was viewed cautiously, mainly because there were too few patients to draw firm conclusions. The advisors also commented that there is likely to be considerable cultural and ethnic influences that were not controlled for in the statistical model. Few firm conclusions could be drawn from these data other than that increased weight gain is not a US-only phenomenon.

Dr Aman then presented data on the relationship between weight gain, use of psychostimulants (PSTIMs), and clinical symptoms. He pointed out that, although there is no age-group by hyperkinesis interaction, when hyperkinesis is included in the statistical model, there is a main effect of age; this raises the possibility of a "suppressor effect", ie, when the variance attributable to some given factor is removed from the model, the contribution of another factor may become evident. The advisors summarized these data as follows:

- Hyperactive patients who were already stabilized on PSTIMs when they entered the study gained as much weight as hyperactive patients who were not on PSTIMs

Key Messages/Communications Points

- The data suggests that the weight gain associated with risperidone treatment was approximately 10% greater than what would normally be expected (based on CDC growth charts)
- The weight gain associated with risperidone treatment appears to plateau at 6 months
- Children who are already heavy appear to be at the greatest risk of weight gain
- Few patients increase more than 1 percentile category in weight

Subgroup Analysis: Prolactin

Carin Binder and Dr Gahan Pandina

The next 2 presentations focused mainly on the prolactin data. Carin Binder 's presentation focused on data addressing the change in prolactin levels over time, the relationship between prolactin and risperidone dose, age, and gender, and comparisons between children with prolactin levels below versus above 50 ng/mL.

The data suggest that prolactin level peaks at Week 4 to 7 irrespective of gender or age. On average, prolactin levels increase to above ULN at that time point, then gradually decrease to levels below ULN (ULN was defined as 18 ng/mL in boys and 30 ng/mL in girls). Although mean prolactin level continued to decrease over the course of the study, it is uncertain whether they will return to baseline values. There was some discussion about what the upper limit of normal is for adolescent females. Dr Pandina mentioned that there are some data that suggest prolactin level normally increases during development in girls.

Several advisors asked about outliers, specifically individual patients with elevated prolactin that is prolonged or sustained.

- Only 19 patients had 2 consecutive values ≥50 ng/mL at any time point; of those, only 4 had an endpoint value ≥50 ng/mL
- Only 10 patients had prolactin levels ≥50 ng/mL at endpoint

The main points of the discussion were as follows:

- There appears to be no correlation between risperidone dose and prolactin level at any time point, including at 4 to 7 weeks (when mean prolactin level peaks) and at 40 to 48 weeks (the longest time point evaluated); risperidone dose accounts for less than 1% of variance in prolactin level
- Mean prolactin level in boys appears to remain above ULN longer than in girls; ie, it takes longer for mean prolactin level to return to normal in boys compared with girls; but there are too few girls in the analysis to draw any meaningful conclusions

- Although it is generally agreed that prolactin levels increase in girls as they enter puberty, there are no good data on normal prolactin levels during development

Dr Pandina then presented data on the relationship between prolactin and side effects hypothetically attributable to prolactin (SHAP), motor effects, clinical response, and comorbid ADHD and PSTIM. There was a substantial amount of discussion on these issues. Most of the discussion focused on SHAP and motor effects. It was clear that the advisors were less concerned about elevated prolactin levels *per se* as opposed to side effects that may be related to elevated prolactin. There was some discussion about the definition of SHAP. The advisors thought that the most inclusive definition of SHAP should be used for transparency. The presentation and ensuing discussion can be summarized as follows:

- There appears to be no relationship between prolactin level and SHAP
- Dr Pandina mentioned that there was no correlation between prolactin level and SHAP in risperidone studies in adults and that little is known about the bioactivity of different monomers of prolactin
- The incidence of SHAP in normally developing children is higher than widely recognized
- When communicating these data to physicians, it should be made clear that transiently elevated prolactin *per se*, is not an adverse drug reaction, and that few patients in the DBD database had sustained elevations in prolactin level; in this respect, the prolactin data should be presented within a clinical context

There was a lengthy discussion about motor effects, focusing on how motor effects were defined and how they were assessed. Dr Pandina pointed out that motor effects (TD in particular) were based on the clinician's impression, not a structured assessment. Therefore, the apparent incidence of motor effects was higher than expected. For example, an advisor mentioned that in one case, a child who was restless and had difficulty settling down before going to bed was coded as having hyperkinesia. In addition, it is very likely that neither of the 2 children with TD actually had TD.

As to why prolactin may be related to motor effects, Judy Rapoport mentioned that prolactin level may be considered a surrogate marker for dopamine receptor occupancy. Therefore, one might expect the incidence of motor effects to coincide with peak prolactin level. No such relationship was apparent in the data. In fact, the incidence of motor effects at baseline (ie, before patients received risperidone and when prolactin levels were lowest) was similar to that at all subsequent time points. In addition, there was no significant difference between the incidence of motor effects in patients with normal versus above ULN prolactin levels. The advisors asked about the correlation between investigator-rated "EPS" and scores on standardized motor-dysfunction scales.

Dr Pandina then presented the data on NCBRF responders (defined as ≥25%, ≥35%, and ≥50% response). The results can be summarized as follows:

- Other than at the 16 to 24 week time point (for response ≥25% or ≥35%), there were no significant differences in percentage of responders in children with normal prolactin levels versus those with prolactin levels above ULN
- There were no appreciable differences in prolactin level between responders and nonresponders
- There appeared to be no relationship between prolactin level and score on the conduct problem subscale

There followed a lengthy discussion about the clinical importance of prolactin. The discussion can be summarized as follows:

- Transiently elevated prolactin, in itself, is not cause for concern
- There is no reason to monitor prolactin levels unless there are specific symptoms that the clinician feels may be related to elevated prolactin
- Routine monitoring of prolactin levels in children treated with risperidone is not necessary
- Clinicians may consider measuring prolactin if endocrine side effects emerge, Advisors indicated that reasons for prolactin increases in adolescents are varied, and only in the case of extreme concern should physicians monitor prolactin. Due to the transient increase and return to below ULN, advisors indicate that timing of measurement would be difficult to predict.

A number of general clinical questions were asked regarding the importance of monitoring and interpreting prolactin levels. These are summarized as follows:

- How should physicians interpret elevated prolactin levels, particularly in the absence of symptoms?
- For what endocrine symptoms potentially related to risperidone should physicians be alert?

Key Messages/Communications Points

- The data suggests that there appears to be no relationship between prolactin level and SHAP or Tanner stage
- There appears to be no relationship between prolactin level and motor effects
- Prolactin levels appear to peak at 4 to 7 weeks and decline steadily thereafter to within ULN
- The available data suggest that routine monitoring of prolactin levels in children treated with risperidone is not necessary.
- Clinicians should be informed that endocrine symptoms may occur as part of normal development and, therefore, are not necessarily caused by treatment-related transient elevations in prolactin level

LONG-TERM RISPERIDONE TREATMENT AND GROWTH AND DEVELOPMENT

Dr Gahan Pandina

Dr Gahan Pandina presented the results of the Tanner stage analysis. Some prolactin data (eg, data on the relationship between prolactin and Tanner) were included in this presentation. The results were discussed at length, followed by a brief discussion on the overall analysis of the DBD database. Most of the discussion focused on the prolactin data.

Dr Pandina reviewed the Tanner scale for boys and girls and commented on the difficulty of determining Tanner stage in children with disruptive behavior disorders. He then defined the analyses populations:

- The growth population was defined as patients who received a treatment with risperidone for 12 months and had both a baseline and 12-month height measurements
- The sexual maturation population was defined as girls ≥9 years and boys ≥10 years old who had received treatment for 12 months and had both a baseline and 12 month Tanner staging

An advisor commented on the low IQ for a randomly selected DBD population and mentioned that IQ is important particularly in children with moderate mental retardation because pubertal development is different in these children. Dr Pandina noted that patients who changed one or more Tanner stage gained more weight above their expected weight than those who did not change Tanner stage.

Overall, the data suggest that transiently elevated prolactin levels have no adverse effect on growth and development. In addition, there appears to be no relationship between prolactin level and deviation from expected growth. An advisor mentioned that the prolactin data on olanzapine are similar with respect to time course. Questions were raised with respect to training of the investigators in assessing Tanner stage. The advisors commented that it is difficult for non-specialists to determine the Tanner stage of an individual, particularly when distinguishing between stage 1 and 2.

The risk/benefit ratio of risperidone was discussed at length and the following conclusions were made:

- Risperidone has a very favorable risk-benefit ratio; this may or may not be a class effect.
- The issue of benefit should be addressed over the short-term; the issue of risk needs to be addressed in the long-term

Key Messages/Communications Points

- The data suggests that there is no effect of risperidone treatment on sexual maturity and development

EFFICACY AND SAFETY OF RISPERIDONE IN THE TREATMENT OF CHILDREN WITH AUTISTIC DISORDER AND OTHER PERVASIVE DEVELOPMENTAL DISORDERS

Carin Binder

Carin Binder presented the results of a study of risperidone in the treatment of children with autistic disorder and PDD. The objective of the study was to assess the safety and efficacy of risperidone oral solution in the treatment of behavioral symptoms in children with pervasive developmental disorders, including autism. Carin Binder reviewed the study design and major inclusion/exclusion criteria. The mean dose was 0.04 milligrams per kilogram, and at the end of the study physicians had the option to split the dose; to give it either in the evening or in the morning.

Primary efficacy measures included:

- Change from baseline in aberrant behavior checklist (ABC) irritability subscale score (scored by the parent or caregiver under the supervision of the investigator)

Secondary efficacy measures included:

- Change from baseline in 4 ABC subscales: hyperactivity/non-compliance; lethargy/social withdrawal; stereotypic behavior; inappropriate speech
- Number of responders (responders were defined as patients who achieved a ≥50% decrease in two ABC subscales with no worsening (≥10%) in other subscales)
- Change from baseline in 6 Nisonger Child Behavior Rating Form subscales (NCBRF; parent version):
  - Conduct problem; hyperactive; self-isolated/ritualistic; insecure/anxious; overly sensitive; and self-injury/stereotypic
- Change from baseline in visual analogue scale (VAS) rating for the most troublesome symptom
- Change from baseline in Clinical Global Impression - Change (CGI-C) score

The results of the study are summarized as follows:

- There was a significantly greater reduction in irritability subscale score in the risperidone group (-62%) compared with the placebo group (-32%)
- There were significantly greater reductions in score for each ABC subscale with risperidone compared with placebo
- The response rate in the risperidone and placebo groups was 71.8% and 44.7%, respectively
- There was a significantly greater reduction in the conduct problem score for risperidone compared with placebo and greater decreases in other subscales for risperidone compared with placebo
- There were significantly greater reductions in VAS ratings with risperidone compared with placebo
- Significantly more patients were rated as 'much' or 'very much' improved in CGI-C with risperidone compared with placebo
- EPS was reported as adverse events in 10 (25%) subjects in the risperidone group and 4 (10.3%) subjects in the placebo group
- There was no significant difference from baseline to any study time point in mean total ESRS score between the two treatment groups

Ms Binder concluded from these results that risperidone oral solution is efficacious and well tolerated in this patient population. The presentation was well received by the advisors. There were no suggestions for re-analyses or further study.

Risperidone and Affective Symptoms in Children With Disruptive Behavior Disorders

Dr Eric Mick

The final presentation of the day was given by Dr Eric Mick. Dr Mick presented the analysis of the effect of risperidone on affective symptoms in children with DBD using the USA-RIS-93 data. He began by showing background data indicating that there is considerable comorbidity between conduct disorder and pediatric bipolar disorder; approximately 40% of children with conduct disorder will have BPD and approximately 40% of children with BPD will have conduct disorder. Dr Mick discussed the candidate symptoms for depression and mania from the NCBRF that were chosen for analysis.

- Depression factors included:
  1. Overly sensitive, easily hurt; feelings easily hurt; sulky, is silent and moody
  2. Feeling worthless or inferior; saying no one likes them
  3. Apathetic or unmotivated; underactive, slow; unhappy or sad, withdrawn, uninvolved with others
  4. Cling to adults, too dependent; crying with tearful episodes; having difficulty concentrating
- Mania factors included:
  1. Explosive, easily angered; irritable; physically attacking people; exhibiting sudden changes in mood; having temper tantrums
  2. Overactive, doesn't sit still; restless, high energy
  3. Exaggerated ability or achievements; skips from topic to topic when talking; talking too loud or too much
  4. Being cheerful or happy; overly excited, exuberant

The results are summarized as follows:

- There was a greater decrease from baseline in NCBRF scores for candidate symptom clusters for depression and mania in children receiving risperidone versus those receiving placebo
- When the factors above were studied separately, the reduction in score for each of these factors, with the exception of factor 4 mania, was greater in the risperidone group versus the placebo group; this difference was statistically significant in all factors but factor number 3 depression (see above)
- The results of the analysis of the mania factors were more robust than the depression factors

Dr Mick emphasized that these factors are not measuring true BPD but they do reflect symptom profiles that are typical of BPD. Dr Gahan pointed out that these patients were selected for their disruptive behavior symptoms, not their BPD symptoms. An advisor commented that the term "mania" was misleading because the factors actually reflect aggression, impulsive behavior, and hyperactivity.

Dr Mick concluded that:

- The results are consistent with reports that affective symptoms are common in children with DBD
- Risperidone reduced the severity of affective symptoms, as well as behavioral symptoms, in children with DBD
- This analysis supports further study of risperidone in patients with both affective and disruptive behavioral symptoms, including long-term response to treatment

Dr Mick ended his presentation by discussing future studies, including validation using more data (CAN-19), and long-term studies including a meta-analyses of USA-97, CAN-20, and INT-41.

The discussion focused on whether the factors that were identified can be extrapolated to different pediatric conditions.

- Dr Pandina commented that one of the objectives of this study was to examine the changes in these affective symptoms in patients who were not selected for their affective symptoms. He also commented on the overlap between mania factors and aggression.

- An advisor asked if there were any results using the Child Behavior Checklist (CBCL) for comparison with the results on the NCBRF, but noted that the CBCL has not been used to assess the effects of therapy.
- Dr Rapoport commented that if it can be shown that "aggression" functions similarly across different conditions (similar to fever or pain), the FDA may be more predisposed to granting an indication for "aggression" as opposed to granting an indication for the specific psychiatric disorder

MEETING ADJOURNMENT

Dr Gahan closed the meeting by asking the advisors for their closing thoughts (action items are included in the appropriate sections above). He then thanked the advisors for their feedback and mentioned that the results of the re-analyses suggested at this advisory board meeting will be presented at the next advisory board meeting.

Action Items Based on the Outcome of This Meeting

Weight gain

Time course and degree of weight-gain

1. Examine the apparent plateau in weight gain at 6 months as follows:
   - A random-regression (or growth curve) analysis rather than an ANCOVA because it would have more power to tease out individual factors associated with weight gain. Several advisors suggested a mixed-model regression analysis of weight gain in each quartile. Divide the population by quartile (4 curves) and plot every data point by age versus absolute weight change superimposed on CDC growth curve. These data can also be further broken out by sex, although there may not be enough girls for an analysis
   - A logistic regression analysis on those patients whose weight increases 1 or 2 percentiles to identify predictive factors, ie, what factors increase the probability of shifting 1 or more percentiles
   - A subanalysis of patients at weeks 22 to 30, breaking them into 2 groups: those who continued to gain weight at later time points and those whose weight stabilized
   - In scatter-plots, examine the slope of weight gain at different time points by age
   - Use LOCF, excluding the 38 to 43 week time point and adjusting the last value for expected weight gain based on CDC growth curves
2. Examine the correlation between absolute risperidone dose (as opposed to weight-adjusted dose) and weight gain; using weight-adjusted dose confounds analysis
3. The advisors suggested more analyses on the effects of risperidone on BMI because BMI takes into account both weight and height
4. Additional analyses on height to better identify patients with excessive weight gain above what would be expected based on their height-predicted weight
5. Examine the records of individuals who decreased weight to identify potential predictive factors

Outliers analyses

6. Examine patients whose weight shifted into the upper percentile or who shifted more than one percentile category
7. Determine how much weight was gained by the 17 patients who discontinued because of weight gain
8. Determine the percentage of patients with "malignant" weight gain. The advisors suggested asking pediatricians what they would consider malignant weight gain

Weight gain, psychostimulants, and clinical symptoms

9. An analysis of shift in percentile weight in patients on PSTIMs versus those not on PSTIMs to answer the question of whether patients on PSTIMs overcompensate; ie, gain more weight proportionally than patients not on PSTIMs
10. Examine the relationship between weight gain and improvement in symptoms; identify where on the weight-gain trajectory clinical response occurs
11. Additional information on use of PSTIMs:
    - What were the doses of PSTIMs used?
    - Which PSTIMs were used?
    - Were there cultural effects in PSTIM use?

Other recommendations

12. Determine the percentage of the patient population who had been receiving previous therapy with psychotropic medication. The advisors suggested asking individual investigators, particularly those at the better-organized sites, to review their records for previous use of antipsychotics
13. Provide risperidone dose information by country
14. If possible, examine the relationship between socioeconomic status of patients and weight gain
15. Do a subgroup analysis of the relationship between weight gain and ethnicity

Prolactin levels

Side-effects hypothetically attributable to prolactin (SHAP)

1. Reanalyze the data on SHAP to include all boys with gynecomastia, not just those under the age of 10
2. Examine the incidence of gynecomastia by Tanner stage
3. The definition of SHAP should be as inclusive as possible; then compared with the incidence of SHAP with the more inclusive definition to that with the more narrow definition
4. When publishing the prolactin results, data on all children with gynecomastia should be included
5. The incidence of SHAP in patients with normal versus >ULN prolactin levels should be compared using nonparametric statistics
6. Examine the relationship between onset of SHAP and peak prolactin level

Motor effects

7. The dataset should be reviewed to examine the correlation between investigator-rated EPS and ESRS score
8. Further clarify the relationship between onset of motor effects and peak prolactin level
9. The incidence of motor effects in patients with normal versus >ULN prolactin levels should be compared using nonparametric statistics

Recommendations regarding publication of the data

10. One of the main messages in publishing this data should be that there is no need to routinely monitor prolactin level
11. Dr Riddle suggested contacting the editor of the target journal and asking to have an expert write a commentary discussing the issue of prolactin and putting the data into a clinical context
12. Publish a review article on the prolactin information presented by Dr Reyes-Harde at the June advisory board meeting

Other recommendations

13. Provide data on the individual variation in prolactin
    - Plot prolactin levels over time in a few representative individuals: eg, a patient with normal prolactin levels over the course of the study; a patient who had a prolactin value above ULN; an outlier with respect to weight gain, etc
14. Compare the prolactin results in the DBD database with the results from the adult database
15. As a purely academic interest, examine the correlation between clinical response and prolactin level from baseline to peak prolactin within individuals, ie, use prolactin level as a surrogate marker for D_2 receptor occupancy

Growth and Development (Tanner Stage)

1. Divide the group into patients who had no change in Tanner stage, those who changed 1 stage, and those who changed 2 or more stages and plot them against weight gain to determine if there is a relationship between change in Tanner and change in weight
2. Examine the relationship between growth/Tanner stage and 1) ADHD versus non-ADHD patients and 2) higher versus lower IQ patients
3. Add IQ to the regression model
4. Examine change in Tanner stage by prolactin level

Affective Symptoms

1. To control for the rater effect, examine each item that was not included in the analysis to see if they have any effect
2. Re-label the factors "possible mood-spectrum symptoms" instead of depression and mania

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