M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PID# D040495

DATE: August 16, 2004

From: Paul Seligman, M.D., M.P.H.
Acting Director, Office of Drug Safety, HFD-400
(hard copy signed 8-16-04)

Anne Trontell, M.D., M.P.H., Deputy Director
Office of Drug Safety, HFD-400
(hard copy signed 8-16-04)

TO: Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: Office of Drug Safety Cover Memorandum
Follow-up Consult of August 16, 2004 by Andrew Mosholder on Suicidality in pediatric clinical trials with paroxetine and other antidepressant drugs:

Drugs: paroxetine, sertraline, venlafaxine, fluoxetine, fluvoxamine, citalopram, nefazodone, mirtazapine, and bupropion

The results of Dr. Mosholder's analyses (dated February 18, 2004) are very similar to those obtained using other statistical methods and a reclassification of suicidality events by Columbia University. Remaining questions to be addressed are whether the overall finding of increased risk applies to all or selected drug products among the nine products studied, and what additional regulatory actions are merited. On those topics, we reference the Office of Drug Safety memorandum written by Anne Trontell and dated March 15, 2004.

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PID# D040495

DATE: August 16, 2004

FROM: Andrew D. Mosholder, M.D., M.P.H., Epidemiologist
Division of Drug Risk Evaluation, HFD-430

THROUGH: Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation, HFD-430
(hard copy signed 8-16-04)

TO: Paul J. Seligman, M.D., M.P.H., Acting Director
Office of Drug Safety, HFD-400

Anne Trontell, M.D., M.P.H., Deputy Director
Office of Drug Safety, HFD-400

SUBJECT: Suicidality in pediatric clinical trials of antidepressant drugs: Comparison between previous analyses and Colombia University classification

Drugs: paroxetine, sertraline, venlafaxine, fluoxetine, fluvoxamine, citalopram, nefazodone, and mirtazapine

BACKGROUND

Please refer to the 3-19-04 consult[1] regarding suicidal adverse events in pediatric clinical trials of antidepressant drugs. That consult described a meta-analysis by the undersigned of suicidal adverse events in short-term placebo-controlled pediatric clinical trials, showing a statistically significant association of suicidal adverse events with antidepressant drug treatment. However, because of concerns regarding misclassification of cases, FDA expanded the case finding algorithm, and arranged to have expert consultants jury the cases prior to any definitive analyses. Please refer to the materials from the February 2, 2004 Advisory Committee Meeting on this topic for additional details.

The aforementioned case reclassification has recently been completed by an expert panel convened by Columbia University. Dr. Tarek Hammad of FDA's Division of Neuropharmacological Drug Products (DNDP) has performed a new meta-analysis, based on the reclassification that was performed by Columbia University, which I will refer to herein as the DNDP analysis. I was asked to examine the impact of the Columbia University reclassification of cases on my analysis performed prior to the Columbia University reclassification, as described in

[1] PID# D030341

the 3-19-04 consult, which I will refer to in this memorandum as the ODS analysis. I have also compared my results, that were obtained using different analytic methods, with those of Dr. Hammad. For these purposes, Dr. Hammad has kindly provided me with his results, which are included below.

METHODS

A full description of the methodology is beyond the scope of this memorandum, so the interested reader should refer to the reviews by Dr. Hammad and myself for details on the analytic methods and clinical trial data. It should be noted that the two analyses used different case ascertainment strategies and different case criteria; the ODS analysis used only cases identified by the sponsors through an electronic search of their adverse event databases, while the DNDP analysis supplemented this approach with additional search methods. Some salient differences between the two analyses are the following: (1) the ODS analysis did not employ a correction for zero cells, whereas the DNDP analysis does; (2) the ODS analysis used rate ratios, with person-time for denominators, while the DNDP analysis uses risk ratios, with numbers of patients for denominators; (3) the ODS analysis included events occurring up to 30 days after discontinuation of treatment, while the DNDP analysis uses a 1-day post-treatment window; and (4) the ODS analysis included taper phase events, which are excluded from the DNDP analysis.

This memorandum will present the following three modes of comparing the DNDP and ODS analyses.

Comparison of risk ratios obtained with ODS and DNDP statistical methods

In order to determine how the two different statistical methods affect the values for the relative risks, we compare the relative risks obtained with identical patient populations and classifications of cases. For this purpose, all possibly suicide-related events were included regardless of whether they were serious or not; this outcome variable was common to both sets of data, thereby allowing a comparison. While this outcome may be accorded relatively little inferential value because of the concerns about case misclassification, it does permit a direct comparison between results from the two statistical methods.

Comparison of case classifications

In order to assess the degree of agreement or lack thereof between the Columbia University and ODS case classifications, the "primary" outcome for the respective analyses must be defined. For the DNDP analysis, this is "Outcome 3," definitive suicidal behavior/ideation, a composite of Columbia University codes 1 (suicide attempt), 2 (preparatory actions towards imminent suicidal behavior), and 6 (suicidal ideation). In contrast, for the ODS analysis, performed using the classification prior to the Columbia University reclassification, the primary outcome was serious suicide-related events, comprising events selected as possibly suicide-related by each sponsor under the search strategy requested by FDA in July 2003, and also designated as serious adverse events by the sponsors under the standard regulatory criteria for "serious." By focusing on these primary outcomes, a comparison of the impact of the two systems of case classification is presented.

Comparison of risk estimates obtained with the two analyses

Finally, the risk estimates obtained from the two analyses are directly compared.

RESULTS

Comparison of statistical methods

Table 1 below displays the relative risks obtained by the two analytic methods when identical patient populations and classification of cases are used in the respective analyses.

Table 1: Comparison of results from two methods for sponsor's classification of suicide related events

Category of trials	All sponsor-defined suicide-related events	
	ODS analysis: Combined incidence rate ratios*	DNDP analysis: Risk ratios*
Paroxetine	2.69 (1.20-6.00)	2.47 (1.16-5.27)
Sertraline	2.03 (0.51-8.16)	1.72 (0.50-5.89)
Venlafaxine	3.33 (1.08-10.33)	3.03 (1.04-8.80)
Fluoxetine	0.88 (0.34-2.30)	0.98 (0.38-2.50)
Citalopram	1.41 (0.66-3.00)	1.49 (0.72-3.06)
Mirtazapine	0.53 (0.007-41.45)	0.52 (0.003-8.27)
Nefazodone	†	2.17 (0.23-20.08)
Fluvoxamine	†	3.31 (0.14-79.67)
MDD trials	1.81 (1.19-2.77)	Not done
SSRI** MDD trials	1.58 (0.99-2.52)	1.62 (1.03-2.54)
Non-MDD trials	2.36 (0.67-8.33)	1.93 (0.68-5.45)
All trials	1.86 (1.25-2.78)	1.81 (1.24-2.64)

†Ratio undefined due to zero events in placebo group
*Mantel-Haenszel method, fixed effects model
**includes paroxetine, sertraline, fluoxetine, citalopram, fluvoxamine

There is generally good agreement between the two methods, suggesting that the findings are not sensitive to changes in statistical computing methodology.

Comparison of case classifications

The ODS analysis included a total of 78 serious, suicide-related events, as defined above. Of these 78 cases, 61 (78.2%) were classified by the Columbia University group as Outcome 3 (definitive suicidal behavior). Of the remaining 17 cases, an additional 13 (16.7%) were classified as self-injurious behavior with unknown intent (Code 3), and the remaining 4 cases were classified in other outcomes.

Conversely, the Columbia University group identified a total of 95 cases as definitive suicidal behavior (Outcome 3). Of these 95 cases, 61 (64.2%) were serious, suicide-related events in the ODS analysis; sixteen (16.8%) of the 95 cases were sponsor-defined suicide-related but nonserious events, and thus were excluded from the ODS primary analysis; and 18 cases were new, i.e., were identified through the expanded search for cases that was not part of the ODS analysis.

On a net basis, the DNDP analyses considered 17 more cases than the ODS analysis.

Comparison of risk estimates

Table 2 below compares the risk estimates derived from the two analyses, using the above-mentioned case definitions.

Table 2: Comparison of Columbia University Outcome 3 with Serious suicide-related events

Category of Trials	Total N Drug	Total N Pbo	Incidence rate ratios, serious suicide-related events (ODS analysis)*	Risk ratios, Columbia University Outcome 3, (DNDP analysis)*
Paroxetine	**642**	**549**	**2.19 (0.92-5.24)**	**2.65 (1.00-7.02)**
Sertraline	**281**	**279**	**2.52 (0.49-13.01)**	**1.48 (0.42-5.24)**
Venlafaxine	**339**	**342**	**1.80 (0.52-6.20)**	**4.97 (1.09-22.72)**
Fluoxetine	**249**	**209**	**0.88 (0.32-2.44)**	**0.92 (0.39-2.19)**
Citalopram	**210**	**197**	**2.54 (0.91-7.05)**	**1.37 (0.53-3.50)**
Mirtazapine	**170**	**88**	**†**	**1.58 (0.06-38.37)**
Nefazodone	**279**	**189**	**†**	******
Fluvoxamine	**57**	**63**	**†**	**5.52 (0.27-112.55)**
Bupropion	**71**	**36**	******	******
All MDD trials	**1586**	**1299**	**1.95 (1.19-3.21)**	**1.71 (1.05-2.77)**
SSRI†† MDD trials	**955**	**843**	**1.87 (1.10-3.18)**	**1.41 (0.84-2.37)**
Non-MDD trials	**712**	**653**	**1.31 (0.26-6.72)**	**2.17 (0.72-6.48)**
All trials	**2298**	**1952**	**1.89 (1.18-3.04)**	**1.78 (1.14-2.77)**

*Mantel-Haenszel method, fixed effects model
**No events in either arm
†Ratio undefined due to zero events in placebo group
††includes paroxetine, sertraline, fluoxetine, citalopram, fluvoxamine

The overall risk estimate for the primary outcome for the "all trials" analysis decreased with the Columbia University reclassification analysis from 1.89 to 1.78; the confidence intervals for both risk estimates exclude one. For the category of SSRI MDD trials, the risk estimate decreased and lost statistical significance with the Columbia University reclassification analysis. In terms of results for individual drugs, the risk estimates for paroxetine and venlafaxine increased.

CONCLUSIONS

Consistent with the analysis described in the 3-19-04 consult, the DNDP meta-analysis also indicates a statistically significant association of suicidal events with antidepressant drug treatment in short-term pediatric clinical trials for all indications. In terms of subgroups of trials, the major differences were that the risk estimate for the category of SSRI MDD trials was lower and not statistically significant with the DNDP analysis, while the risk estimates for two drugs (paroxetine and venlafaxine) increased. In all three cases, however, the new point estimate falls within the confidence limits of the previous result.

RECOMMENDATIONS

With respect to what further analyses might be undertaken with the Columbia University dataset, I propose an analysis that examines events occurring after treatment discontinuation, since there appears to be a signal for at least paroxetine in this regard (please refer to the previous consults by the undersigned for details).

Beyond what else may be done with the current dataset, I also propose an analysis with psychiatric inpatient hospitalization as the outcome. While not specific for suicidal behavior, this

might give insight into more general behavioral toxicities, and would have the advantage of being easily determined from the existing case reports. In addition, I agree with the plans to analyze the new data from the NIMH Treatment of Adolescent Depression Study (TADS), which will provide additional data for fluoxetine. With respect to possible regulatory actions, please refer to my recommendations in the 3-19-04 consult; the results from the DNDP meta-analysis using the Columbia University reclassification do not materially affect the recommendations I made previously.

(hard copy signed 8-16-04)
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