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

PID# D030341

DATE: March 15, 2004

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

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

SUBJECT: Office of Drug Safety Cover Memorandum
Follow-up Consult to 9-4-03 consult 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

Dr. Mosholder has concluded from his composite analysis of preliminary data from the randomized clinical trials (RCTs) of selective serotonin reuptake inhibitors (SSRIs) in pediatric psychiatric conditions, that short-term use of these drugs is associated with a statistically and clinically significant elevation in the risk of self-injurious events over placebo. He found the short-term excess risk of SSRIs relative to placebo to be statistically significant in trials of major depressive disorder (MDD), but not in those for nonMDD indications. Based on these findings and the limited number of SSRI trials showing efficacy in pediatric MDD, Dr. Mosholder advocates discouraging antidepressant drugs outside their labeled efficacy indications. Specifically, he notes that only fluoxetine has demonstrated efficacy in pediatric MDD, and that the point estimate of its relative risk for suicide-related events of 0.88 (95% CI 0.34-2.30) "appears most favorable."

Dr. Mosholder's conclusions are based upon thoughtful consideration of what are, at this point, preliminary data. Systematic data collection and coding have not been assured, and unblinded analyses by Dr. Mosholder were not possible. Dr. Mosholder notes these deficiencies, but expresses his belief that only systematic bias could explain away his findings, and so "interim risk management" around labeled efficacy should be done pending definitive analyses.

As Dr. Mosholder's supervisors, Dr. Avigan and I disagree with his proposed interim risk management which implies making treatment recommendations about off-label use for SSRIs in pediatric psychiatric illness. In particular, we disagree that the data are sufficiently robust to advocate preferential use of fluoxetine in pediatric MDD. We note that the point estimate suggesting a modest protective effect in serious suicide-related events was not statistically significant, and that the 95% confidence interval could not rule out a doubling of the risk. We share Dr. Mosholder's concern about the potential excess risk of self-injurious behavior in pediatric patients treated with SSRIs, and agree that these potential concerns should be transmitted widely to physicians, patients, and parents when these drugs are used. Such information-sharing should reinforce prudent use and close patient follow-up in initiating therapy with SSRIs, particularly among patients being treated for MDD. We support additional adjudicated analyses being done by Columbia University, and once they are complete, recommend their comparison to Dr.

Mosholder's preliminary findings with due consideration and appropriate sensitivity analyses around indeterminate cases of self-injury.

Like Dr. Avigan, I believe the current safety data from pediatric SSRI RCTs are insufficiently characterized to assure they are free from nonrandom sources of error that may lead to erroneous conclusions. In particular, I believe they do not warrant making treatment recommendations at this time addressing labeled or unlabeled uses, particularly to suggest relative safety for one product over another.

I agree with Dr. Avigan's comments that the studies as analyzed by Dr. Mosholder may not be sufficiently homogeneous to support their composite analysis. Additional examination of the clinical trial data, along with additional statistical testing for homogeneity should be done to determine if making conclusions based on the combined data is valid. Dr. Avigan notes that differences in the selection of patient populations among the different trials may have led to individual differences in the self-injury risk of patients. This concern is supported by the observation of differences among the placebo rates of suicide-related events among the different trials, as well as the differential rates and relative risk of self-injurious behaviors across individual drug trials. Dr. Mosholder himself notes that the post-hoc ascertainment methods for suicide-related events were different among the sponsors of different drug trials. He does not mention the possibility that ascertainment differences may also have influenced data collection during the RCTs themselves, since self-injurious behaviors were not elicited prospectively or systematically. Investigator practices in eliciting, recording, or coding these events were not likely to have been done in a consistent fashion.

In addition to inconsistent ascertainment of self-injurious adverse events, Dr. Mosholder's analyses do not describe imbalances in individual treatment times (e.g. time-adjusted survival analyses) that may have occurred due to differential dropout rates of placebo patients relative to treated patients. The common side-effect profile of SSRIs (including akathesia) may have led to the loss of true blinding by either the investigator, patient, or both, and so influenced decision-making about continuing participation in the trial. Such a scenario would allow for the possibility that more severely ill patients (perhaps at higher risk of self-injurious behavior) might have been preferentially retained in active treatment.

In conclusion, Division and Office management within the Office of Drug Safety support Dr. Mosholder's concerns that pediatric patients being treated for MDD with SSRIs may experience an increase in self-injurious behaviors that may in turn, place them at greater risk of suicidal behaviors. We disagree as to the conclusiveness of this finding for making of psychiatric treatment recommendations such as the preferential use of fluoxetine in pediatric MDD. We instead advocate widespread information-sharing with clinicians, patients, and parents addressing the potential emergence of self-injurious behavior in the initial treatment of pediatric psychiatric illness, and urge attentive patient follow-up by all parties. We support the timely completion of adjudicated data analyses by Columbia University, and a reexamination of the data and consideration of clinical treatment recommendations when the Joint FDA Pediatric and Neurological Advisory Committee is reconvened later in 2004.

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PID# D030341

DATE: March 6, 2004

From: Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation, HFD-430

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

SUBJECT: Suicidality in pediatric clinical trials with paroxetine and other antidepressant drugs: Follow-up to 9-4-03 consult

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

The attached memorandum from Andrew D. Mosholder, M.D., M.P.H., an epidemiologist in the Division of Drug Risk Evaluation/Office of Drug Safety, contains an analysis of suicidality in pediatric clinical trials with paroxetine and other antidepressant drugs and recommendations for a plan of action. An emphasis has been placed in suicide-related outcomes in the *composite* of randomized controlled trials of each pediatric drug development program. In Dr. Mosholder's analysis, for most but not all drugs of this class, there is a trend towards an increased attributable risk of suicide-related events linked to randomization to active drug, compared to placebo. Moreover, a meta-analysis of Major Depressive Disorder(MDD) studies across all drug programs reveals that the active treatment arm is associated with an increased risk for these events.

This meta-analysis raises critical concerns that must be addressed to optimize pharmacotherapy of pediatric MDD and other psychiatric illness(es). As Director of the Division of Drug Risk Evaluation, I have reviewed this document and support the analyses and conclusions that it contains, with the following exceptions and/or additions:

- Based on limitations in the data-set that has been made available, the meta-analysis that has been performed does not justify a recommendation for a labeled contraindication for use in 'all pediatric patients' of any of the reviewed drugs, at this time.

- As pointed out in Dr. Laughren's review[1], between individual trials, for each drug, there are inconsistencies of results of suicidality. This observation beckons for a more rigorous analysis of similarities and differences between the trials in their design and implementation.

[1] Thomas P. Laughren; Background on Suicidality Associated with Antidepressant treatment; submitted January 5, 2004; presented at Psychopharmacologic Drugs Advisory Committee and Pediatric Subcommittee of the Anti-Infectives Advisory Committee, February 2, 2004

In reviewing the clinical trial database to understand differences in suicidality between trials the following elements should be elucidated:

- *enrollment criteria (patient characteristics)*
- *classification criteria for including/excuding suicidality events*
- *protocols for following and assessing patients before, during and after treatment*

- Reasons for absence of efficacy for different agents in pediatric trials remain unclear. Whether differences in trial results are related to inherent differences in pharmacological properties between agents, or in trial characteristics (enrollment, powering, efficacy measures, etc.) has not yet been elucidated. Thus, at this time, differential labeling of fluoxetine to imply more a more favorable benefit/risk profile should be approached with caution.

- Although the rates of severe agitation and completed suicides have been reported in pediatric patients treated with anti-depressants, other events, including 'possible' and even 'serious' suicide-related events, appear to be much more common. Further information to understand the predictive relationship between these outcomes is critical in the interpretation of safety events associated with clinical trials.

- Dr. Mosholder's recommendation to discourage initiation of 'off-label' treatment of pediatric patients is based on a justifiable concern that in this age group, with the exception of fluoxetine, efficacy to treat MDD has not been demonstrated. Although off-label treatment is not directly discourages, the FDA Public Health Advisory issued on October 27, 2003 states:

  ..'FDA emphasizes that, for the 7 drugs evaluated in pediatric major depressive disorder (MDD), data reviewed by FDA were adequate to establish effectiveness in MDD for only one of these drugs, Prozac (fluoxetine). Failure to show effectiveness in any particular study in pediatric MDD, however, is not definitive evidence that the drug is not effective since trials may fail for many reasons, FDA recognizes that pediatric MDD is a serious condition for which there are few established options, and that clinicians often must make choices among treatments available for adult MDD.'

  'FDA emphasizes that these drugs must be used with caution. ....'

  At this time, because of lack of information, I do not support an explicit labeled instruction to avoid all 'off-label' treatment. Rather, an interim plan should be implemented to comprehensively inform physicians, patients and their families of the possible serious risks attached to treatment (in addition to their underlying psychiatric condition) suggested by some spontaneous reports that the agency has received. As part of this effort, explicit labeling about the association of antidepressant treatment with an increase in agitation, akathisia, aggression, depression, etc., that has been observed in some cases should be adopted. In addition, strategies to effectively communicate this information, in order to enhance vigilance of patients and their families and promote appropriate physician follow-up, should be developed.

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PID# D030341

DATE: February 18, 2004

FROM: Andrew D. Mosholder, M.D., M.P.H., Epidemiologist

THROUGH: Mark Avigan, M.D., Director
Division of Drug Risk Evaluation, HFD-430

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

SUBJECT: Suicidality in pediatric clinical trials with paroxetine and other antidepressant drugs: Follow-up to 9-4-03 consult

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

EXECUTIVE SUMMARY

This consult is a follow-up to the previous consult on this topic, dated 9-5-03. As described in that consult, GlaxoSmithKline (GSK) performed an analysis of suicidal behaviors in their paroxetine pediatric clinical trial database, and found that there was a statistically significant increase in suicide-related adverse events for paroxetine-treated subjects compared to placebo. The method GSK used for their analysis involved an electronic search of the adverse event data for certain events that might have represented suicidal behaviors, followed by a blinded review of these events to select those that appeared to be probably related to suicide. In July 2003, the Division of Neuropharmacological Drug Products (DNDP) requested the sponsors of the other antidepressant drugs to replicate GSK's analysis in their own pediatric clinical trial databases. This consult summarizes the results of these analyses for 22 short-term placebo-controlled trials involving 9 different antidepressant drugs.

These trials included a total of 4250 pediatric subjects, 2298 treated with active drug and 1952 treated with placebo. There were 108 patients with suicide-related events (74 on active drug and 34 on placebo); 78 of these adverse events were serious (54 on active drug and 24 on placebo).

Considering individual development programs separately, the data for venlafaxine and paroxetine showed a statistically significant increase in suicide-related events relative to placebo. Additionally, on one measure (the incidence rate difference for serious suicide-related events) the data for citalopram approached statistical significance (p-value = 0.063). The relative risks for suicide related events with two compounds, fluoxetine and mirtazapine, were below one, raising the possibility of a protective effect. However, the mirtazapine relative risk estimate of 0.5 was based on a very small number of events and had very broad confidence intervals. The relative risk

of suicide-related events for fluoxetine was 0.9 (95% confidence limits 0.3-2.3). (For all the other drugs, the relative risk estimates were greater than one, or undefined because of no events on placebo.)

Overall, comparing active drug treatment to placebo, there was an association of suicide-related events (incidence rate difference 0.08/year, p-value = 0.002) and serious suicide-related events (incidence rate difference 0.06/year, p-value = 0.006) with active drug treatment. This association was observed principally in major depressive disorder (MDD) trials, where the relative risk was 1.8 (95% confidence limit 1.2—2.8) and the attributable risk was 0.24/patient year for drug minus 0.14/patient year for placebo, yielding a value of 0.10 per patient-year of exposure to drug (p-value = 0.013). For serious suicide-related events in MDD trials, the relative risk was 1.9 (95% confidence interval 1.2–3.2), and the attributable risk was was 0.19/patient year for drug minus 0.10/patient year for placebo, yielding a value of 0.085 events per patient-year of exposure to drug (p-value = 0.015), equivalent to approximately 1 excess serious suicide-related event per 12 years of drug treatment. For non-MDD trials, the data also showed a higher rate of events with active drug treatment, but the attributable risk for serious events was much smaller than for MDD trials (0.01/year), and the data were not statistically significant.

There are a number of limitations to this analysis, the chief among them being that the clinical trial data are limited to short-term use of these drugs. Unfortunately, there are not comparable data available regarding safety and efficacy of long-term use of these drugs in pediatric patients. Also, although there were attempts to standardize the methodology and case definitions among the various sponsors, in practice there may have been differences because each sponsor conducted their own separate analysis.

At the present time, a number of additional steps are under way to enhance the quality of the data for the assessment of this signal. These initiatives include arranging for a blinded review of the clinical trial cases by suicidology experts at Columbia University, requesting additional details on how each sponsor conducted their analysis, and obtaining electronic clinical trial datasets for each study to permit a more sophisticated statistical analysis.

However, while these efforts will yield valuable information, particularly at the level of the data for individual trials and drugs, in my view it is unlikely that the new information will alter the basic finding of an association of suicide-related events and serious suicide-related events with active treatment. This is because of the size of the effect and the statistical significance of the overall finding. Also, it seems less likely that misclassification or failure to identify relevant events would produce a false positive signal; rather, those types of errors tend to weaken a signal. Only systematic bias could be reasonably expected to yield a false positive signal of this magnitude, and that seems unlikely.

Recommendations: Given the strength of the association shown by the present data, the clinical importance of the apparent effect (i.e., an estimated excess of one additional serious suicide-related event per 12 patient-years of active treatment), and the fact that the additional analyses are likely to take several more months to complete while considerable numbers of pediatric patients are being exposed to these drugs, I favor an interim risk management plan regarding use of these drugs in the pediatric population. This might be of value to physicians, patients and families who are faced with the need to make a decision regarding pharmacotherapy at the present time. Specifically, I propose a risk management strategy directed at discouraging off-label pediatric use of antidepressant drugs, particularly the use of drugs other than fluoxetine in the treatment of pediatric MDD. Conceivably, this might include discouraging the initiation of treatment of drug-naïve pediatric MDD patients with off-label drugs, in the absence of some over-riding clinical

consideration. (Of course, all such warnings should be made in a manner that emphasizes the fact that the available data apply only to short-term, acute treatment, and that sudden discontinuation of antidepressant treatment, or discontinuation without medical supervision, are unwise.)

I recommend this approach for two reasons. First, of all the drugs with pediatric MDD clinical trial programs, only fluoxetine is approved for pediatric MDD, on the basis of two positive clinical studies (out of two MDD studies conducted). Of course, the failure to demonstrate efficacy in pediatric MDD trials with other antidepressants does not necessarily mean that these other drugs are ineffective in pediatric MDD. Still, for drugs other than fluoxetine, judgement regarding their efficacy in pediatric MDD must remain a matter of speculation until further trials are conducted. Secondly, although the confidence limits are broad, fluoxetine is the drug for which the estimate of the relative risk of suicidal events appears most favorable.

BACKGROUND

This memorandum is in follow-up to our consult to DNDP dated 9-5-03. On May 22 of this year, GlaxoSmithKline submitted an analysis of adverse events related to suicidal behaviors in pediatric trials of paroxetine (Paxil, NDA 20-031). The sponsor performed this analysis by conducting an automated, electronic search of the safety database from their pediatric trials for adverse event terms that would suggest suicidal behaviors. This analysis showed a statistically significant increase in such behaviors with paroxetine treatment, compared to placebo. A previous consult reviewed these data, and also provided a preliminary analysis of data from seven other pediatric development programs for other antidepressant drugs.[2] Overall, there was a statistically significant increase in suicidal adverse events for active drug treatment compared to placebo, similar to the findings from the paroxetine trials. These findings were discussed at a CDER Regulatory Briefing.[3]

However, this preliminary review of pediatric trials with the other antidepressant drugs was limited to a manual search of the reports submitted to FDA. In order to provide a meaningful comparison to the paroxetine findings, the Division of Neuropharmacological Drug Products requested the sponsors of eight other drugs (sertraline, venlafaxine, fluoxetine, fluvoxamine, citalopram, nefazodone, mirtazapine, and bupropion) to conduct a search of their databases similar to the analysis performed by GlaxoSmithKline. All of the 8 sponsors responded to this request within the next few months. The purpose of this memorandum is to summarize the findings reported in those submissions.

With respect to pediatric indications for the antidepressant drugs, clomipramine, fluvoxamine, sertraline and fluoxetine are approved for pediatric obsessive compulsive disorder. (Clomipramine is an older tricyclic compound that was not part of this analysis.) For pediatric major depressive disorder (in children 8 years and up), the only drug approved is fluoxetine. Appendix table 5 presents a summary of the efficacy results from placebo-controlled trials with the aforementioned drugs, along with the regulatory status of the drugs for pediatric use.

METHODS

The sponsors of the aforementioned 8 drugs all received identical information request letters from DNDP dated 7-22-03. The letters asked for the following analyses for all randomized, placebo-

[2] PID# D030341, 9-4-03.
[3] CDER Regulatory Briefing 9-16-03

controlled trial involving pediatric subjects (the indented text below is reproduced from the letters):

> The identification of the following events should be done blinded to treatment to avoid bias. All adverse events occurring within 30 days of the last dose of drug should be included in the search.
>
> "Suicide-related events" should be identified using the following algorithm:
> • Any events coded to preferred terms that include the text strings "suic" or "overdos"
> • Exclude "accidental overdose" cases
> • Regardless of the preferred term to which the verbatim term is mapped, all verbatim terms should be searched for the following text strings: "attempt", "cut", "gas", "hang", "hung", "jump", "mutilat-", "overdos-", "self damag-", "self harm", "self inflict", "self injur-", "shoot", "slash", "suic-"
> • Any terms identified by this search because the text string was a substring of an unrelated word should be excluded (for example, the text string "cut" might identify the word "acute")
> • In addition to the algorithm above, narratives of all serious adverse events (SAEs) should be reviewed (in a blinded fashion) to identify any additional cases of suicidality or self- harm. In particular, SAEs related to mania and hostility should be examined closely for suicidality or self-harm.
> • Any death found to be due to suicide or overdose should be included (if not already identified by the previous search methods).
>
> We are also interested in an analysis of suicide attempts. "Suicide attempts" are a subset of the "suicide-related events" identified above; they should be identified using a blinded hands-on review of the records of all patients identified by the above algorithm as having a "suicide-related event". For the purposes of this analysis, any case in which the patient exhibited self-injurious behavior should be considered as a suicide attempt. Any case in which the patient's suicidal ideation did not lead to self-injurious behavior should be excluded from this subset.
>
> Separate analyses should be performed for the group of "suicide-related" events and the group of "suicide attempts". Both the risk (# of events/# of patients) and the rate (# of events/person-time exposure) should be presented by treatment group. All treatment groups should be presented, including active controls. If a study has a blinded extension phase, events identified while the patient is in that extension phase should be excluded.
>
> In addition to presenting the overall risks and rates across all indications and within each indication, the following stratified analyses should be performed:
> • Child (<12) vs. Adolescent (>= 12).
> • On-therapy vs. On-therapy + 30 days.
> • Within each indication, data from each trial should be presented separately.

Also requested were detailed clinical data about the patients identified as having suicidal events, in the form of narrative summaries and tabulations.

The analyses submitted by each sponsor are summarized herein. A brief description of the relevant pediatric clinical trials is presented for each drug. Also, Appendix table 3 lists each pediatric subject having a suicide-related event.

Although I reviewed all the narrative summaries of the identified adverse events, I have not reclassified any events myself; the sponsors maintained the blind on treatment when they categorized these events, and this is obviously not possible for me. Instead, I have simply noted the few cases where in my opinion a different classification of the event might reasonably have been made. For a few patients who experienced more than one event of interest, I have chosen to count each patient only once in the analysis, at the time of their first event; their subsequent events are described under "Comments" in appendix table 3. Also described under "Comments" are any other adverse events that were prominently associated with the suicidal events. For a few of the clinical development programs, there were a sufficient number of cases to warrant a discussion of possible contributing clinical factors such as dose and duration of treatment, and I have included those details where appropriate.

Also included is a summary analysis of the clinical trial data, both overall and by drug and indication, with statistical testing. This analysis examines the question of the association of these events with active drug treatment in two ways: by calculation of the attributable risk (more precisely, the incidence rate difference between drug and placebo), as well as the relative risk (i.e., incidence rate ratios for drug:placebo). All statistical calculations were performed with Stata version 7.0 software. (Grateful acknowledgement is made to Dr. Yi Tsong of OPSS for his comments on the statistical methods.)

RESULTS

Including the previously reviewed data on paroxetine, this analysis comprised a total of 22 randomized, placebo-controlled trials with 9 different antidepressant drugs in the pediatric population. A total of 2298 pediatric subjects were exposed to active drug, for a total of 406.9 patient-years; for placebo, there were 1952 subjects exposed for a total of 347.6 patient-years. (One trial, Study 329 for paroxetine, included an imipramine arm as an active control, in which the rate of suicide-related events was intermediate between paroxetine and placebo at 0.24 per patient-year, but I have omitted those data from this analysis. Also, patient-years of exposure were not available for the single trial with bupropion.)

The sponsors identified a total of 108 patients with suicide-related events in these trials, 74 on active drug and 34 on placebo. There were no completed suicides. All 83 patients with suicide-related events described in the previous consult were included among these 108 patients. Seventy-eight patients had events classified as serious (54 on drug and 24 on placebo), and 75 had events classified as "suicide attempts" under the method described above (with 49 suicide attempts on drug, and 26 on placebo). Appendix Table 1 presents the complete data on the numbers of these events from all 22 clinical trials, and Appendix Table 2 presents the derived rates of these events for each trial. Appendix Figures 1-4 depict graphically the rates enumerated in Appendix table 2, for MDD and non-MDD studies. Note that the placebo rates of events vary considerably from trial to trial, even within the subgroup of MDD studies. With respect to the classification of events, discussion at the 9-16-03 CDER Regulatory Briefing and subsequently has raised questions about the appropriateness of the "suicide attempts" classification, since this category actually includes all types of deliberate self-injury. Accordingly, in the following I have chosen to emphasize the category of serious suicide-related events, rather than the category of suicide attempts, as being perhaps more clinically meaningful. The data for the category "suicide attempt" are included in Appendix Tables 1 and 2 for completeness.

Overview of each sponsor's submission.

Bupropion (Wellbutrin, NDA 18-644, GlaxoSmithKline, submission dated 8-22-03)

There were no pediatric studies for the indications of major depressive disorder (MDD) or smoking cessation. There was one placebo-controlled pediatric study for the indication of attention deficit hyperactivity disorder (ADHD), as shown below. The requested electronic search of adverse event data revealed no suicide-related events in this study.

Indication	Protocol	No. of sites	Age range (yrs)	Duration (wks)	N	
					Bupropion	Placebo
ADHD	75	4	6-12	6	71	36

Thus, there are no available data on pediatric suicidality with bupropion in the relevant patient populations.

Mirtazapine (Remeron, NDA 20-415, Organon, submission dated 8-21-03 and email dated 11-24-03)

There was only one clinical protocol in the mirtazapine development program, described below; the sponsor conducted two identical studies under that protocol, which were combined for the analysis of safety information.

Indication	Protocol	No. of sites	Age range (yrs)	Duration (wks)	Dose (mg/day)	N	
						Mirtazapine	Placebo
MDD	003-045	34	7-17	8	15-45	170	88

The electronic search of the adverse events terms in study 003-045 yielded a total of 13 adverse events; these were listed in Organon's email submission dated 11-24-03. Of these 13 events, 10 were obviously not related to suicidal behaviors and were excluded, leaving 3 cases for further review; one of these cases ocurred pre-randomization and so was not part of the analysis. Additionally, a subject who was hospitalized for suicidal ideation was identified from the review of all serious adverse events (subject 0404), yielding a total of 3 cases, summarized in Appendix table 3. Note, however, that Organon excluded one of these events from the analysis: subject 0801, a 9 year old boy receiving mirtazapine treated in the emergency room for an overdose on 4 Depakote tablets. This was not considered a suicide attempt because the boy took the tablets "on a dare."

Fluoxetine (Prozac, NDA 18-936, Lilly)

N.B. The following summary is based primarily upon Lilly's submission to Health Canada dated 10-7-03, and not their submission to FDA dated 9-2-03, because Lilly discovered an additional fluoxetine-associated event while preparing their Canadian submission. For details, please refer to Lilly's correspondence dated 10-9-03.

There were four clinical trials relevant to this analysis, three in MDD and one in obsessive-compulsive disorder (OCD). Study HCCJ, a pilot study in adolescent depression, was excluded from the sponsor's Integrated Summary of Safety for the pediatric supplement, but is included in this analysis.

Indication	Study	No. of sites	Age range (yrs)	Duration (wks)	Dose (mg/day)	N	
						Fluoxetine	Pbo
OCD	HCJW	22	7-18	13	10-60	71	32
MDD	HCJE	22	8-18	19*	20	109	110
MDD	X065	1	8-18	8	20	48	48
MDD	HCCJ	1	12-17	6	20-60	21	19

*includes subacute phase (weeks 10-19), during which poorly responding patients could receive a higher dose of double-blind study medication

Lilly's search for adverse events of interest yielded a total of 220 possibly relevant events. Of these, 176 were considered obviously unrelated to the issue of suicidality and were not reviewed further (a list of these adverse events was provided by email 11-17-03, and I concur with the

sponsor that none of the events involve self-harm). The remaining cases are summarized in the sponsor's table, reproduced below.

Number of patients in pediatric fluoxetine MDD and OCD trials, by search category (reproduced from sponsor's submission)

Patient Category	Number of Patients
1) Suicide-related events with suicide attempts (acute/subchronic phases[a])	10
2) Suicide-related events with no suicide attempts (acute/subchronic phases[a])	7
3) Accidental overdose/death	1
4) Could be suicide related, but insufficient information	3
5) Suicide-related event prior to treatment phase	14
6) Suicide-related event during extension phase	2
7) Suicide-related event that was not treatment emergent	7

[a] Defined as the acute treatment phases for Studies HCCJ, X065, and HCJW, and the acute and subchronic phases from Study Periods III through V of Study HCJE.

Lilly provided narratives on all the cases listed, in their aforementioned submission to Health Canada and also in their email submission 11-18-03. My own review of these narratives substantiated Lilly's categorization of them.

The 17 events in categories 1 and 2 above were included in the analysis; a listing of these patients appears in appendix table 3.

A few observations can be made regarding the clinical details of these cases. With respect to dose, among the 9 fluoxetine-treated subjects with suicide-related events, the daily dose at the time of event was 20 mg for 7 subjects, 30 mg for one, and 60 mg for one. Median duration of treatment for fluoxetine subjects at the time of their event was 38 days, and the corresponding median for placebo subjects was 33 days. The adolescent age category predominated; children under 12 years of age comprised 43% of the total sample of 458 clinical trial subjects, but only 3 (18%) of the 17 suicide-related events occurred in children, which is not surprising given the relative infrequency of suicidal behavior among children compared to adolescents. Of the 17 suicide-related events, 13 (76.5%) occurred in female subjects, although females comprised only 228 (49.8%) of the 458 subjects.

Regarding the relationship to drug discontinuation, only one of the events (a drug overdose by fluoxetine patient 001-6401 in study HCCJ) occurred during the 30-day follow-up period. This patient was regarded as having discontinued by virtue of being non-compliant with study medication. However, Lilly acknowledged that "events occurring after study completion were not systematically collected," and so some events in the 30-day follow-up period may have been missed.

Nefazodone (Serzone, NDA 20-152, Bristol Myers Squibb, submission dated 8-21-03)

The table below provides the details for the two randomized, placebo-controlled pediatric studies with nefazodone.

Indication	Protocol	No. of sites	Age range (yrs)	Duration (wks)	Dose (mg/day)	N	
						Nefazodone	Placebo
MDD	CN104141	15	12-18	8	100-600	95	95
MDD	CN104187	28	7-17	8	100-300 or 200-600	184 (both arms)	94

The sponsor performed the requested search and identified two suicide-related events in these trials, both occurring in nefazodone-treated patients (please refer to Appendix table 3). (In addition to these events, the sponsor reported a total of 5 suicide-related events that occurred during open label treatment with nefazodone in follow-up to study 187. However, only the two events during double-blind treatment are relevant for this analysis.)

Fluvoxamine (Luvox, NDA 21-519, Solvay, submission dated 8-22-03)

There was one randomized, placebo controlled pediatric trial with fluvoxamine, described in the table below.

Indication	Protocol	No. of sites	Age range (yrs)	Duration (wks)	Dose (mg/day)	N	
						Fluvoxamine	Placebo
OCD	114	20	8-17	10	50-200	57	63

Solvay's search of the safety dataset for this trial revealed a single suicide-related event in a fluvoxamine-treated patient.

Sertraline (Zoloft, NDA 19-839, Pfizer, submission dated 9-12-03)

There were three randomized, placebo-controlled trials in the pediatric population, summarized in the table below. In addition, Pfizer is conducting a pediatric trial in post-traumatic stress disorder, for which the treatment is still blinded. Note that there were two studies for MDD conducted under the same protocol, and these have been combined in this analysis.

Indication	Protocol	No. of sites	Age range (yrs)	Duration (wks)	Dose (mg/day)	N	
						Sertraline	Placebo
OCD	498	12	6-17	12	25-200	92	95
MDD	1001/1017	51	6-17	10	50-200	189	184

The electronic search of adverse event terms yielded 89 potential events from these trials. Pfizer's blinded review of the 89 cases identified 25 patients with possibly relevant events, and further review of these cases excluded 19 events (mostly associated with accidental injuries). This yielded a total of 9 events occurring among 8 subjects that were considered suicide-related. (My own review of the listing of these 89 events did not disclose any additional events that were obvious omissions.) In addition, Pfizer performed the requested review of all serious adverse events in these trials, yielding one additional case relevant to the analysis (subject 1001-29533-2006, who was hospitalized for suicidal ideation). Thus there were a total of 9 patients with suicide-related events. It should be noted, however, that in their submission Pfizer questioned the clinical relevance of events in two sertraline-treated patients (subject 30506-1076, with self-mutilation, and subject 6193-1022, who was hospitalized for suicidal threats), although they did not exclude these events from their analysis.

Although the number of events was probably too small for any meaningful characterizations, the median age among the 6 sertraline treated patients with events was 10 years, somewhat younger than seen in other development programs. These 6 subjects included 3 males and 3 females; their median dose was 100 mg/day, and all had MDD.

There were no events reported within the 30-day period after discontinuation of study medication, and no events in the OCD trial. Of the nine events, six occurred on drug and three on placebo. Six of the nine events occurred in female subjects. With respect to age, there was a somewhat different pattern from that seen in other clinical trial programs, since four events out of the nine occurred in children rather than adolescents (one event considered a suicide attempt occurred in a 6 year old boy). The duration of treatment among the six sertraline-associated events ranged from 21 to 50 days.

Citalopram (Celexa, NDA 20-822, Forest, submission dated 8-21-03)

There were two randomized, controlled clinical trials in the citalopram pediatric development program, summarized below.

Indication	Protocol	No. of sites	Age range (yrs)	Duration (wks)	Dose (mg/day)	N	
						Citalopram	Placebo
MDD	CIT-MD-18	21 in U.S.	7-17	8	20-40	89	85
MDD*	94404	31 in Europe	13-18	12	10-40	121	112

*subjects could be inpatients or outpatients

Note that in addition to these two completed trials, the sponsor is conducting study SCT-MD-15, a randomized, double blind, placebo controlled trial of escitalopram, the s-isomer of citalopram, in children and adolescents with MDD. This trial is still blinded; the total number of subjects planned is 264, and there have been two suicide-related events thus far.

Forest made a couple of departures from the requested methods for the adverse event search. They included an analysis of 8 patients who experienced worsening of depression, but not suicidal thoughts or behaviors; all these patients were treated with placebo. These events were not included in the analysis presented here; the interested reader should refer to their submission for details. Forest also reported that their search of all serious adverse events for events involving suicidality was not performed blind to treatment. (I reviewed the serious adverse events in these two trials myself, and although I was not blind to treatment group either, I did not find any cases that were obvious omissions. However, among the serious adverse events, there were 6 placebo-treated and 2 citalopram-treated patients in study 94404 with psychiatric hospitalizations. These events were not counted in the analysis, however, because suicidality was not specifically documented.)

In addition to the events selected for the analysis, Forest reported that the electronic search identified 11 patients with "false positives" who were excluded.[4] In addition to the electronic search, Forest conducted a manual search of all adverse events and patient narratives from the

[4] Email dated 11-17-03

two trials, yielding 6 patients with relevant events that were not disclosed in the electronic search. This made a total of 30 patients with events. In addition, one patient who took an extra dose of medication by mistake was considered to have taken an accidental overdose (patient 485 in study 94404); this event was not included in the analysis. Two events occurred prior to randomized treatment, yielding a total of 28 patients for the analysis (please refer to Appendix table 3 for a list of these patients). Note that 27 of the 28 events were classified as suicide attempts. However, Forest indicated in an email dated 11-17-03 that six of the study 94404 patients classified with "suicide attempts" (patients 664, 693, 867, 607, 152, and 713) were so categorized simply because the recorded preferred term was suicide attempt, and not because the event description documented self-injurious behavior.

Four placebo-treated patients and four citalopram-treated patients had events during the 30-day follow-up period after the end of randomized treatment. However, two of these 4 placebo patients also had events during double blind treatment, and so are counted as having events while on-treatment. Note that patient 007 in study 94404 was actually receiving fluoxetine, not citalopram, at the time of the event during the post-study period.

The median age of the 28 patients with events was 16 years; 19 were females and 9 males. Among the 13 patients receiving citalopram at the time of their event, the median dose was 20 mg/day, and the median duration on treatment was 27 days. Forest noted that 11 of the 16 citalopram-treated patients with suicide-related events in study 94404 had a past history of suicidality.

Forest also provided an analysis of scores on the suicidality item of the depression rating scales in the two trials; i.e., the CDRS-R in study CIT-MD-18, and the K-SADS in study 94404. There was a greater improvement on the suicidality item in study CIT-MD-18 with citalopram treatment compared to placebo, and this almost reached statistical significance. However, the mean change from baseline on item IX from the K-SADS in study 94404 was approximately equal between citalopram and placebo.[5]

Paroxetine (Paxil, NDA 20-031, GlaxoSmithKline)

Please refer to the consult dated 9-5-03 for details regarding the paroxetine pediatric clinical trial data. Subsequently, GSK provided the agency with a copy of their report to the Committee for Proprietary Medicinal Products of the European Agency for the Evaluation of Medicinal Products .[6] Included in this is an analysis of suicide-related events in adult trials with paroxetine that mirrors GSK's analysis of the pediatric clinical trials. The results of the adult trial analysis show essentially no difference in the rates of suicide-related events between paroxetine and placebo treatment groups, for all studies combined or for the subset of MDD trials. This is in contrast to the previously described pediatric trial data, which showed a statistically significant increase with paroxetine treatment. The sponsor's tables describing both the adult and the pediatric analyses are reproduced in Appendix Figure 5.

Venlafaxine (Effexor and Effexor XR, NDAs 20-151 and 20-699, Wyeth)

There were four randomized, double blind, placebo-controlled venlafaxine trials in pediatric patients, summarized in the following table. The sponsor also reported that two additional

[5] NDA 20-822 8-21-03 submission
[6] NDA 20-031 11-7-03 electronic submission

pediatric placebo-controlled trials, one in social anxiety disorder and one in panic disorder, have been completed but are not fully analyzed yet.

Indication	Protocol	No. of sites	Age range (yrs)	Duration (wks)	Dose* (mg/day)	N	
						Venlafaxine	Placebo
MDD	382	16	7-17	8 + taper	37.5-225	80	85
MDD	394	37	7-17	8 + taper	37.5-225	102	94
GAD**	396	39	6-17	8 + taper	37.5-225	80	84
GAD	397	35	6-17	8 + taper	37.5-225	77	79

*administered as Effexor XR in all trials; dosage based upon weight of subject, and tapered over ≤2 weeks following double-blind treatment
**Generalized Anxiety Disorder

Wyeth identified 16 randomized patients with suicide-related events, along with two MDD patients who had events before beginning the study and who were not counted in the analysis. Additionally, one more event was identified through review of adverse event narratives, yielding a total of 17 patients who experienced a total of 20 events of interest. Wyeth counted all 20 events, rather than simply enumerating the number of patients with events.[7] Note that two patients were considered to have had separate events a few days apart (patients 39402-0041 and 39428-1087); after review of the narrative summaries, I have elected to count these instead as single events. A third patient also had two events, patient 38211-012, but these were separated by approximately 3 weeks and I have elected to count only the first event in the analysis that follows. Thus, the analysis shown below is based upon the number of patients with events, rather than the number of events (as in Wyeth's analysis). The listing in the Appendix provides further details about the patients.

The patient-years of exposure were not provided in the response to the July 2003 letter, since only rates were displayed in that submission; however, the exposures were available from the original pediatric exclusivity supplement. Additionally, in Wyeth's analysis, the "on-therapy" period does not include the taper period, but only the period of randomized treatment during which patients received their full dose of study medication. Therefor, "on-therapy period + 30 days" does not include a full 30 days from the last dose of study medication, if the patient had a taper following the end of their study treatment. This is slightly different from GlaxoSmithKline's analysis of the paroxetine pediatric trials, in which the "on-therapy" period included the taper phase, through the last dose of study medication, and the "on-therapy + 30 days" period included a full 30 days from the last dose of study medication.

With respect to classification of events, there were some issues with the "suicide attempts" category. The reason that patient 38205-019 was not counted in the suicide attempt category for taking an overdose was unclear. Also, I was unable to verify Wyeth's count of 3 suicide attempts on venlafaxine and 2 on placebo in study 382.[8] Instead, I have used the counts from Wyeth's "Abbreviated Table of Patient Characteristics."[9]

The median age among the 17 patients with suicide-related events was 13 years. For the 13 venlafaxine-treated patients, at the time of the event the median dose was 112.5 mg/day, and the median duration of treatment was 24 days. Wyeth counted any events occurring within 1 day of

[7] NDA 20-151 submission 8-28-03
[8] Table 3A, NDA 20-151 submission 8-28-03
[9] Table 4A, NDA 20-151 submission 8-28-03

the last full dose of study medication as having occurred on-therapy. Five of the 17 events did not occur on-therapy, 3 with venlafaxine and 2 with placebo.

Risk estimates

Analysis of attributable risk

Pooling the exposure and event data by drug and by indication provides the results shown in tables 1 and 2. Appendix figure 6 displays these same results graphically. Here, an incidence rate difference greater than zero would indicate a risk associated with active drug versus placebo, while an incidence rate difference less than zero would indicate a protective effect of the drug.

Table 1.

Attributable risks (incidence rate differences) per patient-year for suicide-related events in pediatric trials			
Trials	**Incidence rate difference, drug minus placebo**	**95% confidence interval**	**p-value**
Citalopram	**0.14**	**-0.16-0.43**	**0.374**
Fluoxetine	**-0.03**	**-0.20-0.14**	**0.737**
Fluvoxamine	**0.11**	**-0.10-0.32**	**0.485**
Mirtazapine	**-0.04**	**-0.21-0.14**	**0.691**
Nefazodone	**0.05**	**-0.02-0.12**	**0.367**
Paroxetine	**0.12**	**0.04-0.20**	**0.005**
Sertraline	**0.06**	**-0.05-0.17**	**0.327**
Venlafaxine	**0.17**	**0.02-0.33**	**0.029**
All MDD trials	**0.10**	**0.02-0.18**	**0.013**
All non-MDD trials	**0.04**	**-0.01-0.09**	**0.114**
All trials	**0.08**	**0.03-0.14**	**0.002**

Table 2

Attributable risks (incidence rate differences) per patient-year for serious suicide-related events in pediatric trials			
Trials	**Incidence rate difference, drug minus placebo**	**95% confidence interval**	**p-value**
Citalopram	**0.24**	**-0.01-0.48**	**0.063**
Fluoxetine	**-0.02**	**-0.18-0.14**	**0.775**
Fluvoxamine	**0**	**-**	**-**
Mirtazapine	**0.04**	**-0.04-0.12**	**0.654**
Nefazodone	**0.03**	**-0.02-0.08**	**0.606**
Paroxetine	**0.08**	**0.01-0.15**	**0.038**
Sertraline	**0.06**	**-0.04-0.16**	**0.276**
Venlafaxine	**0.06**	**-0.07-0.18**	**0.379**
All MDD trials	**0.09**	**0.02-0.15**	**0.015**
All non-MDD trials	**0.01**	**-0.02-0.05**	**0.498**
All trials	**0.06**	**0.02-0.11**	**0.006**

The incidence rate differences by drug for MDD trials alone are shown in Appendix Tables 6 and 7. These data are displayed graphically in Appendix Figure 7.

It can be seen that overall the data are consistent with an increased risk of suicidal events with active drug treatment; the comparison between active treatment and placebo for all trials pooled together is statistically significant (p-value = 0.002 for all suicide-related events, and p-value = 0.006 for serious suicide-related events). For serious suicide-related events in MDD trials, the attributable risk was was 0.19/patient year for drug minus 0.10/patient year for placebo, yielding a value of 0.085 events per patient-year of exposure to drug (p-value = 0.015), equivalent to approximately 1 excess serious suicide-related event per 12 years of drug treatment. The observed serious event incidence rate differences are larger in MDD trials (0.085/year) than in trials with OCD, GAD and Social Anxiety Disorder (SAD) (0.014/year).
With respect to individual drugs, the incidence rate differences for all suicide-related events are largest for paroxetine, venlafaxine and citalopram, reaching statistical significance for paroxetine and venlafaxine. For serious suicide-related events, citalopram showed the largest incidence rate difference, which approached statistical significance (p-value = 0.063).

Analysis of relative risk

In addition to estimating the excess risk attributable to drug, the data can also be analyzed in terms of the relative risk, or more precisely, the ratio of the incidence rates for drug and placebo. Accordingly, Mantel-Haenszel combined incidence rate ratios were calculated, stratified by study. This approach has the advantage of providing stratification by study, while the analysis of excess risk shown above simply involved summing all the relevant data without regard for differences between trials. In addition to calculating the combined incidence rate ratio, the Stata software also tests for homogeneity of the individual study ratios.

The Stata output for the "All trials" category is shown in Appendix table 3. There were two studies by themselves that showed statistically significant rate ratios for suicide-related events, Paroxetine Study 329 and Venlafaxine Study 394. No individual study showed a statistically significant protective effect.

Table 3 below displays the relative risks (more precisely, the incidence rate ratios) for suicide-related events and serious suicide-related events for each of the antidepressant drugs, and for all 21 clinical trials combined. Here placebo is the reference, and thus a value less than one indicates a protective effect of the drug, and a value greater than one a risk associated with drug treatment. For each combined incidence rate ratio calculated, the Mantel-Haenszel chi-square test showed no lack of homogeneity (i.e., indicating that data from the individual studies can be combined statistically).

Table 3. Combined incidence rate ratios for suicide-related events and serious suicide-related events

Drug	Number of pediatric trials	Incidence rate ratios* (95% confidence interval), by drug	
		All suicide-related events	Serious suicide-related events
Paroxetine	**5**	**2.69 (1.20-6.00)**	**2.19 (0.92-5.24)**
Sertraline	**2**	**2.03 (0.51-8.16)**	**2.52 (0.49-13.01)**
Venlafaxine	**4**	**3.33 (1.08-10.33)**	**1.80 (0.52-6.20)**
Fluoxetine	**4**	**0.88 (0.34-2.30)**	**0.88 (0.32-2.44)**
Citalopram	**2**	**1.41 (0.66-3.00)**	**2.54 (0.91-7.05)**
Mirtazapine	**1**	**0.53 (0.007-41.45)**	†
Nefazodone	**2**	†	†
Fluvoxamine	**1**	†	†
MDD trials	**14**	**1.81 (1.19-2.77)**	**1.95 (1.19-3.21)**
Non-MDD trials	**7**	**2.36 (0.67-8.33)**	**1.31 (0.26-6.72)**
All trials	**21**	**1.86 (1.25-2.78)**	**1.89 (1.18-3.04)**

†Ratio undefined due to zero events in placebo group
*Mantel-Haenszel method

It will be seen that the suicide-related event incidence rate ratios for venlafaxine and paroxetine indicate an association with drug treatment, and that the corresponding confidence intervals exclude one. Overall, the incidence rate ratio of approximately 1.9 for both suicide-related events and the subcategory of serious suicide-related events indicate an association of these events with drug treatment. Put another way, compared to placebo, treatment with active drug increased the rate of suicide-related events by an estimated 85%, and by an estimated 87% for serious suicide-related events. For the subgroup of MDD trials, the incidence rate ratios were also statistically significant, while for non-MDD trials the incidence rate ratio estimates had very wide confidence intervals.

DISCUSSION AND CONCLUSIONS

In short-term pediatric trials, antidepressant drug treatment is associated with an increase in suicidal adverse events compared to placebo. This finding is seen for both the broad category of any suicide-related event, and the more specific category of serious suicide-related events. The association is more prominent in the MDD trial data, where the relative risk of serious suicide-related events is approximately 1.9. The rate of serious suicide-related events in MDD trials among drug-treated patients was 0.19/patient-year, and was 0.10/patient-year among placebo-treated patients. These rates represent one serious event per 5.4 patient-years for drug, and one serious event per 9.9 patient-years for placebo, yielding an attributable risk of one additional serious suicide-related event per 11.8 patient-years of drug treatment. The finding appears to be statistically robust, inasmuch as the p-value for the incidence rate difference for all suicide-related events across all trials is 0.002.

With respect to individual drugs, the data for paroxetine and venlafaxine show a statistically significant increase in suicide-related events with active treatment in their pediatric development programs. Also, the incidence rate difference for serious suicide-related events with citalopram was close to statistical significance (p-value = 0.063). For fluoxetine and mirtazapine, the point estimates were consistent with a protective effect, but the confidence intervals for mirtazapine were very broad, and even for fluoxetine the confidence interval on the incidence rate ratio includes a relative risk of greater than 2. Put another way, although an increase in suicide-related

events reached statistical significance for two drugs (paroxetine and venlafaxine), for no drug was a protective effect demonstrated at a statistically significant level.

This analysis has several limitations. Most importantly, it is limited to short-term trials only. Conceivably, long-term treatment in patients who have responded positively to a drug might not produce an increased risk, or might even provide a protective effect. In other words, it may not be appropriate to extrapolate a finding of a risk in short-term trials to use of the drug for long-term maintenance treatment, especially if the patients have manifested a clinical response to the drug. Unfortunately, there is very little long-term controlled pediatric trial data for antidepressant drugs that is available for analysis.

Another limitation of this analysis is that although there is evidence of a class effect overall, it is difficult to know to what extent it applies to particular members of the class. Inspection of the confidence intervals for the risk estimates will show that the confidence limits for individual drugs overlap considerably. The existing clinical trial data, moreover, cannot provide a fair comparison between drugs, since the sizes of the clinical development programs and the specific indications studied vary from drug to drug, not to mention the fact that the intrinsic pharmacologic and pharmacokinetic properties of the drugs themselves are different.

A third limitation pertains to the difficulties in standardizing the methodology used by the nine different sponsors. Although all sponsors were given the same set of instructions in the letters issued 7-22-03, there were some discrepancies in how these instructions were applied. For example, Forest (sponsor of citalopram) performed not only the requested electronic search of all adverse event terms, but also a manual search, which yielded cases not found with the electronic search. Also, the 30-day follow-up period was interpreted differently by GSK (paroxetine) and Wyeth (venlafaxine). GSK counted followed-up time for 30 days after the last dose of study medication, and the taper phase was not part of that 30-day period. However, Wyeth began the 30-day period from the last full dose of study medication, so that the period of dosage taper was included in the 30-day follow-up time. Also, Lilly (sponsor of fluoxetine) reported that adverse event data was not consistently collected once patients discontinued their study treatment.

As Appendix figures 1-4 illustrate, there was considerable variability in the rates of these events from trial to trial, even within the same indication. This could be due to differences in the patient population (some trials included children, for example), or to differences in ascertainment of suicide-related events, or to both. This, of course, raises questions about whether it is appropriate to combine the data from different trials. The Mantel-Haenszel chi square test for homogeneity of the rate ratios, however, did not reveal any statistically significant lack of homogeneity.

The increase in suicidal events was most clearly demonstrated in MDD trials. However, events with active drug treatment were more frequent than events with placebo in non-MDD trials, although the numbers are small and the risk estimates are very uncertain. Nonetheless, this leaves open the possibility of a drug-associated risk of such behaviors for non-MDD patients, although at a much lower incidence rate difference than for MDD patients.

With respect to clinical factors that might be contributory, as described in the previous consult, the paroxetine data suggested a possible role for drug withdrawal, but this pattern was not as prominent in the data for other drugs. However, this observation might point to a lack of consistency across development programs with respect to ascertainment of adverse events following the end of double-blind treatment.

The absence of completed suicides in these data is only reassuring to a limited degree. The total drug exposure time in these trials was 407 patient-years. For assessing the rate of a rare event such as completed suicide with active drug treatment, this is a relatively small data set. To illustrate, the upper confidence limit (one sided, 95% level) for the actual rate in the population given an observation of no suicides in 407 patient-years is 1 completed suicide in approximately 136 patient years.

In contrast to the paroxetine pediatric data, the analysis of suicide-related events in adult paroxetine trials, employing methods identical to the corresponding analysis of pediatric trial data, failed to show an increase in the rate of such events with paroxetine treatment relative to placebo. This was despite the fact that the placebo rate for these events was similar between the adult MDD trials (0.10/year) and the pediatric MDD trials (0.13/year). This suggests that adults and pediatric patients may have different responses to paroxetine with respect to suicidality.

Several steps are being taken at the moment to evaluate this signal further. First, a joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee will be held 2-2-04 to discuss this issue.[10] Secondly, DNDP has requested electronic data sets from the sponsors of these clinical trials that will permit a more sophisticated statistical analysis. This analysis will permit examination of a number of issues that were beyond the scope of this consult, such as adjustment for a number of relevant covariates and exploration of risk factors such as agitation and relevant family history. Thirdly, DNDP has arranged for a group of suicidology experts at Columbia University to review the clinical narrative summaries for all of the identified cases; this will permit a more sophisticated case classification, particularly with regards to whether the event was a serious suicide attempt, a gesture, or self-mutilation. Fourthly, on 11-24-03 DNDP sent a memo to all the sponsors requesting a more detailed description of the methods each sponsor used to generate the submissions reviewed in this consult, to ensure the highest possible quality of data for review by the Columbia University experts.

One suggestion can be made for the expert group involved in the review of the cases. Because the nature and quality of the case reports received from the sponsors (as listed in Appendix Table 3) vary considerably, it is likely that even experts in classifying suicidal behaviors will have some uncertainty about how to classify some of the case reports. Accordingly, it will be important to reserve a category of indeterminate cases with which to do a sensitivity analysis. The principle here would be to do an analysis including the doubtful cases, and another analysis excluding them, to see if the results are very dependent upon how uncertain cases are classified.

These initiatives should indeed provide higher-quality data for evaluation of this signal. However, in my view, the new analyses are more likely to change the findings for individual studies and drug compounds where the numbers are relatively small, than they are to alter the overall finding of an increase in suicide-related adverse events and serious suicide-related events with active drug treatment compared to placebo. There are, I believe, several reasons for this. First, the aggregate findings are statistically robust (e.g., p-value = 0.002). Secondly, the counts of serious suicide-related events are, in my view, less likely to be unstable, because of the methods routinely employed to account for serious adverse events in clinical trials, and the greater amount of clinical information that is often collected about serious adverse events compared to non-serious events. Additionally, to the extent that events have been misclassified or overlooked in the sponsor's searches, this would generally be expected to introduce "noise" that would weaken the signal and produce a false negative, not generate a false positive. Only a systematic bias that

[10] Federal Register Vol. 68, No. 211 Friday, October 31, 2003

caused events in the placebo group to be missed while events in the drug group were captured would be expected to produce a false positive, and it is difficult to conceive of what could produce such a bias.

As previously noted, fluoxetine is currently the only drug approved for pediatric MDD, although several drugs are approved for pediatric OCD (see Appendix table 5). As shown in that table, all of the four pediatric OCD trials were positive and provided evidence of efficacy for approval of the drugs for pediatric OCD. This is in contrast to the experience with pediatric MDD trials, for which only 3 of the 15 trials have been judged positive, two with fluoxetine and one with citalopram.

In sum, short-term pediatric clinical trials of antidepressant drugs demonstrate an increased rate of suicidal events with active drug compared to placebo.

Recommendations: Given the strength of the association shown by the present data, the clinical importance of the apparent effect (i.e., an estimated excess of one additional serious suicide-related event per 12 patient-years of active treatment), and the fact that the additional analyses are likely to take several more months to complete while considerable numbers of pediatric patients are being exposed to these drugs, I favor an interim risk management plan regarding use of these drugs in the pediatric population. This might be of value to physicians, patients and families who are faced with the need to make a decision regarding pharmacotherapy at the present time. Specifically, I propose a risk management strategy directed at discouraging off-label pediatric use of antidepressant drugs, particularly the use of drugs other than fluoxetine in the treatment of pediatric MDD. Conceivably, this might include discouraging the initiation of treatment of drug-naïve pediatric MDD patients with off-label drugs, in the absence of some over-riding clinical consideration. (Of course, all such warnings should be made in a manner that emphasizes the fact that the available data apply only to short-term, acute treatment, and that sudden discontinuation of antidepressant treatment, or discontinuation without medical supervision, are unwise.)

I recommend this approach for two reasons. First, of all the drugs with pediatric MDD clinical trial programs, only fluoxetine is approved for pediatric MDD, on the basis of two positive clinical studies (out of two MDD studies conducted). Of course, the failure to demonstrate efficacy in pediatric MDD trials with other antidepressants does not necessarily mean that these other drugs are ineffective in pediatric MDD. Still, for drugs other than fluoxetine, judgement regarding their efficacy in pediatric MDD must remain a matter of speculation until further trials are conducted. Secondly, although the confidence limits are broad, fluoxetine is the drug for which the estimate of the relative risk of suicidal events appears most favorable.

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Appendix Table 1. Summary of pediatric clinical trial data on suicidal adverse events

Drug	Indication	Study	Drug					Placebo				
			N	Patient-years	Suicide-related events	Serious suicide-related Events	Suicide attempts	N	Patient-years	Suicide-related events	Serious suicide-related events	Suicide attempts
Paroxetine*	MDD	329†	93	13	8	7	5	88	13	1	1	0
	MDD	377	181	41	9	7	8	95	21	4	4	4
	MDD	701	104	16	3	3	2	102	17	2	1	1
	OCD	704	99	19	1	1	0	107	22	0	0	0
	SAD	676	165	51	4	0	1	157	47	0	0	0
	Paroxetine Total		*642*	*140*	*25*	*18*	*16*	*549*	*120*	*7*	*6*	*5*
Sertraline	MDD	1001/1017	189	32.2	6	5	3	184	32.5	2	2	2
	OCD	498	92	18.8	0	0	0	95	19.7	1	0	0
	Sertraline Total		*281*	*51*	*6*	*5*	*3*	*279*	*52.2*	*3*	*2*	*2*
Venlafaxine	MDD	382	80	11.01	5	3	1	85	11.73	3	3	3
	MDD	394	102	15.95	7	3	3	94	15.47	0	0	0
	GAD	396	80	13.08	0	0	0	84	13.56	0	0	0
	GAD	397	77	11.63	1	1	1	79	11.44	1	1	1
	Venlafaxine Total		*339*	*51.67*	*13*	*7*	*5*	*342*	*52.2*	*4*	*4*	*4*
Fluvoxamine	OCD	114	57	9.37	1	0	0	63	9.95	0	0	0
Mirtazapine	MDD	003-045	170	24.05	1	1	0	88	12.7	1	0	1
Fluoxetine	MDD	HCJE	109	31.57	4	3	1	110	27.96	4	3	2
	MDD	HCCJ	21	2.11	1	1	1	19	2.11	1	1	1
	MDD	X065	48	6.71	2	2	2	48	5.83	2	2	0
	OCD	HCJW	71	15.12	2	2	2	32	5.98	1	1	1
	Fluoxetine Total		*249*	*55.51*	*9*	*8*	*6*	*209*	*41.88*	*8*	*7*	*4*
Nefazodone	MDD	141	95	13.6	1	0	1	95	12.5	0	0	0
	MDD	187	184	25.4	1	1	1	94	12.9	0	0	0
	Nefazodone Total		*279*	*39*	*2*	*1*	*2*	*189*	*25.4*	*0*	*0*	*0*
Citalopram	MDD	CIT-MD-18	89	12.8	1	0	1	85	12	2	0	1
	MDD	94404	121	23.5	16	14	16	112	21.3	9	5	9
	Citalopram Total		*210*	*36.3*	*17*	*14*	*17*	*197*	*33.3*	*11*	*5*	*10*
Bupropion	ADHD	75	71	**	0	0	0	36	**	0	0	0
Grand Total			**2298**	**406.9**	**74**	**54**	**49**	**1952**	**347.63**	**34**	**24**	**26**

*Paroxetine patient-years of exposure were provided only to the nearest integer **Patient-years of exposure data were not provided †Imipramine arm omitted

Appendix Table 2. Rates of suicidal adverse events, per patient-year, in pediatric clinical trials

Drug	Indication	Study	Drug				Placebo			
			Patient-years	Rate of Suicide-related events	Rate of Serious suicide-related Events	Rate of Suicide attempts	Patient-years	Rate of Suicide-related events	Rate of Serious suicide-related events	Rate of Suicide attempts
Paroxetine	MDD	329	13	0.62	0.54	0.38	13	0.08	0.00	0.08
	MDD	377	41	0.22	0.17	0.20	21	0.19	0.19	0.19
	MDD	701	16	0.19	0.19	0.13	17	0.12	0.06	0.06
	OCD	704	19	0.05	0.05	0.00	22	0.00	0.00	0.00
	SAD	676	51	0.08	0.00	0.02	47	0.00	0.00	0.00
Sertraline	MDD	1001/1017	32.2	0.19	0.16	0.09	32.5	0.06	0.06	0.06
	OCD	498	18.8	0.00	0.00	0.00	19.7	0.05	0.00	0.00
Venlafaxine	MDD	382	11.01	0.45	0.27	0.09	11.73	0.26	0.26	0.26
	MDD	394	15.95	0.44	0.19	0.19	15.47	0.00	0.00	0.00
	GAD	396	13.08	0.00	0.00	0.00	13.56	0.00	0.00	0.00
	GAD	397	11.63	0.09	0.09	0.09	11.44	0.09	0.09	0.09
Fluvoxamine	OCD	114	9.37	0.11	0.00	0.00	9.95	0.00	0.00	0.00
Mirtazapine	MDD	003-045	24.05	0.04	0.04	0.00	12.7	0.08	0.08	0.00
Fluoxetine	MDD	HCJE	31.57	0.13	0.10	0.03	27.96	0.14	0.07	0.11
	MDD	HCCJ	2.11	0.47	0.47	0.47	2.11	0.47	0.47	0.47
	MDD	X065	6.71	0.30	0.30	0.30	5.83	0.34	0.34	0.00
	OCD	HCJW	15.12	0.13	0.13	0.13	5.98	0.17	0.17	0.17
Nefazodone	MDD	141	13.6	0.07	0.00	0.07	12.5	0.00	0.00	0.00
	MDD	187	25.4	0.04	0.04	0.04	12.9	0.00	0.00	0.00
Citalopram	MDD	CIT-MD-18	12.8	0.08	0.00	0.08	12	0.17	0.08	0.00
	MDD	94404	23.5	0.68	0.60	0.68	21.3	0.42	0.42	0.23
Total			406.9	0.18	0.13	0.12	347.63	0.10	0.07	0.07

Appendix Table 3. Listing of all patients with suicide-related events in pediatric antidepressant drug trials.

MIRTAZAPINE

Study	Indication	Patient ID	Age Sex	Treatment	Dose (mg/day) at time of event	Duration (days)	Event	Serious (y/n)	Comments
003-045	MDD	0404	15 M	Mirtazapine	15	7	Hospitalization for suicidal ideation	Y	
003-045	MDD	0801	9 M	Mirtazapine	45	52	Depakote overdose "on a dare"	Y	*Excluded by sponsor*
003-045	MDD	1603	12 F	Placebo	-	56	Self inflicted cuts	N	

FLUOXETINE

Study	Indication	Patient ID	Age Sex	Treatment	Dose (mg/day) at time of event	Duration (days)	Event	Serious (y/n)	Comments
HCCJ	MDD	001/6401	17 F	Fluoxetine	30	40	Overdose, details unknown; discontinued from trial	y	Patient poorly compliant with study drug
HCCJ	MDD	001-6408	13 M	Placebo	-	33	Overdose of aspirin	y	
HCJE	MDD	008-0806	15 M	Placebo	-	37	Hospitalized for suicidal ideation and self-mutilation	y	
HCJE	MDD	008/0804	15 F	Placebo	-	60	Overdose on study medication	y	
HCJE	MDD	009-0901	15 F	Fluoxetine	60	101	Self-mutilation	n	
HCJW	OCD	006-0609	15 F	Placebo	-	71	Self-injurious behavior	Y	No details provided
HCJW	OCD	013-1300	12 F	Fluoxetine	20	25	Tylenol overdose	Y	Hospitalized
HCJW	OCD	018-1811	7 F	Fluoxetine	20	60	Self-destructive cutting	y	
X065	MDD	001-2051	16 F	Fluoxetine	20	14	Multiple drug overdose	Y	Other adverse events included manic reaction
X065	MDD	001-2163	17 F	Fluoxetine	20	12	Overdose on unknown pills	Y	No psychiatric family history, no previous attemtps
HCJE	MDD	004-0419	13 F	Fluoxetine	20	67	Hospitalized for suicidal ideation	Y	
HCJE	MDD	022-2216	15 F	Fluoxetine	20	38	Suicidal ideation	Y	
HCJE	MDD	003-0302	17 F	Fluoxetine	20	32	Suicidal thoughts	y	
HCJE	MDD	019-1901	11 F	Placebo	-	?	"wanting to die"	N	
HCJE	MDD	022-2203	9 M	Placebo	-	9	Suicidal ideation, intermittent	Y	Displayed self-injurious behavior during later extension phase of trial
X065	MDD	001-2052	16 M	Placebo	-	33	Suicidal ideation X 1 day (not hospitalized)	Y	Considered serious
X065	MDD	001-2087	14 F	Placebo	-	6	Hospitalized for suicidal ideation	y	

NEFAZODONE

Study	Indication	Patient ID	Age Sex	Treatment	Dose (mg/day) at time of event	Duration	Event	Serious (y/n)	Comments
141	MDD	3-1065	12 M	Nefazodone	600	38	Self mutilation (superficial cutting)	n	
187	MDD	18-322	13 F	Nefazodone	0	4 days post d/c	Overdose on 14 tablets of study medication	y	Hospitalized

FLUVOXAMINE

Study	Indication	Patient ID	Age Sex	Treatment	Dose (mg/day) at time of event	Duration (days)	Event	Serious (y/n)	Comments
RH1140201	OCD	65815	15 M	Fluvoxamine	200	36	Suicidal ideation	N	Self-mutilation during open label extension phase

SERTRALINE

Study	Indication	Patient ID	Age Sex	Treatment	Dose (mg/day) at time of event	Duration (days)	Event	Serious (y/n)	Comments
498	OCD	90N0242-19	12 F	Placebo	-	12	Suicidal ideation	N	
1001	MDD	29533-2006	12 M	Sertraline	100	49	Suicidal ideation	y	Hospitalized
1001	MDD	29534-1089	10 F	Sertraline	100	35	Suicidal ideation	Y	Hospitalized
1001	MDD	30506-1076	9 F	Sertraline	100	37	Self mutilation	n	Second episode of self mutilation on day 46
1001	MDD	6193-1022	10 M	Sertraline	100	21	Suicidal ideation	Y	Hospitalized. Also had mild agitation.
1017	MDD	29384-4022	16 F	Sertraline	150	50	Multidrug overdose	Y	Also noted to have restlessness
1017	MDD	30627-3095	6 M	Sertraline	100	34	Threatened to jump from vehicle, suicidal ideation	Y	Hospitalized; also experienced agitation
1017	MDD	31940-4329	17 F	Placebo	-	9	Attempted self-immolation	Y	Minor burn wounds. Subject later denied suicidality
1017	MDD	31942-4321	15 F	Placebo	-	63	Attempted suicide by hanging	Y	Second suicide attempt by overdose on day 66

CITALOPRAM

Study	Indication	Pt ID	Age Sex	Treatment	Dose (mg/day) at time of event	Duration (days)	Event	Serious (y/n)	Comments
CIT-MD-18	MDD	193	9 M	Citalopram	20	37	Cut self with knife	N	Agitation reported on previous day
CIT-MD-18	MDD	137	10 M	Placebo	-	31	Attempted to hang self (but not designated as a serious event)	N	Personality disorder; 24 days post-tx had another suicide-related event
CIT-MD-18	MDD	519	12 F	Placebo	-	41	Severe suicidal tendency (no details)	N	
94404	MDD	007	15 M	Citalopram	-	25 days post tx	Multiple drug overdose	Y	*Patient had received fluoxetine X 25 days since completing trial*
94404	MDD	009	17 F	Citalopram	20	15	Hospitalized for suicidality; overdose on naproxen on day 6 of hospitalization	Y	
94404	MDD	121	18 F	Citalopram	-	12 days post tx	Overdose of chlorxazone	Y	Patient had been discontinued from study on day 8 because of abnl clinical laboratories
94404	MDD	148	17 F	Citalopram	20	47	Overdose of 4-6 citalopram tablets	Y	Made a second overdose later in trial
94404	MDD	426	14 F	Citalopram	20	70	Overdose on 11 paracetamol tablets; denied suicidal intent	Y	Event coded as medication error
94404	MDD	573	14 F	Citalopram	20	88	Intentional ingestion of cigarettes	Y	Subject was an inpatient at screening
94404	MDD	575	14 F	Citalopram	20	55	Suicidal ideation, cut arm	Y	Subject was an inpatient at screening
94404	MDD	664	15 M	Citalopram	20	10	Re-hospitalized for suicidality	Y	Subject was an inpatient at screening
94404	MDD	713	16 M	Citalopram	30	27	Re-hospitalized for suicidality	N	Subject was an inpatient at screening. No explanation for why this was not designated a serious event.
94404	MDD	715	17 F	Citalopram	20	14	Hospitalized for suicidality, cut wrists, denied suicidal intent	Y	
94404	MDD	729	16 M	Citalopram	10	63	Ingested 15 caffeine pills plus alcohol	N	Event coded as medication error
94404	MDD	761	13 M	Citalopram	-	1 day post tx	Hospitalized for suicidality, event designated as a suicide attempt	Y	Also developed agitation, mood lability
94404	MDD	776	17 F	Citalopram	-	1 day post tx	Multiple drug overdose; only dose of study medication was the previous day	Y	Subject was an inpatient at screening. Also experienced anxiety
94404	MDD	867	17 F	Citalopram	30	20	Hospitalization due to suicidal thoughts	Y	Also experienced anxiety
94404	MDD	874	17 f	Citalopram	20	13	Overdose	Y	Patient cut her wrist 4 days after overdose
94404	MDD	884	16 F	Citalopram	20	16	Hospitalized after overdose on diazepam (9 tablets)	Y	On day 22, re-hospitalized for suicidality, and on day 81, another overdose
94404	MDD	071	16 F	Placebo	-	16	Hospitalized after self-inflicted wrist laceration	Y	Re-hospitalized for suicidality on day 36
94404	MDD	152	14 F	Placebo	-	8 days post tx	Hospitalized for suicidality	Y	Treated with citalopram after hospitalization
94404	MDD	412	18 F	Placebo	-	1 day post tx	Overdose on mother's medication	Y	Also receiving oxazepam for anxiety

Study	Indication	Pt ID	Age Sex	Treatment	Dose (mg/day) at time of event	Duration (days)	Event	Serious (y/n)	Comments
94404	MDD	605	13 M	Placebo	-	35	Self mutilation (forearm)	N	
94404	MDD	607	17 M	Placebo	-	62	Suicidal ideation and tension, treated with lorazepam	N	Inpatient at screening.
94404	MDD	691	17 F	Placebo	-	29	Self mutilation (palms)	N	
94404	MDD	693	16 F	Placebo	-	2	Hospitalized for suicidal ideation	Y	Later in trial had self-inflicted scratches on arm. After completing trial, started citalopram and was re-hospitalized for suicidal ideation 8 days later
94404	MDD	787	13 F	Placebo	-	29	Self-mutilation	N	
94404	MDD	871	17 F	Placebo	-	25	Overdose on 8 tablets of tolfenamic acid	Y	

PAROXETINE (Sources: 6-16-03 submission and Excel spreadsheet courtesy of Dr. Judith Racoosin, Division of Neuropharmacological Drug Products)

Study	Indication	Pt ID	Age	Sex	Treatment	Dose (mg/day) at time of event	Duration (days)	Event	Serious (y/n)	Comments
329	MDD	32900300313	18	M	Paroxetine	20	11	Command hallucinations, self mutilation	Y	Hospitalized
329	MDD	32900400015	16	F	Paroxetine	20	31	Mild self mutilation	N	
329	MDD	32900600038	15	F	Paroxetine	20	57	Multiple drug overdose	Y	
329	MDD	32900200245	14	F	Paroxetine	20	13	Acetaminophen overdose (27-28 capsules)	Y	Treated in emergency room and released
329	MDD	32900500250	15	F	Paroxetine	30	28	Overcompliance (by 124%) with study medication	Y	Coded as "overdose intentional." (Same patient subsequently overdosed on 20 capsules of study medication during continuation treatment.)
329	MDD	32900100065	14	M	Paroxetine	20	13	Angry outburst (with destruction of property) followed by suicidal thoughts	Y	
329	MDD	32900500333	16	F	Paroxetine	20	+4 post study	Hospitalized for severe suicidal ideation	Y	
329	MDD	32900200106	15	F	Paroxetine	40	51	Combative with mother, threatened suicide	Y	Hospitalized
377	MDD	37701100061	17	F	Paroxetine	40	75	Overdose (28 tablets of study medication)	Y	Hospitalized
377	MDD	37702400158	14	F	Paroxetine	30	86	Slapping herself in the face (automutilation)	N	
377	MDD	37702300172	16	M	Paroxetine	30	38	Overdose on 5 gm paracetamol plus 600 mg aspirin	N	Considered a non-serious event by investigator
377	MDD	37703000181	18	F	Paroxetine	40	56	Hostility, depression, writing suicide notes; possible drug abuse (cannabis)	Y	Hospitalized
377	MDD	37700900225	17	F	Paroxetine	20	78	Overdose on study medication	Y	Hospitalized
377	MDD	37704200310	15	F	Paroxetine	20	23	Self-inflicted wrist lacerations, superficial	Y	

Study	Indication	Pt ID	Age	Sex	Treatment	Dose (mg/day) at time of event	Duration (days)	Event	Serious (y/n)	Comments
377	MDD	37705300508	14	F	Paroxetine	20	54	Cut left wrist after arguing with mother	Y	
377	MDD	37704200315	15	F	Paroxetine	20	+4 post study	Overdose on 5 acetaminophen pills and two other pills, agitation, anxiety	Y	Hospitalized
377	MDD	37704900479	17	M	Paroxetine	40	+2 post study	Suicidal ideation, irritability	Y	Hospitalized
676	SAD	67601124283	15	M	Paroxetine	30	+1 post study	Vague suicidal ideation	N	
676	SAD	67601424376	13	F	Paroxetine	40	34	Worsening panic attacks, suicidal ideation	N	
676	SAD	67610024705	16	F	Paroxetine	20	43	Self-inflicted scratch on wrist	N	
676	SAD	67610124629	14	F	Paroxetine	40	99	Threatened suicide when brother hospitalized	N	
701	MDD	70116325718	16	F	Paroxetine	50	41	Patient reported taking an overdose of 100 paroxetine tablets	Y	Overdose not confirmed by urine drug screen
701	MDD	70118025639	15	F	Paroxetine	30	+2 post study	Cut arms, overdose on acetaminophen	Y	Required ICU admission
701	MDD	70118327620	11	F	Paroxetine	20	+4 post study	Threatened to hang self	Y	Hospitalized
704	OCD	70403325513	15	M	Paroxetine	40	25	Hospitalization due to suicidal thoughts	Y	
329	MDD	32900100123	16	F	Placebo	-	45	Worsening depression, suicidal thoughts	Y	
377	MDD	37700500231	14	F	Placebo	-	31	Overdose of study medication and chlorazepate	Y	
377	MDD	37701000068	14	F	Placebo	-	83	Overdose on 21 alprazolam tablets	Y	Hospitalized
377	MDD	37702900024	17	F	Placebo	-	29	Tried to kill herself with scissors	Y	Details not provided
377	MDD	37704100294	14	F	Placebo	-	84	Overdose on 10 gm of acetaminophen	Y	Hospitalized
701	MDD	70115425768	13	M	Placebo	-	5	Wrecked parent's car and became suicidal	Y	Hospitalized
701	MDD	70118327617	12	F	Placebo	-	3	Mild self-mutilation of arms	N	

VENLAFAXINE

Study	Indication	Pt ID	AGE	Sex	Treatment	Dose (mg/day)	Duration (days)	Event	Serious (y/n)	Comments
382	MDD	38202-036	13	F	Placebo	-	+18 post tx	Angry, kicked a cabinet	Y	Resulted in ER visit
382	MDD	38204-023	11	F	venlafaxine ER	112.5	21	Suicidal ideation	N	
382	MDD	38205-008	12	M	venlafaxine ER	75	29	Suicidal ideation, auditory hallucinations	Y	Hospitalized
382	MDD	38205-019	8	F	venlafaxine ER	NA	13	Overdose on venlafaxine 300 mg	Y	Hospitalized
382	MDD	38207-008	12	M	Placebo	-	+17 post tx	Suicidal ideation, scratching on arms	Y	Hospitalized
382	MDD	38207-023	14	F	Placebo	-	3	Overdose on study medication (~8 capsules)	Y	Treated at ER and released
382	MDD	38209-020	13	F	venlafaxine ER	37.5	13	Suicidal ideation with plan to overdose	Y	Hospitalized
382	MDD	38211-012	10	F	venlafaxine ER	112.5	23	Mild self-injurious behavior	N	On day 43 of trial, hospitalized for swallowing aftershave

394	MDD	39402-0041	7	M	venlafaxine ER	75	25 and 29	Suicidal ideation, plan to stab self	Y	Hospitalized (considered 2 events by sponsor)
394	MDD	39404-0126	14	M	venlafaxine ER	75	15	Suicidal and homicidal ideation	Y	Hospitalized
394	MDD	39411-0405	14	F	venlafaxine ER	150	51	Cut arm in context of family discord	N	Treated at ER and released
394	MDD	39420-0769	13	M	venlafaxine ER	225	36	Mild suicidal ideation	N	
394	MDD	39428-1087	16	M	venlafaxine ER	150	47 and 50	Rage attack, suicidal, homicidal	Y	Hospitalized; drug screen positive for PCP (considered 2 events by sponsor)
394	MDD	39435-1366	17	F	venlafaxine ER	37.5	5	Mild self-mutilation	N	
394	MDD	39440-1561	12	F	venlafaxine ER	-	+6 post tx	Overdose on study medication (17 capsules)	N	Treated at ER and released. Not considered a serious event
397	GAD	39701-0012	17	F	Placebo	-	15	Overdose of 18 Excedrin PM tablets following fight with boyfriend	Y	Hospitalized
397	GAD	39710-0361	10	M	venlafaxine ER	-	+3 post tx	Suicidal (wrapped cord around neck), agitated, and physically agressive	Y	Hospitalized

BUPROPION No cases

Appendix table 4. Stata outputs for calculation of combined incidence rate ratios

Category: Suicide-related events

Study	IRR	[95% Conf.	Interval]	M-H Weight	
003-045	.5281385	.0067291	41.45135	.6543909	(exact)
1001/1017	3.028078	.5414406	30.67137	.9953421	(exact)
114	.	.0272237	.	0	(exact)
141	.	.0235638	.	0	(exact)
187	.	.0130205	.	0	(exact)
329	8	1.072641	354.959	.5	(exact)
377	1.152439	.3216551	5.121634	2.645161	(exact)
382	1.775317	.3454063	11.43182	1.452651	(exact)
394	.	1.39804	.	0	(exact)
396	.	.	.	0	(exact)
397	.9837456	.0125341	77.21001	.5040969	(exact)
498	0	0	40.8801	.4882943	(exact)
676	.	.6083716	.	0	(exact)
701	1.59375	.1825649	19.08565	.969697	(exact)
704	.	.0296822	.	0	(exact)
94404	1.611357	.6704749	4.137106	4.720969	(exact)
CIT-MD-18	.46875	.0079441	9.004248	1.032258	(exact)
HCCJ	1	.0127412	78.48575	.5	(exact)
HCJE	.8856201	.1649537	4.754807	2.121318	(exact)
HCJW	.7910853	.0411829	46.67882	.7165671	(exact)
X065	.8689261	.0629945	11.98569	1.070133	(exact)
Crude	1.859448	1.223071	2.879198		(exact)
M-H combined	1.863115	1.246773	2.784147		

Test of homogeneity (M-H) chi2(13) = 7.67 Pr>chi2 = 0.8642

Category: Serious suicide-related events

Study	IRR	[95% Conf.	Interval]	M-H Weight	
003-045	.	.0135386	.	0	(exact)
1001/1017	2.523398	.4131554	26.50048	.9953421	(exact)
114	.	.	.	0	(exact)
141	.	.	.	0	(exact)
187	.	.0130205	.	0	(exact)
329	7	.8993189	315.599	.5	(exact)
377	.8963415	.2278526	4.175488	2.645161	(exact)
382	1.06519	.1426495	7.953972	1.452651	(exact)
394	.	.4008445	.	0	(exact)
396	.	.	.	0	(exact)
397	.9837456	.0125341	77.21001	.5040969	(exact)
498	.	.	.	0	(exact)
676	.	.	.	0	(exact)
701	3.1875	.2559633	167.3341	.4848485	(exact)
704	.	.0296822	.	0	(exact)
94404	2.537888	.8637632	9.002482	2.62276	(exact)
CIT-MD-18	.	.	.	0	(exact)
HCCJ	1	.0127412	78.48575	.5	(exact)
HCJE	.8856201	.1186016	6.613087	1.590989	(exact)
HCJW	.7910853	.0411829	46.67882	.7165671	(exact)
X065	.8689261	.0629945	11.98569	1.070133	(exact)
Crude	1.922267	1.168124	3.25143		(exact)
M-H combined	1.890265	1.175603	3.039376		

Test of homogeneity (M-H) chi2(10) = 6.44 Pr>chi2 = 0.7768

Appendix table 5. Summary of efficacy findings from eight pediatric antidepressant development programs

Drug	Indication	Approval status for pediatric use*	Study	N		
				Drug	Placebo	Efficacy results on primary variable
Paroxetine	MDD	NA	329	93	88	Failed (but + on secondary variables)
			377	181	95	Failed
			701	104	102	Failed
	OCD	AE	704	99	107	+
	SAD	Not submitted	676	165	157	? (not submitted)
Sertraline	MDD	NA	1001/1017	189	184	Two studies under same protocol, both failed (but + if data pooled)
	OCD	AP	498	92	95	+
Venlafaxine	MDD	NA	382	80	85	Failed
			394	102	94	Failed
	GAD	NA	396	80	84	Failed, by a small margin (p=0.09)
			397	77	79	+
Fluvoxamine	OCD	AP	114	57	63	+
Mirtazapine	MDD	NA	003-045	170	88	Two studies under this protocol, both failed
Fluoxetine	MDD	AP	HCJE	109	110	+
			X065	48	48	+
	OCD	AP	HCJW	71	32	+
Nefazodone	MDD	NA	141	102	99	Failed, by a small margin (p=0.08)
			187	184	94	Failed
Citalopram	MDD	NA	CIT-MD-18	89	85	+
			94404	121	112	Failed

* NA not approvable, AE approvable, AP approved

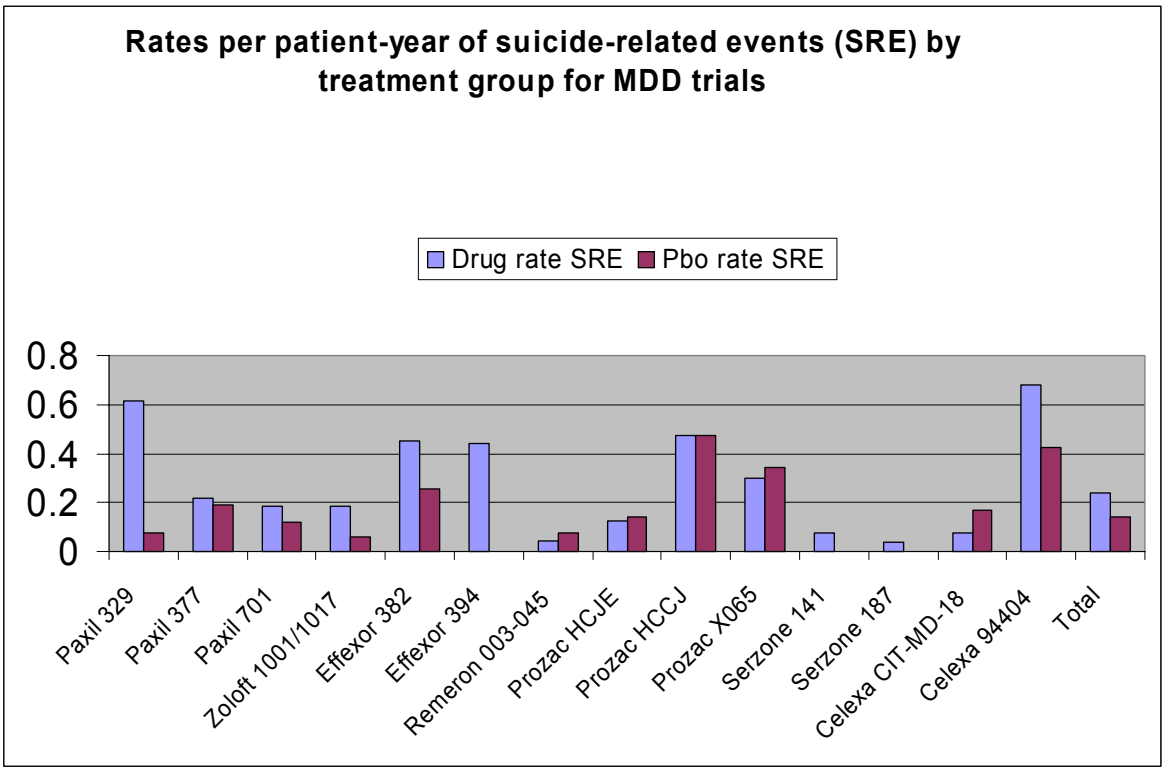
Appendix Table 6.

Attributable risks (incidence rate differences) per patient-year for suicide-related events in pediatric MDD trials			
Drug	**Incidence rate difference, drug minus placebo**	**95% confidence interval**	**p-value**
Citalopram	**0.14**	**-0.16-0.43**	**0.374**
Fluoxetine	**-0.02**	**-0.21-0.17**	**0.829**
Mirtazapine	**-0.04**	**-0.21-0.14**	**0.691**
Nefazodone	**0.05**	**-0.02-0.12**	**0.367**
Paroxetine	**0.15**	**-0.01-0.31**	**0.088**
Sertraline	**0.12**	**-0.05-0.30**	**0.176**
Venlafaxine	**0.33**	**0.05-0.62**	**0.020**
All MDD trials	**0.10**	**0.02-0.18**	**0.013**

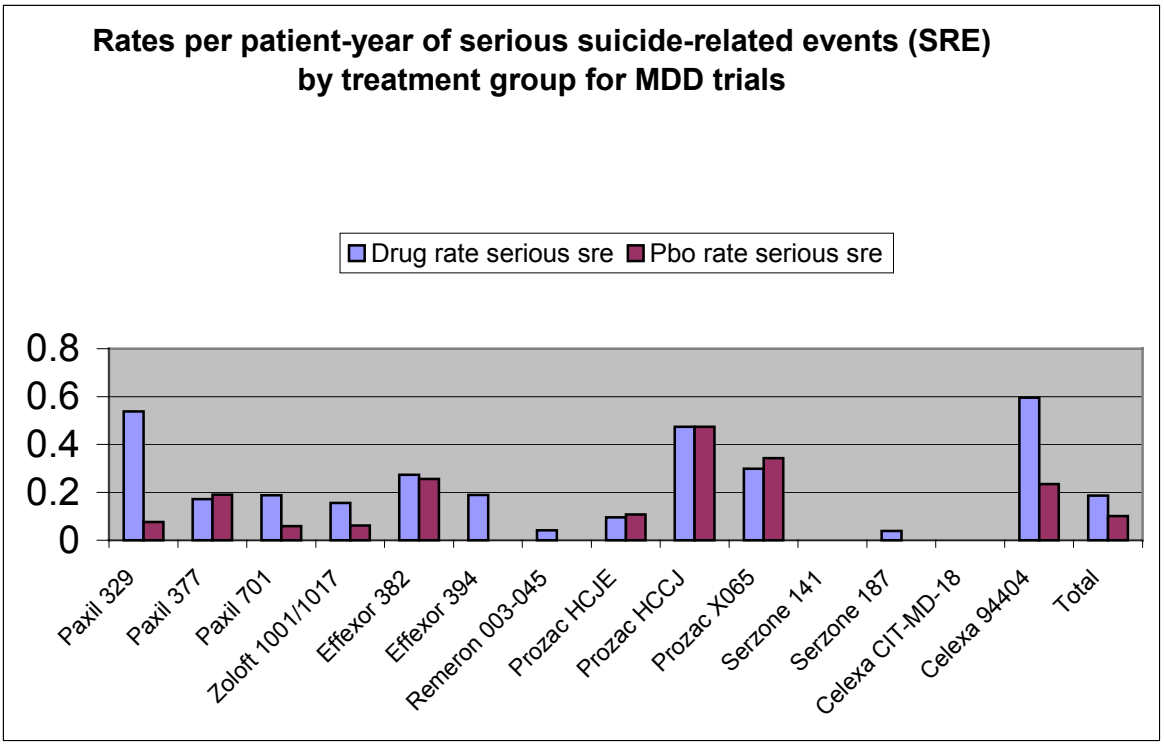
Appendix Table 7.

Attributable risks (incidence rate differences) per patient-year for serious suicide-related events in pediatric MDD trials			
Drug	**Incidence rate difference, drug minus placebo**	**95% confidence interval**	**p-value**
Citalopram	**0.24**	**-0.01-0.48**	**0.063**
Fluoxetine	**-0.02**	**-0.20-0.16**	**0.842**
Mirtazapine	**0.04**	**-0.04-0.12**	**0.654**
Nefazodone	**0.03**	**-0.02-0.08**	**0.606**
Paroxetine	**0.13**	**-0.02-0.27**	**0.121**
Sertraline	**0.09**	**-0.07-0.25**	**0.284**
Venlafaxine	**0.11**	**-0.11-0.33**	**0.337**
All MDD trials	**0.09**	**0.02-0.15**	**0.015**

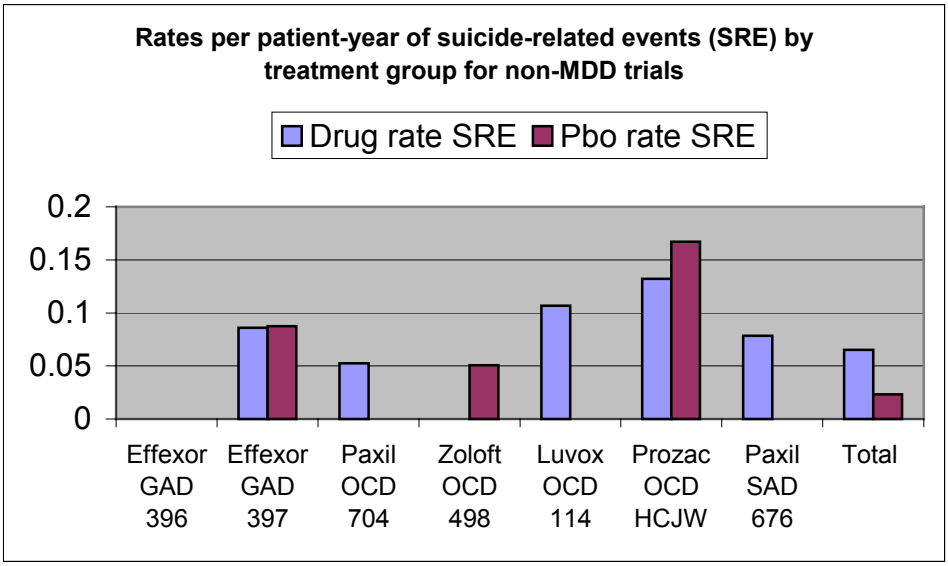
Appendix Figure 1.



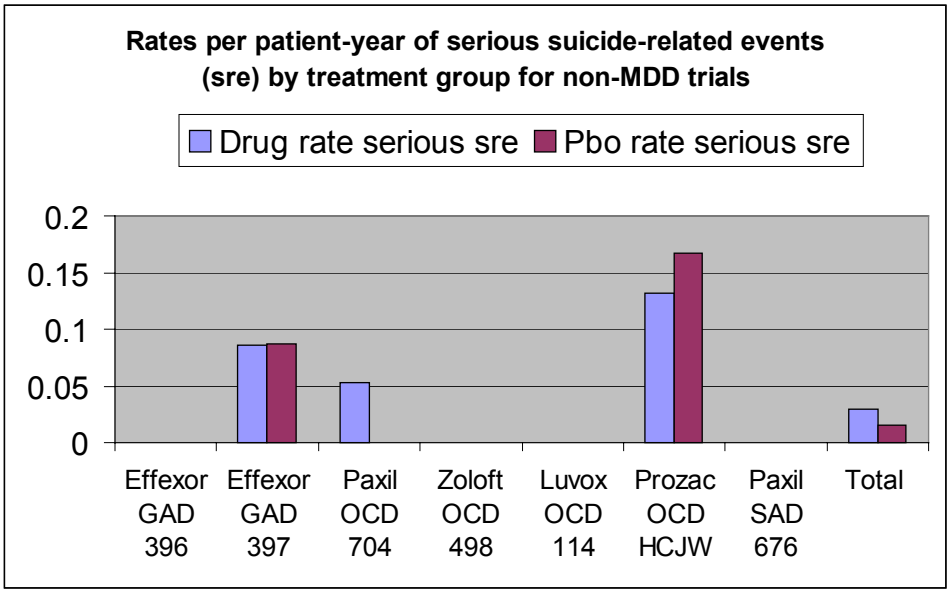
Appendix Figure 2.



Appendix Figure 3.



Appendix Figure 4.



Appendix Figure 5 (reproduced from the sponsor's submission)

Table 2.9 Incidence and Incidence Density for Possibly Suicide-Related Events by Treatment Group and Indication Paediatric Placebo Controlled Trials On-Therapy (including Taper Phase) plus 30 days post-therapy

Indication		Paroxetine	Placebo	Odds Ratio (95% CI)	P value
Overall	n/N (%)	25/738 (3.4%)	8/647 (1.2%)	2.80 (1.25 , 6.25)	0.012
	PYE	176	149		
	n/PYE	0.14	0.05		0.017
Depression	n/N (%)	20/378 (5.3%)	8/285 (2.8%)	1.93 (0.84 , 4.46)	0.12
	PYE	85	61		
	n/PYE	0.24	0.13		0.16
OCD	n/N (%)	1/195 (0.5%)	0/205 (0.0%)		0.49
	PYE	41	41		
	n/PYE	0.02	0.00		
SAD	n/N (%)	4/165 (2.4%)	0/157 (0.0%)		0.12
	PYE	51	46		
	n/PYE	0.08	0.00		

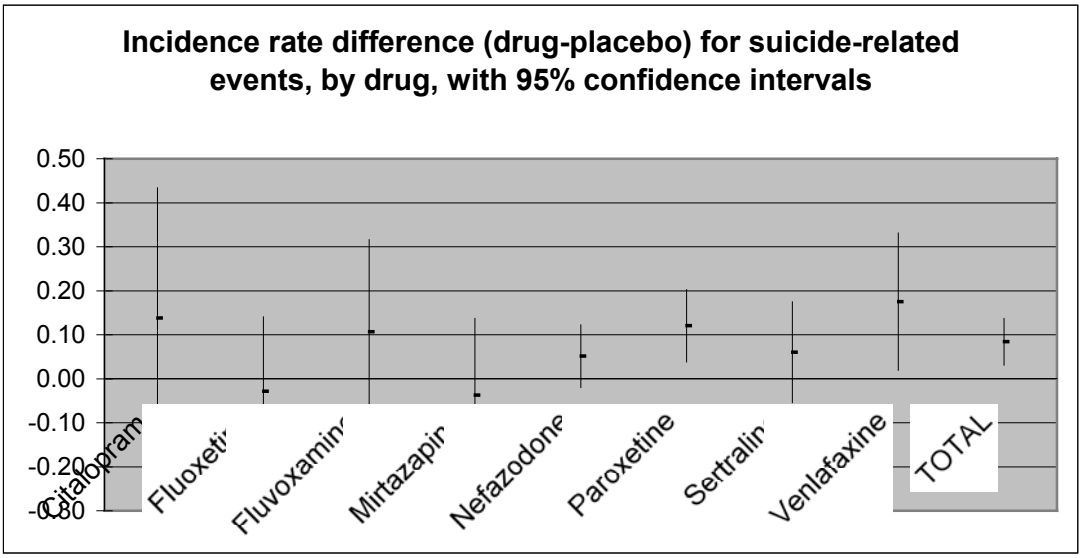
Data Source: Appendix 2B, Table 2.56

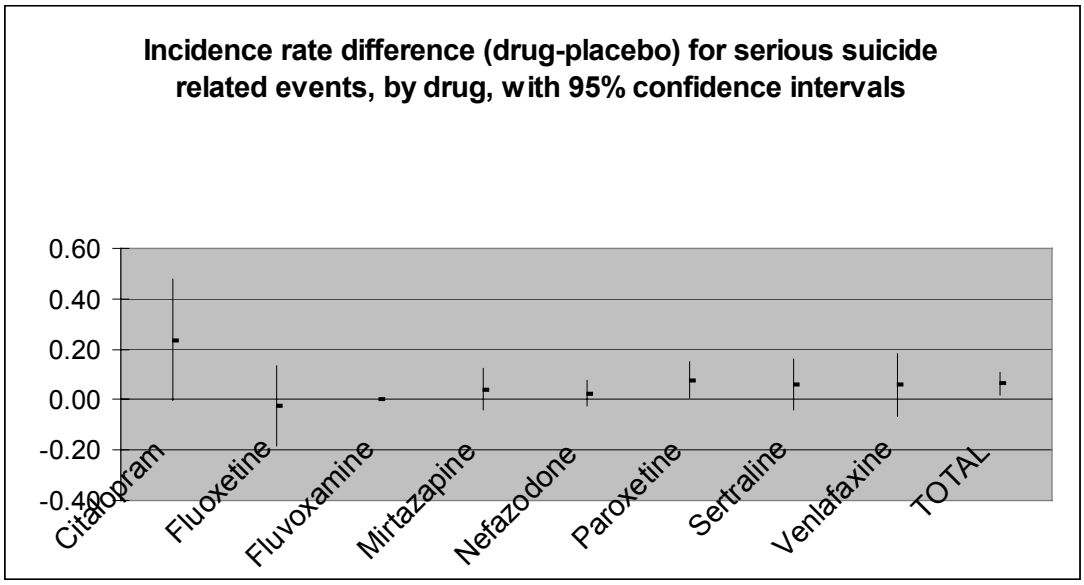
Table 2.5 Incidence and Incidence Density for Possibly Suicide-Related Events by Treatment Group and Indication Adult Placebo Controlled Trials On-Therapy (including Taper Phase) plus 30 days post-therapy

Indication		Paroxetine	Placebo	Odds Ratio (95% CI)	P value
Overall	n/N (%)	92/8481 (1.1%)	63/5808 (1.1%)	1.00 (0.72 , 1.38)	1.00
	PYE	1916	1313		
	n/PYE	0.05	0.05		1.00
Depression	n/N (%)	74/3421 (2.2%)	44/2117 (2.1%)	1.04 (0.71 , 1.52)	0.92
	PYE	671	428		
	n/PYE	0.11	0.10		0.71
GAD	n/N (%)	2/1182 (0.2%)	2/985 (0.2%)	0.83 (0.12 , 5.92)	1.00
	PYE	259	211		
	n/PYE	0.01	0.01		0.84
OCD	n/N (%)	3/542 (0.6%)	4/265 (1.5%)	0.36 (0.08 , 1.63)	0.23
	PYE	141	61		
	n/PYE	0.02	0.07		0.14
PMDD	n/N (%)	0/760 (0.0%)	0/379 (0.0%)		
	PYE	208	102		
	n/PYE	0.00	0.00		
PTSD	n/N (%)	7/786 (0.9%)	6/598 (1.0%)	0.89 (0.30, 2.65)	1.00
	PYE	174	138		
	n/PYE	0.04	0.04		0.89
Panic	n/N (%)	3/920 (0.3%)	4/780 (0.5%)	0.63 (0.14, 2.84)	0.71
	PYE	237	186		
	n/PYE	0.01	0.02		0.48
SAD	n/N (%)	3/870 (0.3%)	3/684 (0.4%)	0.79 (0.16 , 3.90)	1.00
	PYE	225	187		
	n/PYE	0.01	0.02		0.82

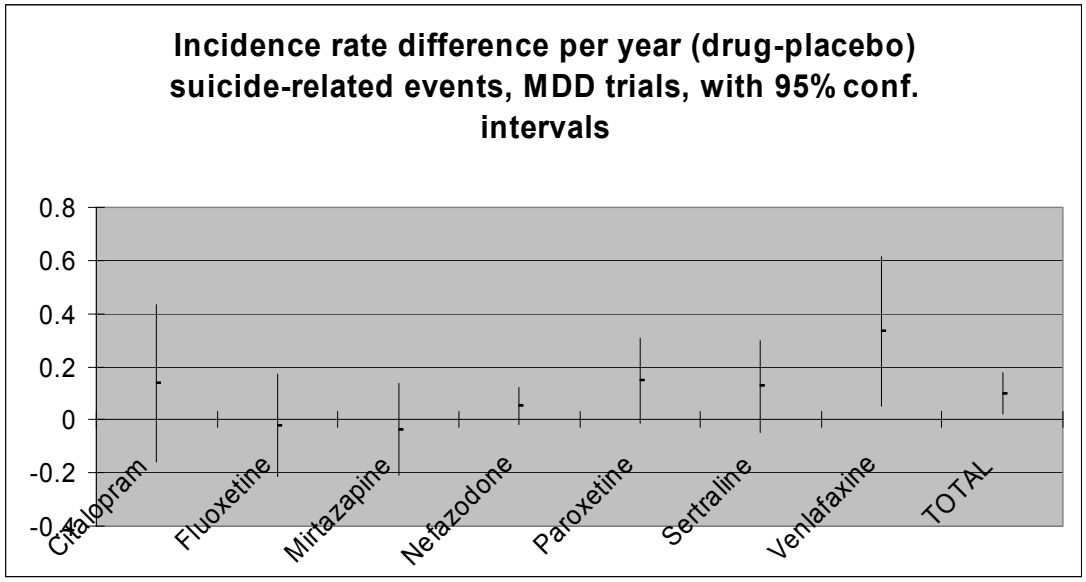
Data Source: Appendix 2B, Table 2.02

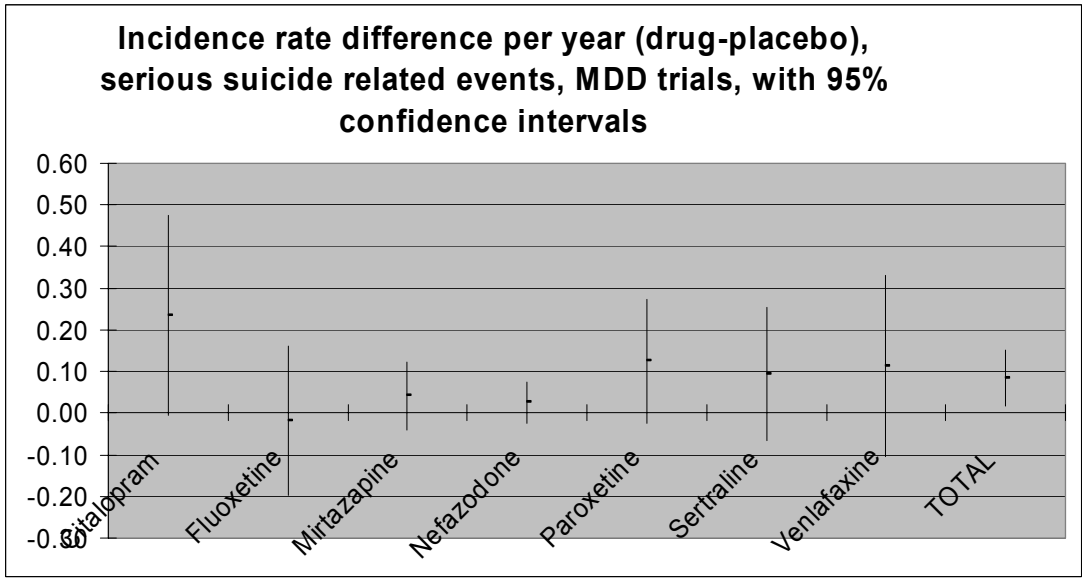
Appendix Figure 6.





Appendix Figure 7.





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