M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 16, 2006

FROM: Thomas P. Laughren, M.D.
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HFD-130

SUBJECT: Overview for December 13 Meeting of Psychopharmacologic Drugs Advisory Committee (PDAC)

TO: Members of PDAC

On December 13th, the PDAC will meet to consider new information on the occurrence of suicidality in the course of treatment of adult patients with various antidepressants. This meeting is followup to two meetings on antidepressants and suicidality in pediatric patients held in February and September, 2004. The focus of the 2004 meetings was on a finding of an increased risk of suicidal thinking and behavior (suicidality) in pediatric patients associated with the use of antidepressants, based on a meta-analysis of 24 short-term, placebo-controlled trials. Subsequent to those meetings, the division was asked to expand this exploration for suicidality in antidepressant trials to the adult population. This has been a major effort, involving 372 placebo-controlled antidepressant trials and almost 100,000 patients. The purpose of the December 13th meeting is to update the committee with our findings from this meta-analysis. We will present our findings and our interpretations of the data, and we will generally discuss our plans for labeling modifications based on these findings.

Background on Suicidality as a Risk of Antidepressant Treatment

The occurrence of suicidality in the context of treating patients with depression and other psychiatric illnesses has been a concern and a topic of interest and debate for decades. In fact, antidepressant labeling had, for many decades before the very recent addition of a black box warning, carried the following standard language under Precautions, alerting clinicians to closely monitor patients during initial drug therapy out of concern for the possible emergence of suicidality:

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

Of course, this standard Precautions statement did not explicitly warn of the possibility that antidepressant drugs may have a causal role in the emergence of suicidality early in treatment, but whether explicit or not, the statement allowed for that interpretation. In fact, as early as medical school, many physicians learn of this concern, and it has been part of medical lore for many decades that antidepressants may have an early activating effect that perhaps gives depressed patients the energy to follow through on suicidal impulses before the mood improvement associated with antidepressant treatment takes effect. Following is a statement from a textbook of psychiatry published over 40 years ago that is referring to observations in patients during initial treatment with tricyclic antidepressants [**Clinical Psychiatry, by Mayer-Gross, Slater, and Roth, 1960, p. 231**]:

> "With beginning convalescence (following initiation of treatment with tricyclic antidepressants), the risk of suicide once more becomes serious as retardation fades."

In fact, this particular mechanism proposed to explain a possible increase in suicidality early in antidepressant treatment is so well known that it is referred to as the "roll back" phenomenon. It is but one of several mechanisms that have been proposed to explain the clinical observation that some patients being treated with antidepressants, particularly early in treatment, may have an increase in suicidality. While this and other mechanisms all have some plausibility as explanations for the clinical observation of worsening depression or suicidality in depressed patients being treated with antidepressants, proposing a mechanism is quite a different matter from demonstrating empirically that there is a causal association between antidepressant use and induction of suicidality. The pediatric data presented at the September, 2004 PDAC meeting represented the first systematic demonstration of a causal link (**Hammad, et al, 2006**). This meta-analysis of the pediatric data was based on a total of 24 placebo-controlled trials involving over 4400 patients.

This finding, in a sense, confirmed a view that, as noted, is already widely prevalent in clinical lore, whatever the mechanism. Despite this fairly widely held view, however, the use of antidepressants has obviously increased in recent decades rather than declined. This fact suggests that, as a group, clinicians may place more weight on their beliefs in the longer-term benefits of antidepressants than their concerns about possible early risks of actually increased suicidal behavior. In fact, the dual findings of an early increase in the risk of suicidality but also a longer-term benefit with antidepressant treatment would, if both true, not necessarily be inconsistent. It is quite possible for a drug to have opposite effects over time, even within the same domain.

Brief Regulatory History of Antidepressants and Suicidality

The debate on this question with regard to adult depression intensified in 1990, at which time Martin Teicher, a psychiatrist from Harvard Medical School, along with several colleagues, published a paper describing a series of 6 adult patients with depression who, in their view, became suicidal as a result of being treated with Prozac (fluoxetine) **(Teicher, et al, 1990)**. This paper and the ensuing discussion led Lilly, the manufacturer of Prozac, to conduct new analyses of their controlled trials data for Prozac to explore for the emergence of suicidality. This renewed interest in the possible induction of suicidality in association with the use of

antidepressant treatment also led FDA to fully re-evaluate its spontaneous reports database to try to detect whether or not a signal of increased risk could be observed. Ultimately, this issue was brought to a PDAC meeting in September, 1991. This one-day meeting consisted of several hours of statements made by family members and others in the open public session, and presentations by representatives from FDA, Lilly, and NIMH. Statements in the open session were made mostly by family members of suicide victims whose deaths the families attributed to their taking Prozac. FDA gave an update on the very substantial number of spontaneous reports of suicidality in association with Prozac use, but also showed how the pattern of reporting was clearly linked to the publication of the Teicher, et al, paper and other publicity about this concern. A representative from NIMH gave that agency's perspective on this issue, essentially making the case that depression is a serious disorder that itself is associated with suicidality, and arguing that the data available to date did not support the view that antidepressants further increase the risks of suicidality in this population. Finally, Lilly presented the results of its analysis of data pooled over its extensive clinical trials, revealing no signal of increased suicidality in association with the use of Prozac **(Beasley, et al, 1991)**. At the end of a long day, a majority of the committee concluded that there was no clear evidence of an increased risk of suicidality in association with the use of Prozac in adults, and they did not recommend any changes to Prozac labeling with regard to this issue.

Over the next several years, additional data were accumulated as applications for newer antidepressants were submitted and reviewed, and these drugs came to market. Several groups have, in recent years, conducted pooled analyses for adult data on completed or attempted suicides from these programs, in order to continue the search for a possible signal of risk, either by virtue of being assigned to placebo, since the ethics of conducting placebo controlled trials in depression were being challenged, or due to assignment to drug treatment. Arif Khan, a psychiatrist from the Northwest Clinical Research Center, Bellevue, Washington, published a paper in 2000 based on adult data he obtained under FOI from FDA reviews. He concluded that the risk of completed suicide was the same, regardless of treatment assignment **(Khan, et al, 2000)**. Jitschak Storosum, a physician from the Medicines Evaluation Board of the Netherlands, did an analysis of attempted suicides from adult data available to his group, and he reached the same conclusion **(Storosum, et al, 2001)**. FDA has done several analyses on completed suicides for adult data sets provided to us in response to a request for patient level data for all relevant studies involving 9 antidepressant drugs studied in 251 randomized controlled trials with MDD and various anxiety disorders. Based on our analyses of these data, albeit quite limited because of the small number of completed suicides, we reached a similar conclusion, i.e., that there does not appear to be an increased risk of completed suicide associated with assignment to either active drug or placebo in adults with MDD or various anxiety disorders **(Hammad, et al, 2006)**.

Based on the finding of a signal for an increased risk of suicidality in association with short-term antidepressant use in pediatric patients, the PDAC recommended at the September, 2004 meeting that FDA add a box warning to antidepressant labeling and require a medication guide to alert patients, families, and caregivers to this risk. Both of these changes were implemented early in 2005. The new warning language warns of the risk of suicidality in pediatric patients and advises that prescribers balance this risk with clinical need in deciding on the use of an antidepressant in this population. The risk is characterized in terms of risk difference, i.e., the average risk of events representative of suicidality was 4% in drug-treated patients compared to

2% in placebo-treated patients during the initial few months of treatment. There were no completed suicides among these patients. Prescribers are advised to observe patients closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers are advised of the need for close observation and communication with the prescriber.

Recent Published Literature

BMJ Papers on Antidepressant Use and Suicidality in Adults (February, 2005)

A February 17, 2005 issue of the BMJ included 3 papers pertinent to the question of adult antidepressant use and suicidality. Two papers involved systematic reviews of data from controlled trials of antidepressants in adults (**Fergusson, et al, 2005** and **Gunnell, et al, 2005**). The third paper reported on a nested case-control study (**Martinez, et al, 2005**).

Fergusson, et al: The Fergusson, et al, review focused on data available from published reports of controlled trials of antidepressants in adults being treated for depression and various other indications. They found a two-fold increase in risk of suicide attempts in users of SSRIs compared to placebo or other interventions (OR 2.3; CI 1.1-4.6), but no difference in the risk seen with tricyclic antidepressant (TCA) use. There was no difference, however, in completed suicides across groups. There were serious limitations to this review, most important being a lack of any information on adverse events for 58% of the patients eligible for the analysis.

Gunnell, et al: The Gunnell, et al, review focused on data available from MHRA's reviews of data for various SSRIs submitted by pharmaceutical companies to that regulatory agency. They looked at both self harm behavior and suicidal thoughts. There was a finding of a weak but not statistically significant odds ratio (SSRIs vs placebo) for self harm behavior (1.6) and a finding in the opposite direction, i.e, suggesting a protective effect of drug treatment, for suicidal thoughts (0.8, again not statistically significant). As with the Fergusson, et al, review, there was no difference across treatment groups for completed suicides. Although this group had better access to data than the Fergusson, et al, group, they still did not have access to trial or patient level data, and so could not conduct certain analyses, e.g., stratifying by age.

Martinez, et al: This paper reported on a nested case-control study based on the General Practice Research Database. It examined self harm behavior and suicide in adult and pediatric patients with depression who were treated with either an SSRI or TCA. Overall, there was no difference in risk between the two groups, however, there was a suggestion of an increased risk of self harm behavior in patients aged 18 and younger prescribed SSRIs compared to TCAs (OR 1.59; CI 1.01-2.50). This study had all the limitations of a case-control study, including the possibility of differential prescribing based on perceived higher risk of suicidal behavior, and there was no placebo group for comparison.

Clearly there was overlap in the studies included in our meta-analysis of adult antidepressant trials and those included in the Fergusson, et al, and the Gunnell, et al, systematic reviews. We did have access to trial and patient level data, an important difference between these reviews. We will comment on differences in our results from those reported in these papers.

Papers Suggestive of Possible Differential Risk of Antidepressant-Associated Suicidality Across the Age Spectrum

One of our findings that merits some discussion is the suggestion of a differential risk of antidepressant-induced suicidality across the age spectrum, with a greater risk at the younger end of the spectrum, and a declining risk with aging, and perhaps even a protective effect in elderly depressed patients. In fact, there has already been some suggestion in the literature of a differential risk across the age spectrum. I've already mentioned the case-control study by **Martinez, et al, 2005** that found no overall difference in risk between SSRIs and TCAs, but did find a suggestion of an elevated risk of suicidality for SSRIs compared to TCAs in patients aged 18 and younger. Another recent case-control study (**Olfson, et al, 2006**) looked at suicide attempts and suicides in severely depressed adults and children who required inpatient treatment. Antidepressant treatment was not associated with suicide attempts (OR 1.10; CI 0.86-1.39) or suicide (OR 0.90; CI 0.52-1.55) in adults. However, there was a significant association with both suicide attempts (OR 1.52; CI 1.12-2.07) and suicides (OR 15.62; CI 1.65-infinity) in children and adolescents (6-18). Both studies are, of course, subject to the possible confounding of differential prescribing to patients perceived to be sicker and at greater risk of suicidal behavior. A third case-control study (**Juurlink, et al, 2006**) looked at suicides in elderly depressed patients and the comparison was with SSRI use vs use of other antidepressants. They found a nearly 5-fold greater risk of suicide in SSRI-treated patients compared to patients receiving other antidepressants (OR 4.8; CI 1.9-12.2), but only in the first month of treatment.

Ecological Studies Comparing Trends in Suicide Rate and Antidepressant Prescribing Over Time

There have been a number of studies in recent years looking at US trends in absolute suicide rates in comparison with trends in antidepressant prescribing. **Grunebaum, et al, 2004** looked at the period 1985 to 1999 and found an overall decrease in the suicide rate of 13.5% at the same time that antidepressant prescribing increased 4-fold, with the increase due mostly to SSRI prescribing. A study by **Gibbons, et al, 2005** looked at a narrower time window (1996-1998) and focused on county-level suicide rates across the age spectrum, with adjustments for age, sex, income, and race. They found no overall relationship between antidepressant prescribing and suicide rate, however, there were significant relationships within antidepressants of different classes. SSRIs and other new-generation antidepressants prescribing was associated with lower suicide rates, while TCA prescribing was associated with increased suicide rates. A more recent study by this same group (**Gibbons, et al, 2006)** looked at this same time window (1996-1998) and used similar methods, but focused on children aged 5-14 and SSRI treatment. They found that higher SSRI prescribing was associated with lower suicide rates. **Milane, et al, 2006** looked specifically at fluoxetine prescribing and suicide rates between the years 1988 and 2002. As others have found, this group also noted a decline in suicide rates since the introduction of this SSRI. Using their modeling they estimated that roughly 33,600 lives have been saved by the introduction of fluoxetine into the US market. As all of the authors of these papers and others note, it is not possible to reach causal conclusions based on these aggregate data. Nevertheless, this consistent finding of declining suicide rates during the same period that antidepressant prescribing has increased is undeniably part of the context for the discussion of risks and benefits of antidepressants.

Goals of the Meeting

We plan to present to you the findings from our meta-analysis of the adult antidepressant suicidality data and our interpretation of these findings. We will also briefly outline our plan for requesting labeling modifications based on these findings. There will not be any specific questions to vote on. However, we will ask you to discuss these findings and our plans for labeling modifications, and we seek your feedback.

Open Public Hearing

There will be an open public session from 10:00 am to 12:00 noon, to provide an opportunity for others in the community to make statements pertinent to this concern about antidepressant drug treatment and emergent suicidality.

Background Package

The background package for this meeting will include several documents in addition to this cover memo. There are two separate review documents, one from Drs. Marc Stone and Lisa Jones from the safety group and a second from Drs. Mark Levenson and Chris Holland from the statistical group. All four reviewers were part of the adult suicidality working group that has worked for many months on this project. Although this was in large part a common effort with extensive cooperation to assemble the data for analysis, there were also individual efforts by these two groups in the data analysis because of somewhat different perspectives on how best to approach these complex data. Since these were exploratory analyses, in the sense that assessing the effect of drugs on suicidality was not a prespecified primary activity for any of these trials, we considered it appropriate to permit parallel analysis efforts to proceed along somewhat different paths for this common data set. In fact, we were gratified to find that the results for these slightly different analytical approaches were substantially the same, as were the conclusions. We feel that the finding of overlapping results from different methods serves to strengthen the results and conclusions.

- A review by Drs. Marc Stone and Lisa Jones from the safety group on a meta-analysis of the adult antidepressant suicidality data.

- A review by Drs. Mark Levenson and Chris Holland from the statistical group on a meta-analysis of the adult antidepressant suicidality data.

- The following published papers:

Fergusson D, Doucette S, Glass KC, et al: Association between suicide attempts and selective serotonin reuptake inhibitors: systemic review of randomized controlled trials. BMJ 2005;330:396-399.

Gunnell D, Saperia J, Ashby D: Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: meta-analysis of drug company data from placebo-controlled, randomized controlled trials submitted to the MHRA's safety review. BMJ 2005;330:385-388.

Hammad T, Laughren T, Racoosin JA: Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry 2006;63:332-339.

Hammad T, Laughren T, Racoosin JA: Suicide rates in short-term randomized controlled tirals of newer antidepressants. J Clin Psychopharmacology 2006;26:203-207.

Martinez C, Rietbrock S, Wise L, et al: Antidepressant treatment and the risk of fatal and non-fatal self harm in first episode depression: nested case-control study. BMJ 2005;330:389-393.

Additional background information on this general topic of antidepressants and suicidality, including documents generated in relation to the February 2nd and September 13-14th advisory committee meetings in 2004 can be found at the following link: http://www.fda.gov/cder/drug/antidepressants/default.htm. Transcript for these meetings can be found at this link as well.

The FDA relies on the knowledge, judgement, experience and wisdom of scientists and practitioners like you to help determine how to move forward and address newly emerging issues related to drug development. We thank you for your time and effort, and we look forward to seeing and hearing from you on December 13th.

References

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Fergusson D, Doucette S, Glass KC, et al: Association between suicide attempts and selective serotonin reuptake inhibitors: systemic review of randomized controlled trials. BMJ 2005;330:396-399.

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Gibbons RD, Hur K, Bhaumik DK, Mann JJ: The relationship between antidepressant prescription rates and rate of early adolescent suicide. Am J Psychiatry 2006;163:1898-1904.

Grunebaum MF, Ellis SP, Li S, Oquendo MA, Mann JJ: Antidepressants and suicide risk in the United States, 1985-1999. J Clin Psychiatry 2004;65:1-7.

Gunnell D, Saperia J, Ashby D: Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: meta-analysis of drug company data from placebo-controlled, randomized controlled trials submitted to the MHRA's safety review. BMJ 2005;330:385-388.

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Martinez C, Rietbrock S, Wise L, et al: Antidepressant treatment and the risk of fatal and non-fatal self harm in first episode depression: nested case-control study. BMJ 2005;330:389-393.

Mayer-Gross W, Slater E, Roth M: *Clinical Psychiatry*. London, England:Bailliere, Tindall, and Cassell; 1960:231.

Milane MS, Suchard MA, Wong M, Licinio J: Modeling of the temporal patterns of fluoxetine prescriptions and suicide rates in the United States. PLoS Med 2006; 3:1-9.

Olfson M, Marcus SC, Shaffer D: Antidepressant drug therapy and suicide in severely depressed children and adults. Arch Gen Psychiatry 2006; 63:865-872.

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Teicher MH, Glod C, Cole JO: Emergence of intense suicidal preoccupation during fluoxetine treatment. Am J Psychiatry 1990; 147:207-210.

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/s/

Thomas Laughren
11/16/2006 06:02:12 PM
MEDICAL OFFICER

CLINICAL REVIEW: RELATIONSHIP BETWEEN ANTIDEPRESSANT DRUGS AND SUICIDALITY IN ADULTS

Application Type	NDA
Submission Number	Bupropion (018-644) Citalopram (020-822, 021-046) Duloxetine (021-427) Escitalopram (021-323, 021-365) Fluoxetine (018-936, 021520) Fluvoxamine (75-888,021-519) Mirtazapine (020-415) Nefazodone (020-152) Paroxetine (020-031, 20-710, 20-936, 021-299) Sertraline (019-839, 020-990) Venlafaxine (020-151, 020-699)
Reviewers' Names	Marc B. Stone, M.D. M. Lisa Jones, M.D.
Review Completion Date	November17, 2006
Established Name	Multiple
(Proposed) Trade Name	Multiple
Therapeutic Class	Multiple Antidepressants
Applicant	Multiple
Formulation	Multiple
Dosing Regimen	Multiple
Indication	Multiple
Intended Population	Users of Antidepressant Products

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1. INTRODUCTION

1.1 Documents and Data Reviewed

1.1.1 FDA Documents

1. Statistical Review and Evaluation: Post-Marketing Drug or Drug Class Safety Evaluations – Statistical Evaluation of Adults treated with Antidepressants. Prepared by Mark Levenson, PhD and Chris Holland, MS. Dated November 17, 2006.
2. Review and Evaluation of Clinical Data: Relationship between psychotropic drugs and pediatric suicidality. Prepared by Tarek Hammad, MD, PhD, MSc, MS. Dated August 16, 2004.
3. Advice for the Pharmaceutical Industry in Exploring their Placebo-Controlled Clinical Trials Databases for Suicidality and Preparing Datasets for Analysis by FDA. Prepared by the Division of Neuropharmacological Drug Products (DNDP). Initial guidance dated November 18, 2004, with revisions dated April 28, 2005, July 21, 2005, and August 2, 2005.
4. NDA Letters: Information Request Letters to Sponsors – Guidance on Preparing Suicidality Datasets. Prepared by the DNP. Dated from December 24, 2004 to May 25, 2005.
5. Review and Evaluation of Clinical Data: Suicidality Studies by Gunnell et al., Fergusson et al., and Martinez et al. Prepared by Alice Hughes MD. Dated May 3, 2005.
6. FDA Public Health Advisory: Suicidality in Children and Adolescents Being Treated with Antidepressant Medications at http://www.fda.gov/cder/drug/antidepressants/SSRIPHA200410.htm. Dated October 15, 2004.
7. FDA Internet Publication: Background Information on the Suicidality Classification Project at http://www.fda.gov/cder/drug/antidepressants/classificationProject.htm.

1.1.2 Sponsor Datasets and Documents

1. NDA 18-644 (Bupropion/Wellbutrin ®): Suicidality Datasets. Prepared by GlaxoSmithKline. Dataset for trials in Major Depressive Disorder (MDD) submitted[1] September 16, 2005, January 26, 2006, July 13, 2006, August 17, 2006 and September 20, 2006. Dataset for all other indication submitted December 21, 2005, January 26, 2006, July 13, 2006, August 17, 2006 and September 20, 2006.
2. NDA 20-822, 021-046 (Citalopram/Celexa ®): Suicidality Datasets. Prepared by Forest Pharmaceuticals. Dataset for trials in Major Depressive Disorder (MDD) submitted September 16, 2005. Dataset for all other indication submitted November 22, 2005.
3. NFA 021-427 (Duloxetine/ Cymbalta ®): Suicidality Datasets. Prepared by Eli Lilly and Company. Datasets for all indications submitted September 15, 2005.
4. NDA 021-323, 021-365 (Escitalopram/Lexapro ®): Suicidality Datasets. Prepared by Forest Pharmaceuticals. Dataset for trials in Major Depressive Disorder (MDD) submitted September 16, 2005, January 31, 2006, April 4, 2006 and July 26, 2006. Dataset for all other indication submitted November 22, 2005, January 31, 2006, April 4 2006 and July 26, 2006.

1 Submission date refers to the date the datasets were available to FDA reviewers within the FDA's electronic document room. The dates of information submitted through other channels, such as by electronic mail, are not included in this listing.

5. NDA 18-936 (Fluoxetine/Prozac ®): Suicidality Datasets. Prepared by Eli Lilly and Company. Dataset for trials in Major Depressive Disorder (MDD) submitted September 29, 2005, January 30, 2006, April 24, 2006, and June 19, 2006 . Dataset for all other indication submitted November 17, 2005, January 30, 2006, April 24, 2006, and June 19, 2006.
6. NDA 21-519, 75-888 (Fluvoxamine/Luvox ®): Suicidality Dataset. Prepared by Solvay, Dataset for trials in Major Depressive Disorder (MDD) submitted September 16, 2005. Dataset for all other indication submitted December 21, 2005.
7. NDA 20-415 (Mirtazapine/Remeron ®): Suicidality Dataset. Prepared by Organon. Dataset for trials on all indications submitted October 3, 2005 and January 30, 2006.
8. NDA 20-152 (Nefazodone/Serzone ®): Suicidality Dataset. Prepared by Bristol Myers Squibb. Dataset for trials in Major Depressive Disorder (MDD) submitted November 15, 2005, January 26, 2006, and June 20, 2006. Dataset for all other indication submitted December 8, 2005, January 26, 2006, and June 20, 2006.
9. NDA 20-031, 20-710, 20-936, 021-299 (Paroxetine/Paxil ®): Suicidality Dataset. Prepared by GlaxoSmithKline. Dataset for trials in all indications submitted December 23, 2005, January 25, 2006, March 8, 2006, April 5, 2006, and May 8, 2006.
10. NDA 19-839, 20-990 (Sertraline/Zoloft ®): Suicidality Dataset. Prepared by Pfizer. Dataset for trials in Major Depressive Disorder (MDD) submitted September 16, 2005, August 15, 2006, and September 27, 2006. Dataset for all other indication submitted November 17, 2005, August 15, 2006, and September 27, 2006.
11. NDA 20-151 (Venlafaxine/Effexor ®), NDA 20-699 (Effexor XR ®): Suicidality Datasets. Prepared by Wyeth. Dataset for trials in Major Depressive Disorder (MDD) submitted September 16, 2005, June 20, 2006. Dataset for all other indication submitted November 17, 2005.
12. NDA 021-427 (Duloxetine/ Cymbalta ®): Preliminary Report: Suicidality Data Update – Age Subgroup Analysis. Prepared by Eli Lilly and Company. Dated July 9, 2006.
13. NDA 20-031, 20-710, 20-936, 021-299 (Paroxetine/Paxil ®): Paroxetine Adult Suicidality Analysis: Major Depressive Disorder and Non-Major Depressive Disorder. Prepared by GlaxoSmithKline, dated April 5, 2006.

1.1.3 Literature Publications

1. Gunnell D, Saperia J, Ashby D. Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: meta-analysis of drug company data from placebo controlled, randomized trials submitted to the MHRA's safety review. BMJ 2005; 330 (7488):385.
2. Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric subjects treated with antidepressant drugs. Arch General Psychiatry 2006 Mar;63(3):332-9.
3. Fergusson D, Douchette S, Glass KC et al. Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomized controlled trials. BMJ 2005;330(7488):396.
4. Bradburn MJ, Deeks JJ, Berlin JA, Localio AR (2006). Much ado about nothing: a comparison of the performance of meta-analytic methods with rare events. Statistics in Medicine 2006. Apr 4 (Electronic publication prior to printed publication) .
5. Hosmer DW and Lemeshow S (2000). Applied Logistic Regression.
6. McCullagh P and Nelder JA (1989). Generalized Linear Models.
7. Whitehead A. (2002). Meta-Analysis of Controlled Clinical Trials.
8. Sauerbrai W and Royston P. Building multivariable prognostic and diagnostic models: transformation of predictors using fractional polynomials. J R Statist. Soc. A 162:71-94.

1.2 Review Content

This review examines the relationship between antidepressant drugs and suicidality in adult subjects, as assessed within randomized, placebo-controlled trials for various indications. This report is patterned after a prior review of pediatric suicidality, performed by FDA reviewer Dr. Tarek Hammad. The trial data analyzed in this review was submitted by the sponsors of the eleven antidepressant drugs studied (bupropion, citalopram, duloxetine, escitalopram, fluvoxamine, fluoxetine, nefazodone, paroxetine, sertraline, mirtazapine, and venlafaxine)[2] in response to FDA requests.

This review also investigates potential sources of inconsistency between trials and/or between drugs by investigating possible sources of variation or imbalance in the data (e.g. trial design, duration of exposure, subject population, age and other potential confounders or effect modifiers).

1.3 Background

1.3.1 Pediatric Suicidality Analysis: Methods

On May 22, 2003, GlaxoSmithKline (GSK) submitted an analysis of suicide-related adverse events in pediatric trials of paroxetine. This analysis found a statistically significant increase in suicidal behavior with paroxetine treatment, as compared to placebo. This finding prompted the Division of Neuropharmacological Drug Products (DNDP) to request that the sponsors of eight other psychotropic drugs tested in children and adolescents perform a search of their databases similar to that performed by GSK. Initial requests for these searches were issued on July 22, 2003. Subsequent requests for additional information were issued on November 24, 2003 and December 9, 2003. The latter requests were issued in part to widen the search, as the DNDP reviewers were concerned that initial event-finding by the sponsors may not have been complete. Based on the initial assessment of the sponsors' responses, the DNDP requested subject-level datasets for covariate exploration to assess possible imbalances among treatment groups. Requests for these data sets were issued on October 3, 2003 and October 28, 2003.

Because of the diverse events subsumed by sponsors under the broad category of "possibly suicide-related," concerns were raised within the Division that not all the captured events represented suicidal thinking and/or behavior. At a joint meeting of the Psychopharmacological Drug Products and Pediatric Subcommittee of the Infectious Diseases Advisory Committees held on February 2, 2004, the Division presented these concerns publicly, and proposed a plan for outsourcing a blinded review of the adverse events of interest to an expert group of suicidologists. Subsequently, all AEs identified by the sponsors as being suicide-related, as well as all serious AEs, all accidental injuries, and all accidental overdoses were independently blindly adjudicated by a group of ten suicidology experts assembled by Columbia University. The adjudication process was applied to the additional AEs mentioned above to provide reassurance that all suicide-related AEs had been identified. In March 2004, while the AEs were being classified by the Columbia panel, DNDP requested additional data on treatment-emergent suicidality as measured by the suicidality item(s) in various depression questionnaires.[3]

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2 Data from drugs containing both an antidepressant and another drug combined, such as Symbyax ®, (a fluoxetine-olanzapine combination drug), were excluded from the analyses contained in this review

3 The two paragraphs in this section (Section 1.3.1) were adapted from the Background section of the pediatric suicidality review performed by Dr. Tarek Hammad, dated August 16, 2004

1.3.2 Pediatric Suicidality Analysis: Results

On September 13 and 14, 2004, the DNDP presented the results of the pediatric suicidality analysis at a joint meeting of the Psychopharmacologic Drugs and the Pediatric Drugs Advisory Committees. The risk of suicidality for these drugs was identified in a combined analysis of short-term (up to four months) placebo-controlled trials of nine antidepressant drugs, including the selective serotonin reuptake inhibitors (SSRIs) and others, in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders. A total of 24 trials involving over 4400 subjects were included. The analysis showed a greater risk of suicidality during the first few months of treatment in those receiving antidepressants. The average risk of such events on drug was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.[4]

No meaningful effect modification or confounding was found for the various covariates analyzed, although it should be noted that the covariates were subject to various degrees of missing data.

1.3.3 Labeling Changes Resulting from the Pediatric Suicidality Analysis

On October 15, 2004, the Food and Drug Administration (FDA) directed manufacturers of all antidepressant drugs to revise the labeling for their products to alert health care providers and subjects to an increased risk of suicidality (suicidal thinking and behavior) in children and adolescents being treated with these agents. These labeling changes were consistent with the recommendations of the Advisory Committee meeting on September 13 and14, 2004 (described in Section 1.3.3 above)[5] and included the following information:

- Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with MDD and other psychiatric disorders.
- Anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need.
- Subjects who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior.
- Families and caregivers should be advised to closely observe the subject and to communicate with the prescriber.
- A statement regarding whether the particular drug is approved for any pediatric indication(s) and, if so, which one(s).

A copy of the “black box” and expanded warnings statements added to the antidepressant labeling is included in Appendix 6.2 of this review.

2. METHODS: DATA COLLECTION

2.1 Data Collection Overview

Due to FDA methodological changes in the collection and coding of data, a series of four data request letters were sent to the sponsors of antidepressant drugs (dated December 24, 2004, April 28, 2005, July 21, 2005, and August 2, 2005). A copy of the August 2005 request letter is provided in Appendix 6.1. The variables included in these datasets provided detailed information about individual subjects. Due to a number of questions and requests that arose during the data

4 http://www.fda.gov/cder/drug/antidepressants/SSRIPHA200410.htm
5 http://www.fda.gov/cder/drug/antidepressants/SSRIPHA200410.htm

cleaning process, sponsor dataset submissions were received by the FDA from September 2005 to September 2006. The datasets were submitted as electronic files (in SAS transport file format).

2.2 Drugs Studied

In total, 8 sponsors of 12 antidepressant products submitted datasets to the DNDP culled from all the randomized controlled trials of their respective drug products conducted in the adult population. The FDA letter requesting this data is included in Attachment 1 of this review.

The antidepressant products included in the request were: bupropion (Wellbutrin®), citalopram (Celexa®), duloxetine (Cymbalta®), escitalopram (Lexapro®), fluoxetine (Prozac®), fluoxetine/olanzapine (Symbyax®)[6], fluvoxamine (Luvox®), mirtazapine (Remeron®), nefazodone (Serzone®), paroxetine (Paxil®), sertraline (Zoloft®), and venlafaxine (Effexor®). The drugs' initial approval date and the class of antidepressant for each drug are summarized in Appendix 6.5.

2.3 Indications Studied

Of note, the FDA request to sponsors was expanded to include randomized, controlled trials of antidepressant drugs for any indication, not only trials for major depressive disorder (MDD). The range of indications in the various studies collected is listed in Appendix 6.4 of this review.

2.4 Trial Inclusion Criteria

The FDA's data request to sponsors (see Appendix 6.1) asked that the trials included in the dataset be limited to completed, double-blind, randomized, placebo-controlled trials. The FDA request letter recommended that only trials with at least 20 subjects per treatment arm be included and stated that trial duration should not be "a limiting factor."

Before the final dataset was submitted, the FDA request letter asked sponsors to provide a list of the trials the sponsor planned to include in and exclude from the dataset. The FDA provided feedback[7] to the sponsors on which trials should be included in the final dataset.

2.5 Trials Excluded

Eight sponsors of twelve primary drugs submitted data from 406 clinical trials incorporating 103,491 subjects. Twenty-eight trials were excluded: 23 because at least one trial arm contained fewer than twenty subjects, two because only adverse event report data could be obtained, three because the active drug was a combination agent consisting of an antipsychotic (olanzapine) and an antidepressant (fluoxetine) and another six trials were duplicated in submission. In addition 608 subjects from other trials were excluded because they were assigned to an active control drug that was not an antidepressant agent. After exclusions and eliminating duplications, there were 372 trials with 99,839 subjects. Table 1 summarizes submissions by sponsor.

6 Data from drugs containing both an antidepressant and another drug combined, such as Symbyax ®, (a fluoxetine-olanzapine combination drug), were excluded from the analyses contained in this review

7 NDA Letters prepared by Russell Katz MD, dated December 24, 2004.

Table 1: Submissions by Sponsor: Trials of Antidepressant Drugs in Adults

	Before Exclusions		After Exclusions	
Sponsor	Trials	Subjects	Trials	Subjects
BMS	26	6121	25	6084
Forest	29	10,371	24	8622
GSK	89	27,202	86	26,706
Lilly	109	27,809	97	26,538
Organon	17	2626	15	2446
Pfizer	68	11,991	60	11,725
Solvay	28	4941	26	4820
Wyeth	40	12,430	39	12,290
Total	406	103,491	372	99,231

2.6 Summary of Trial Characteristics

The FDA data request letter asked sponsors to summarize the characteristics of the trials included in the datasets in the form of two tables: one providing the dose, duration and number of subjects per trial, and the other providing the trial exclusion criteria.

2.7 Dataset Variables

2.7.1 Information Requested in Dataset

The dataset requested from the sponsors was composed of the following variables (Table 2):

Table 2: Variables in the Sponsor Suicidality Datasets requested by the FDA

Variable Category	Variables	Description
Trial identifiers	Indication	Study Indication
	Trial Identifier	Unique Trial Identifier
	Subject Identifier	Unique Subject Identifier
Trial-related variables	Trial Setting	Inpatient or Outpatient
	Trial Location	North America and Non-North America
	Premature Discontinuation from Trial	Subject discontinued before the end of the controlled portion of the trial (Coded as Yes or No)
Subject demographic information	Age	Subject Age
	Gender	Subject Gender
	Race	Subject Race
Treatment-related variables	Treatment Group	Subject's treatment group (drug, placebo or active control)
	Active Control Drug	Name of active control drug, if present
Disease-related variables	Symptom Scale	Primary scale used to rate indication that is focus of the trial (Required for depression trials only)
	History of Prior Suicide Attempt	History of suicide attempt prior to entering the trial, as defined by relevant items within the baseline depression questionnaire (Required for depression trials only)
	History of Prior Suicidal Ideation	History of suicidal ideation prior to entering the trial, as defined by: relevant items within the baseline depression questionnaire (Required for depression trials only)
	Baseline Score	Score of primary scale at baseline (Required for depression trials only)
	End of Trial Score	Score of primary scale at end of trial (Required for depression trials only)
	Response	Whether subject judged as responding to treatment or not
Outcome-related variables	Suicidality Event	This variable contains the code for the subject's most severe suicidality event (See Section 2.8.5 for additional details
	Time to Event or Time on Study Drug	For subjects with more than one event, this variable contained days until the first most severe event. For subjects without events, this variable contained days until end of trial or until premature discontinuation.

2.7.2 Additional Variables on Subject Deaths

Upon review of the initially submitted suicidality datasets, the FDA recognized that the data could potentially be biased by informative censoring. For example, if propensity to suicide was associated with intolerance of drug side effects, subjects who eventually have a suicidality event may leave the study before experiencing the event if they are assigned to drug but stay in the trial if they are assigned to placebo. Conversely, placebo subjects may drop out of a study due to a lack of relief from symptoms other than suicidality and later have a suicidality event but subjects assigned to antidepressants may experience sufficient relief of non-suicidality symptoms that they remain in the trial until a suicidality event occurs. This type of problem is difficult to verify because little information is consistently and reliably available on subjects after they leave a study. We concluded that the only information likely to be consistently available would be information about any deaths that may have occurred in subjects after leaving the study. We therefore requested information on death by any cause occurring within the period ending 90 days after the intended treatment period in order to look for informative censoring.

2.8 Determination of Suicidality Outcomes

2.8.1 Identification of Suicidality Events

In contrast to the FDA's prior review of pediatric suicidality data, possibly suicide-related adverse events (PSRAEs) in the adult subjects were adjudicated by the sponsors and submitted within the dataset without FDA verification. The reason for this difference in methodology was the large number of subjects (approximately 100,000) in the adult suicidality analysis, which made impracticable more detailed adjudication of all potentially suicidal behaviors by the FDA.

The FDA's data request letter asked sponsors to search (1) all preferred terms; (2) all verbatim terms; and, (3) any comment fields within the trials for the following text-strings:

> "accident-", "attempt", "burn", "cut", "drown", "gas", "gun", "hang", "hung", "immolat", "injur-", "jump", "monoxide", "mutilat-", "overdos-", "self damag-", "self harm", "self inflict", "self injur-", "shoot", "slash", "suic-", "poison", "asphyxiation", "suffocation", "firearm"

All events identified by this search were considered PSRAEs, unless they were identified as "false positive" results (See Section 2.8.2 below).

The FDA request letter instructed sponsors that the search should be strictly limited to adverse events occurring during the double-blind phase of treatment, or within one day of stopping randomized treatment (i.e. events occurring prior to randomization or more than one day after discontinuing from randomized treatment should be excluded). The end of trials with a tapering period should be considered as the beginning of the tapering period. Events occurring more than one day after discontinuing from randomized treatment were excluded even if discontinuation occurred before the nominal endpoint of the trial.

The FDA data request letter acknowledged that events preexisting at baseline are generally not counted as treatment emergent if they recur during the course of a trial. However, in the suicidality dataset requests, the sponsors were asked to include suicidality-related events that occurred during the course of the double-blind phase or within one day of beginning taper, switching or stopping treatment, even if they occurred in a subject who had such events at some prior time. The FDA made this request because it is generally difficult to determine, for the

quality of data available in most of these trials, whether suicidality occurring during these trials is new or a continuation of some prior event.

The sponsor was asked to prepare a clinical narrative for all possibly suicide-related events identified by the search described above. Narratives were to be redacted prior to their classification with respect to suicidality so that classifiers would be blinded to treatment assignment when making their assessments.

2.8.2 "False Positive" Events

"False positive" events, which included the key words above but were not suicide-related, were also identified by the sponsor searches (For example, "epigastric pain" identified in the search for the key word "gas"). As per the FDA request, the sponsors submitted listings of the events they classified as "false positives" which included the subject and study number, treatment assignment and the term in which the key word occurred.

2.8.3 Adjudication of Suicidality Events

The FDA data request letter asked the sponsors to perform a rational classification of the possibly suicide-related adverse events (PSRAEs) using the approach developed by Dr. Kelly Posner and others of the Columbia group for the pediatric suicidality narratives.[8] This approach was described at the September 13 and 14, 2004 advisory committee meeting[9], details of which are provided in Appendix 6.3 of this review.

The FDA's data request letter specified that the persons who classify the PSRAE narratives must have the appropriate expertise and training to accomplish this task. The letter also noted that a sponsor may have internal staff with the ability to classify the events, although training from a skilled outside contractor was recommended.

Prior to the rational classification of the PSRAEs, the FDA letter asked sponsors to prepare narratives with details that might bias the classification removed. The details of appropriate blinding of the narratives are described in the transcript from the September 13 and 14, 2004 advisory committee and in other related materials available on FDA's website.

2.8.4 Data Processing

The data received from sponsors underwent quality checks. For each drug, this included verifying the number of trials, the number of subjects within each treatment group for each trial, and the range or set of values for each variable. Questions arising from the quality checks were sent to the appropriate sponsor for resolution. In some cases, the necessary data were not available. The amount of missing data for the analysis variables was minimal.

The values of the variable representing time to event or time in study (for subjects without an event) were compared to the nominal durations of the corresponding trials. Several rules were applied to resolve apparent disparities. For subjects with events, if the value was more than 14 days beyond the nominal duration of the trial, the corresponding event was not counted. If this event was ideation, the variable event was assigned the value of 0. For events more severe than ideation, the sponsor was asked to search for events prior to this event. If the value was missing

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8 Review and Evaluation of Clinical Data: Relationship between psychotropic drugs and pediatric suicidality. Prepared by Tarek Hammad, MD, PhD, MSc, MS. Dated August 16, 2004.
9 http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4065S1_06_FDA-Posner.ppt; http://www.fda.gov/ohrms/dockets/ac/cder04.html#PsychopharmacologicDrugs

and could not be determined by the sponsor, the corresponding event was assumed to occur during the exposure window of the trial. For subject without events, the value was truncated to the nominal duration of the trial plus 14 days. Except for this variable, no missing values were imputed.

2.8.5 Classification of Suicidality Events

The FDA asked the sponsor to classify suicide-related events using the coding in Table 3.

Table 3: Coding of suicide-related events within the suicidality datasets

Event	Coding
Completed suicide	1
Suicide attempt	2
Preparatory acts toward imminent suicidal behavior	3
Suicidal ideation	4
Self-injurious behavior, intent unknown	5
Not enough information (Fatal)	6
Not enough information (Non-Fatal)	9

This ordering can be considered to be a ranking according to specificity for risk of suicide. For subjects with multiple outcomes, the sponsors were asked to submit only the most severe outcome, as ranked by the coding table above (e.g., a completed suicide [Code 1]), would rank higher than a suicide attempt [Code 2], and a subject with both events would be coded as a completed suicide only). Because sponsors were asked to report only the most specific event that occurred for each subject, only completed suicide can be considered by itself. Because it is not known from this dataset whether subjects for whom one outcome is reported also had other events that were less specific, it is necessary to assess these outcomes in a hierarchical manner; each level of outcome listed must also include the more specific outcomes. For example, analyses of suicidal ideation cannot address suicidal ideation alone. The analysis must be of suicidal ideation *or worse*, including preparatory acts, suicide attempts and completed suicides.

3. METHODS: STATISTICAL ANALYSIS

3.1 Outcome Variables

The primary outcome is suicidal ideation or worse (outcomes 1, 2, 3 or 4 above), also called suicidality or suicidal behavior and ideation. This corresponds to the primary outcome (Definitive suicidal behavior/ideation) used in the study of pediatric suicidality. Secondary analyses use outcome variables of greater or lesser specificity. The principal secondary outcome variable is preparatory actions or worse (outcomes 1, 2, or 3), also called suicidal behavior.

3.2 Principal Hypothesis to be tested

The primary objective of this review is to estimate the effect of antidepressant drugs versus placebo on suicidal outcomes in double-blind, randomized, placebo-controlled clinical trials of adults. The secondary objective of this review is to examine the effect of antidepressant drugs versus placebo on suicidal outcomes in double-blind, randomized, placebo-controlled clinical trials for various subgroups defined by subject-level and trial-level characteristics and indication groups.

H_0: There is no difference in the incidence of suicidality (defined as suicidal ideation or worse) between antidepressant drugs and placebo in clinical trials.

H_A: There is a difference in the incidence of suicidality (defined as suicidal ideation or worse) between antidepressant drugs and placebo in clinical trials.

The alternative hypothesis is stated to include either a positive or negative association.

3.3 Methods of Pooling

3.3.1 Trial-level Meta-analysis

In order to obtain results that are most comparable to the results reported in the analysis of pediatric suicidality, trial-level results were pooled using meta-analytic methods using both fixed effects (Mantel-Haenszel) and random effects (DerSimonian-Laird) models. The statistic pooled was the odds ratio calculated from the number of subjects with and without events in the treatment and control arms. Trials that had no outcome events in either arm were not included in these meta-analyses and the results from active control arms were also excluded (including active control arms would require double-counting of placebo arms). For trials with events in one group and no events in its comparison group, a "continuity correction" of 0.5 was added to each of the four cells used to calculate the odds ratio. For purposes of consistency, the result of the fixed effects model was considered the principal analysis for hypothesis testing.

These approaches to estimating the odds ratio are asymptotic. The validity of asymptotic methods may be questionable when the number of trials, the number of patients per trial, and the rate of events are not high or when there are imbalances in the sizes of the treatment groups. In the present review, the rate of events is low and treatment group size is often imbalanced; this may call into question the validity of asymptotic methods. For certain subgroup analyses, the number of patients per trial may be low, as well.

An alternative to asymptotic methods is the "exact method." The method is valid even under the conditions described above, such as low event rates and small numbers of patients per trial. The exact method is based on trial-level summaries and assumes that each trial is independent. Like other methods based on trial-level summaries, the active control data could not be considered in the same analysis as the primary drug analysis, because the inclusion would violate the independence assumption.

The exclusion of trials with no events in either placebo or primary active drug arms is problematic. The absence of events provides some information because of the background rate of events independent of drug effect. There is, in fact, a potential inclusion bias created by systematically excluding trials with no events in either arm that is similar to publication bias, the tendency to publish small studies only if they have positive results. If there are consistently more subjects in the active drug arms, the absolute number of events that occur simply due to background event rates (without any drug effect) will be greater in the active drug arms, the probability of having at least one event in any single trial will be greater in the active drug arms and the probability of no events will be greater in the placebo arms. This means there should be more studies with events in the active drug arm and no events in the placebo arm than the converse even if there is no drug effect. For the same reason, the absence of events in either arm would be weak evidence of a lesser propensity for events in the larger (active drug) arm but this evidence would be excluded.

3.3.2 Individual Data Stratified by Trial

The trial level meta-analysis method has drawbacks and limitations. Most importantly, it does not take advantage of the availability of individual level data. Individual level data allows the examination of the effects of covariates such as age and gender and specific adjustments for length of exposure. Another problem is the arbitrariness of the "continuity correction" when there are arms with no events which could create a biased estimate of the relative risk and its confidence intervals.

These problems are avoided by analyzing the individual data from all trials as a single dataset. These data cannot, however, be treated as the results of a single experiment. The proportions of subjects allocated to active drug or placebo differ across trials and the trials themselves differ in length and other aspects of protocol. For this reason it is necessary to stratify the results by trial and adjust standard errors for intra-trial correlation.

Logistic regression models can be used to model the odds ratio on the patient level and allow for the adjustment and modeling of patient-level characteristics. Also, because the model requires that patients, not trials, be independent conditional on the model, active-control arms of the trials can be included. The basic logistic regression model uses a maximal likelihood approach to estimation. Maximal likelihood has asymptotic properties; its use is justified when the number of patients relative to the number of parameters is large. In the meta-analysis model, there is a parameter for each trial. If the number of patients per trial is not high, maximal likelihood estimation may not be valid.[10] An alternative is to use conditional logistic regression. Conditional logistic analysis differs from regular logistic regression in that the data are grouped and the likelihood is calculated relative to each group; i.e., a conditional likelihood is used.[11] The conditioning and the resulting likelihood is the same as in the exact method. For these reasons, conditional logistic regression was chosen as the principal statistical approach for this meta-analysis. To look for heterogeneity of effect, analyses were repeated, first with a treatment*drug interaction term then with a treatment*drug class interaction term.

3.3.3 Methods that Consider Random Effects

Another issue in estimating an overall odds ratio is the assumption that the individual trials have a common odds ratio. Methods that assume a common odds ratio across trials, such as Mantel-Haenszel, conditional logistic regression and the exact method are known as "fixed effects" models. Models that relax this assumption to allow for the odds ratios to vary across a normal distribution are known as "random effects models. The method of DerSimonian and Laird is a traditional meta-analysis random effect method.[12] The method generalizes the inverse-weighting method to allow for a variance component due to trial effect heterogeneity. For meta-analysis with low event rates, the method is not recommended because like the inverse-weighting method, it makes use of the within-trial variance estimates, which may be imprecise in the low event setting.[13] A generalization of the logistic model, known as a generalized linear mixed model (GLMM) was used to explore allowing the odds ratios to vary by trial.[14]

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10 McCullagh P and Nelder JA (1989). Generalized Linear Models. p.266 and Hosmer DW and Lemeshow S (2000). Applied Logistic Regression, p. 224.

11 See McCullagh and Nelder (1989) chapter 7 and Hosmer and Lemeshow (2000) chapter 7. The conditional models do not include a parameter for each trial and do not require that the number of patients per trial be large in order to use asymptotic methods.

12 Whitehead A. (2002). Meta-Analysis of Controlled Clinical Trials.

13 Bradburn MJ, Deeks JJ, Berlin JA, Localio AR (2006). Much ado about nothing: a comparison of the performance of meta-analytic methods with rare events. Statistics in Medicine, in press.

14 McCulloch CE and Searle SR (2001). Generalized, Linear, and Mixed Models.

3.3.4 Methods that Consider Time to Event

The conditional logistic regression model does not consider length of exposure or time to event. Length of exposure may be important for two reasons. First, the background incidence rate of suicidality among subjects will obscure over time any differences in rates that may be attributable to drug; as the length of a trial increases, the odds ratio for suicidality will approach unity. Second, the likelihood of suicidality may be affected by the length of exposure to drug.

3.4 Subgroups

The submitted datasets contain a number of fields with which to describe subject and trial characteristics that may have influence on the incidence or detection of suicidality. For purposes of exploration, analyses were performed according to sex, trial location (within or outside North America) and whether a drug was the primary trial drug or an active control.

Treatment indications were classified into one of five groups by medical officers in the Divisions of Psychiatric Products and Neurology Products. Four cumulative indication groups were created based on a hierarchical ordering of these five groups, as shown in Table 4.

Table 4: Hierarchical Classification of Indications

All Indications	*Other Disorders*			
	Psychiatric and Behavioral Indications	*Behavioral Disorders*		
		Psychiatric Indications	*Other Psychiatric Disorders*	
			Depression Indications	*Other Depression Disorders*
				Major Depressive Disorder

Non-cumulative indication groups are italicized.

The indications that make up each group can be found in Appendix 6.4.

A medical officer from the Division of Neurology Products classified the 24 drugs into 5 classes:

1. Selective serotonin reuptake inhibitors (SSRIs)
2. Serotonin-norephrine reuptake inhibitors (SNRIs)
3. Other modern antidepressants
4. Tricyclic antidepressants
5. Other antidepressants.

Table 5 gives the classification of the 24 drugs into the five classes and two general categories, “Newer” and “Older”.

Table 5: Classification of Antidepressant Drugs

Newer Drugs			Older Drugs	
SSRI	**SNRI**	**Other Modern Antidepressants**	**Tricyclics**	**Other Antidepressants**
Citalopram	Duloxetine	Bupropion	Amitriptyline	Mianserin
Escitalopram	Venlafaxine	Mirtazapine	Clomipramine	Trazodone
Fluoxetine		Nefazodone	Desipramine	
Fluvoxamine			Dothiepin	
Paroxetine			Imipramine	
Sertraline				

Because age is a variable of particular interest due to the association of suicidality with antidepressant use in the pediatric population, analyses were performed using age and the interaction of age with treatment to explore linear or curvilinear relationships between age, treatment and measures of suicidality and treatment efficacy using multivariable fractional polynomial models[15]. Extensive categorical analyses of age were also performed (Table 6):

Table 6: Age Categories

	Categories
Young vs. Older Adults	<25, 25+
Young, Middle-aged and Elderly	<25, 25-64, 65+
Age by Decade	<25, 25-34, 35-44, 45-54, 55-64, 65-74, 75+
Age by Double Decade	<25, 25-44, 45-64, 65+

4. RESULTS

4.1 Characteristics of the data

Table 7 shows the number of subjects assigned to drug (as primary drug or active control) and placebo by drug and drug class.

15 Sauerbrai W and Royston P. Building multivariable prognostic and diagnostic models: transformation of predictors using fractional polynomials. J R Statist. Soc. A 162:71-94.

Table 7: Numbers of subjects by drug, drug class and treatment assignment

Drug	Primary	Active Control	Placebo
SSRI			
Citalopram	1,928	733	1,371
Escitalopram	2,567	563	2,604
Fluoxetine	9,070	2,418	7,645
Fluvoxamine	2,187	0	1,828
Paroxetine	8,728	1,223	7,005
Sertraline	5,821	1,129	5,589
SNRI			
Duloxetine	6,361	0	4,172
Venlafaxine	5,693	129	4,054
Other Modern Antidepressants			
Bupropion	6,018	0	3,887
Mirtazapine	1,268	0	726
Nefazodone	3,319	0	2,173
Tricyclic Antidepressants			
Amitriptyline	0	625	627
Clomipramine	0	632	617
Desipramine	0	315	298
Dothiepin	0	106	95
Imipramine	0	2,345	2,304
Other Antidepressants			
Mianserin	0	28	28
Trazodone	0	121	125
All Drugs	**52,960**	**10,367**	**35,904**

The median number of subjects per trial assigned to the primary drug was 109.5 while the median number of placebo subjects was 89. When a trial contained an active control arm the median number of subjects assigned to the active control was 88.5. A summary of demographic information is given in Table 8.

Table 8: Demographic data

Age		
	Mean	43.1
	Median	42
	Range	15-99
	Under Age 25	8.0%
	Age 65+	8.6%
Sex		
	Female	63.1%
	Male	36.9%
Ethnicity		
	White	86.9%
	Black	5.2%
	Hispanic	3.5%
	Asian	2.7%
	Other	1.6%
Location		
	North America	75.5%
	Outside N.A.	24.5%
Indication Class		
	Major Depression	45.6%
	Other Depression	4.6%
	Other Psychiatric	27.6%
	Behavioral	13.5%
	Other	8.7%

The sum of duration of observation for all subjects was 15,505 subject-years. During that period of observation there were eight subjects who committed suicide, 134 subjects who only attempted suicide, ten subjects who made preparatory actions without ever attempting suicide and 378 subjects who reported suicidal ideation without taking any action. The incidence rates for these events per 10,000 subject-years by treatment indication are given in Table 9. The incidence rates for suicidality in subjects with major depression are notably higher than the other diagnostic groups. The incidence rates for other depressive disorders and psychiatric disorders other than depression are similar and, while lower than the incidence rates for major depression, are generally of the same order of magnitude as for major depression. The rates observed for other behavioral disorders and other disorders are associated almost entirely with ideation alone and not suicidal actions. The variability in incidence rates across diagnostic categories would tend to invalidate any pooling of risk differences rather than risk ratios. For subjects in the three psychiatric categories, the ratio of the number of subjects with ideation alone to those who attempted suicide is roughly three to one (361/133) while in the non-psychiatric categories there were eighteen cases of ideation alone but only one suicide attempt ($p=0.03$ by Fisher's exact test).

Table 9: Incidence rates for suicidality events by diagnostic category

Events per 10,000 subject years				Indication
Completed	Attempt	Preparation	Ideation	
5.1	86	6.4	244	All
10	157	12	416	Major Depression
0	81	12	163	Other Depression
4.1	73	4.1	220	Other Psychiatric
0	4.2	0	34	Other Behavioral
0	0	0	60	Other

The differences in incidence rates between the psychiatric and non-psychiatric diagnostic categories have three important implications. First, the incidence of suicidality events in the non-psychiatric categories is so low that these categories will have little influence in any pooled estimate of the influence of antidepressant drugs on suicidality. Second, the differences in the ratios of suicidal ideation to suicide attempts between psychiatric and non-psychiatric diagnoses would suggest that any results based primarily upon subjects with psychiatric diagnoses are not generalizable to subjects with non-psychiatric diagnoses. Finally, the rarity of suicidality events among subjects with non-psychiatric disorders makes it impossible to estimate with any precision what effect, either positive or negative, antidepressant drugs may have on suicidality in these subjects.

4.2 Estimates of Suicidality Risk Associated with Antidepressant Treatment

4.2.1 Adults with All Indications

Table 10 shows estimates of suicidality risk (ideation, preparatory acts, attempts and completed suicide) associated with assignment to antidepressant drug treatment compared to placebo observed from the entire dataset. All of the estimates show a slightly lower risk with antidepressant drug treatment that is not statistically significant.

Table 10: Suicidality Risk for Active Drug relative to Placebo– Ideation or Worse – All Adults – All Diagnoses

Estimate	95% Confidence Interval	p value	Method
0.85	0.71 – 1.02	0.08	Odds Ratio - Conditional Logistic Regression
0.86	0.71 – 1.04	0.12	Odds Ratio – Exact Method (excluding active controls)

The estimated odds ratio for suicide-related behavior (preparatory acts, attempts and completed suicide) associated with assignment to antidepressant drug treatment compared to placebo observed from the entire dataset was 1.12 (95% CI, 0.79 – 1.58, by conditional logistic regression), a slightly higher risk with antidepressant drug treatment that is not statistically significant.

Table 11 and Figure 1 compare suicidality risk by indication group.

Table 11: Suicidality Risk for Active Drug relative to Placebo – Ideation or Worse – All Adults – By Indication

Odds Ratio	95% Confidence Interval	p value	Diagnostic Category
0.85	0.67-1.07	0.16	Major Depression
0.90	0.38-2.14	0.81	Other Depression
0.85	0.68-1.06	0.16	All Depression
0.79	0.56-1.11	0.17	Other Psychiatric Diagnoses
0.83	0.69-1.00	0.05	All Psychiatric Diagnoses
1.43	0.35-5.86	0.62	Behavioral Disorders
1.51	0.42-5.40	0.53	Other Disorders
1.47	0.57-3.79	0.42	Non-Psychiatric Disorders

Note: all estimates were obtained using conditional logistic regression

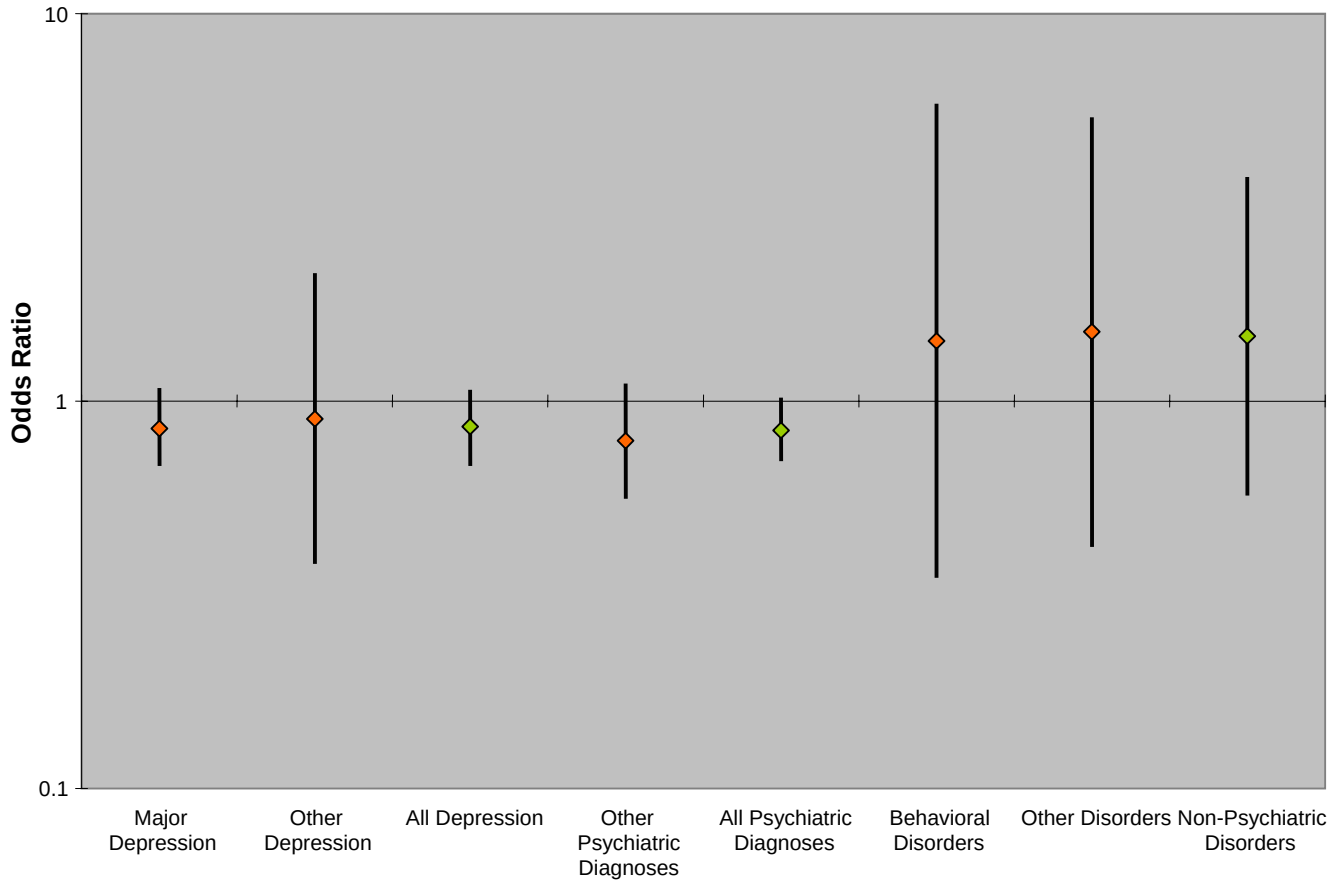

Figure 1: Suicidality Risk for Active Drug relative to Placebo – Ideation or Worse – All Adults – By Diagnostic Category (Bands represent 95% CI)

The odds ratios shown here are not widely different from each other, but the psychiatric diagnostic categories (Major Depression, Other Depression and Other Psychiatric) are remarkably similar while the non-psychiatric categories appear similar to each other but distinct from the psychiatric categories. These differences, however, are not statistically significant (Table 12). Thus while it cannot be concluded that suicidality risk associated with antidepressants is different in the non-psychiatric categories than what is seen in the psychiatric categories, these observations support the idea that there is insufficient information about

suicidality events in the non-psychiatric diagnostic categories to make any conclusions and that a pooled estimate that combines observations across all diagnostic categories will be largely determined by the events observed in trials of subjects with psychiatric diagnoses and may be misleading if it is applied to subjects with non-psychiatric diagnoses. Therefore, unless specified, all further analyses in this review will be limited to clinical trials of subjects with psychiatric diagnoses.

Table 12: Interaction of Treatment with Diagnostic Category for Suicidality Risk – Ideation or Worse – All Adults

Odds Ratio for Interaction	95% Confidence Interval	p value	Comparison
NA	NA	0.76	Equality of Odds Ratio across all categories
NA	NA	0.89	Equality of Psychiatric categories
1.77	0.67-4.65	0.25	Non-Psychiatric vs. Psychiatric

Note: all estimates were obtained using conditional logistic regression
NA – not applicable

4.2.2 Sensitivity to Method

Table 13 compares estimates of suicidality risk attributable to assignment to antidepressant treatment for adults with psychiatric disorders as calculated by the range of methods described in Section 3.3. To assure comparability, all methods exclude subjects treated with active controls.

Table 13: Comparison of Estimates of Suicidality Risk for Adults with Psychiatric Disorders

Estimate	95% Confidence Interval	Method
Fixed Effects Models		
0.81	0.68 – 0.97	Mantel-Haenszel with continuity correction
0.84	0.69 – 1.02	Mantel-Haenszel
0.84	0.69 – 1.02	Exact Method
0.84	0.69 – 1.02	Logistic Regression
Random Effects Models		
0.83	0.68 – 1.01	DerSimonian-Laird
0.84	0.68 – 1.02	Logistic Regression

The results are virtually identical with the exception of the Mantel-Haenszel approach when a continuity correction is included, indicating that the inclusion of this correction in so many trials can bias the results. In contrast, there appears to be no difference between the results obtained with fixed effects and those obtained with random effects models. These findings support the use of fixed effects logistic regression as the principal modeling approach because it is both flexible and computationally efficient and produces results that are very close to those obtained with other methods.

4.2.3 Adults with Psychiatric Disorders

Table 14 shows estimates of the effect of any possible interaction of treatment with subgroups other than age on the risk of suicidality and suicidal behavior. The “relative likelihood” given in the Table is the ratio of the odds ratios for suicidality or suicidal behavior for the factors being compared. None of these factors appears to have had a meaningful effect on the results. Most notably, the estimated odds ratios for active controls are very similar to those obtained with

primary drugs. This would indicate there is little justification for separating primary drugs and active controls in the analyses. Unless noted otherwise, primary drugs and active controls will be considered together.

Table 14: Interaction of Treatment with Subgroups – Adults with Psychiatric Diagnoses

Relative Likelihood	95% Confidence Interval	p value	Comparison
1.05	0.76-1.46	0.75	Primary Drug vs. Active Control – Suicidality (Ideation or Worse)
0.94	0.53-1.65	0.83	Primary Drug vs. Active Control – Suicidal Behavior (Preparation or Worse)
0.85	0.56-1.31	0.46	Outside North America Vs. North America – Suicidality (Ideation or Worse)
0.77	0.38-1.58	0.48	Outside North America Vs. North America – Suicidal Behavior (Preparation or Worse)
0.84	0.58-1.22	0.36	Male vs. Female – Suicidality (Ideation or Worse)
0.97	0.46-2.01	0.93	Male vs. Female – Suicidal Behavior (Preparation or Worse)
NA	NA	0.90	Equality across ethnic groups – Suicidality (Ideation or Worse)
NA	NA	0.85	Equality across ethnic groups – Suicidal Behavior (Preparation or Worse)
NA	NA	1.00	Equality across clinical trials– Suicidality (Ideation or Worse)
NA	NA	1.00	Equality across clinical trials – Suicidal Behavior (Preparation or Worse)

Note: all estimates were obtained using conditional logistic regression
NA – not applicable

As shown in Tables 15 and 16, the odds ratios for suicidality and suicidal behavior attributable to antidepressant treatment in adults with psychiatric disorders are 0.83 and 1.10, respectively. Table 15 and Figure 2 show the odds ratios for suicidality among subjects with psychiatric diagnoses by drug and drug class. Although the values for some individual drugs are statistically significant at the 0.05 level, the significance of those findings must be discounted for the large number of comparisons being made. Most statistical tests for differences in effect among drugs and drug classes were negative, with the exception of an indication of differences among drugs in the SSRI category. The likelihood ratio for suicidality from older drugs relative to newer drugs was 0.84 (95% CI 0.54 – 1.31, p = 0.44).

Table 15: Suicidality Risk for Active Drug relative to Placebo – Ideation or Worse –Adults with Psychiatric Disorders – By Drug and Drug Class

Drug Class Drug	Odds Ratio	95% Confidence Interval	p value
All Drugs	**0.83**	**0.69 - 1.00**	**0.05**
SSRI	**0.86**	**0.69 - 1.06**	**0.16**
Citalopram	2.11	0.90 - 4.94	0.08
Escitalopram	2.44	0.90 - 6.63	0.08
Fluoxetine	0.71	0.52 - 0.99	0.04
Fluvoxamine	1.25	0.66 - 2.39	0.49
Paroxetine	0.93	0.62 - 1.42	0.75
Sertraline	0.51	0.29 - 0.91	0.02
Equality within class	NA	NA	0.02
SNRI	**0.81**	**0.56 - 1.19**	**0.28**
Duloxetine	0.88	0.47 - 1.63	0.68
Venlafaxine	0.71	0.44 - 1.16	0.17
Equality within class			0.60
Other Modern Antidepressants	**0.83**	**0.49 – 1.41**	**0.49**
Bupropion	1.35	0.45 - 4.06	0.59
Mirtazapine	0.97	0.34 - 2.78	0.96
Nefazodone	0.65	0.30 - 1.41	0.28
Equality within class	NA	NA	0.55
Equality across “Newer” drugs	NA	NA	0.16
Tricyclic Antidepressants	**0.71**	**0.45 - 1.12**	**0.14**
Amitriptyline	0	0 - inf	0.99
Clomipramine	0.49	0.18 - 1.34	0.17
Desipramine	0.63	0.06 - 6.25	0.69
Dothiepin	0	0 - inf	0.99
Imipramine	0.88	0.50 - 1.53	0.64
Equality within class	NA	NA	0.91
Other Antidepressants	**0.61**	**0.06 - 5.95**	**0.67**
Mianserin	0.86	0.08 - 9.78	0.90
Trazodone	0	0 - inf	0.99
Equality within class	NA	NA	0.99
Equality across “Older” drugs	NA	NA	0.99
Equality across All Drugs	NA	NA	0.54
Equality across All Classes	NA	NA	0.96
Equality across All Trials	NA	NA	1.00

Note: all estimates were obtained using conditional logistic regression
NA – not applicable

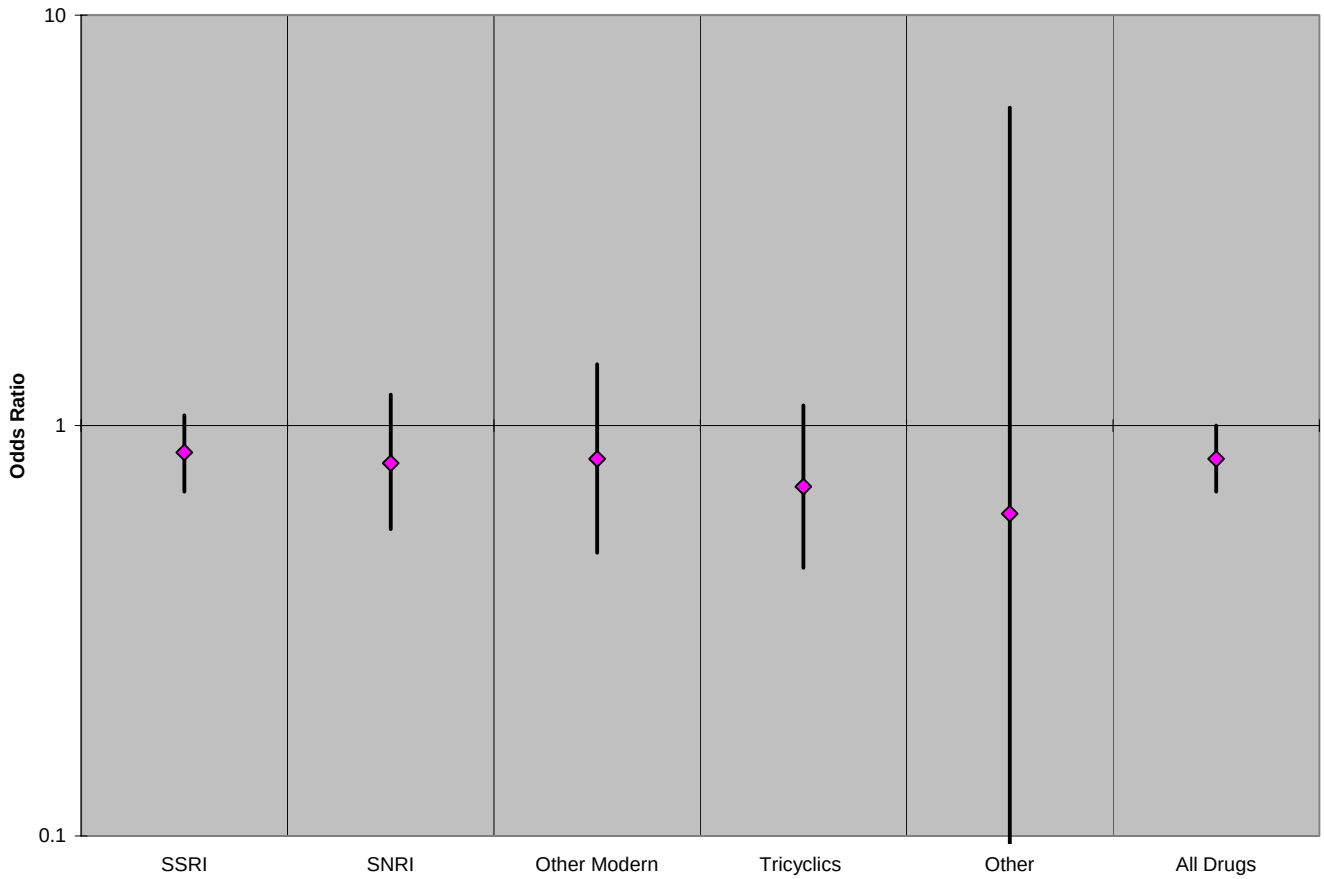

Figure 2: Suicidality Risk for Active Drug relative to Placebo – Ideation or Worse –Adults with Psychiatric Disorders – By Drug Class (Bands represent 95% CI)

Table 16 and Figure 3 show the results for suicidal behavior. They are similar to what is observed with suicidality. The likelihood ratio for suicidal behavior from older drugs relative to newer drugs was 0.76 (95% CI 0.38 – 1.50, p = 0.43).

Table 16: Suicidal Behavior Risk for Active Drug relative to Placebo – Preparation or Worse –Adults with Psychiatric Disorders – By Drug and Drug Class

Drug Class Drug	Odds Ratio	95% Confidence Interval	p value
All Drugs	**1.10**	**0.77 - 1.56**	**0.60**
SSRI	**1.23**	**0.82 - 1.85**	**0.31**
Citalopram	1.97	0.56 – 7.00	0.29
Escitalopram	5.67	0.94 – 34.2	0.06
Fluoxetine	1.08	0.52 – 2.23	0.83
Fluvoxamine	1.31	0.51 – 3.38	0.58
Paroxetine	2.76	1.16 – 6.60	0.02
Sertraline	0.25	0.07 – 0.90	0.03
Equality within class	NA	NA	0.03
SNRI	**0.83**	**0.35 – 1.97**	**0.68**
Duloxetine	1.17	0.18 – 7.53	0.87
Venlafaxine	0.69	0.25 – 1.89	0.46
Equality within class			0.62
Other Modern Antidepressants	**0.99**	**0.46 – 2.10**	**0.97**
Bupropion	2.41	0.48 – 12.1	0.29
Mirtazapine	1.25	0.34 – 4.62	0.73
Nefazodone	0.53	0.15 – 1.82	0.31
Equality within class	NA	NA	0.32
Equality across “Newer” drugs	NA	NA	0.12
Tricyclic Antidepressants	**0.80**	**0.38 – 1.68**	**0.56**
Amitriptyline	0	0 - inf	0.98
Clomipramine	0.77	0.14 – 4.15	0.76
Desipramine	0.83	0.07 – 9.89	0.88
Dothiepin	0	0 - inf	0.98
Imipramine	0.85	0.34 – 2.11	0.73
Equality within class	NA	NA	1.00
Other Antidepressants	**1.12**	**0.10 – 12.8**	**0.93**
Mianserin	1.04	0.09 – 12.2	0.98
Trazodone	-	NA	NA
Equality within class	NA	NA	NA
Equality across “Older” drugs	NA	NA	1.00
Equality across All Drugs	NA	NA	0.44
Equality across All Classes	NA	NA	0.81
Equality across All Trials	NA	NA	1.00

Note: all estimates were obtained using conditional logistic regression
NA – not applicable

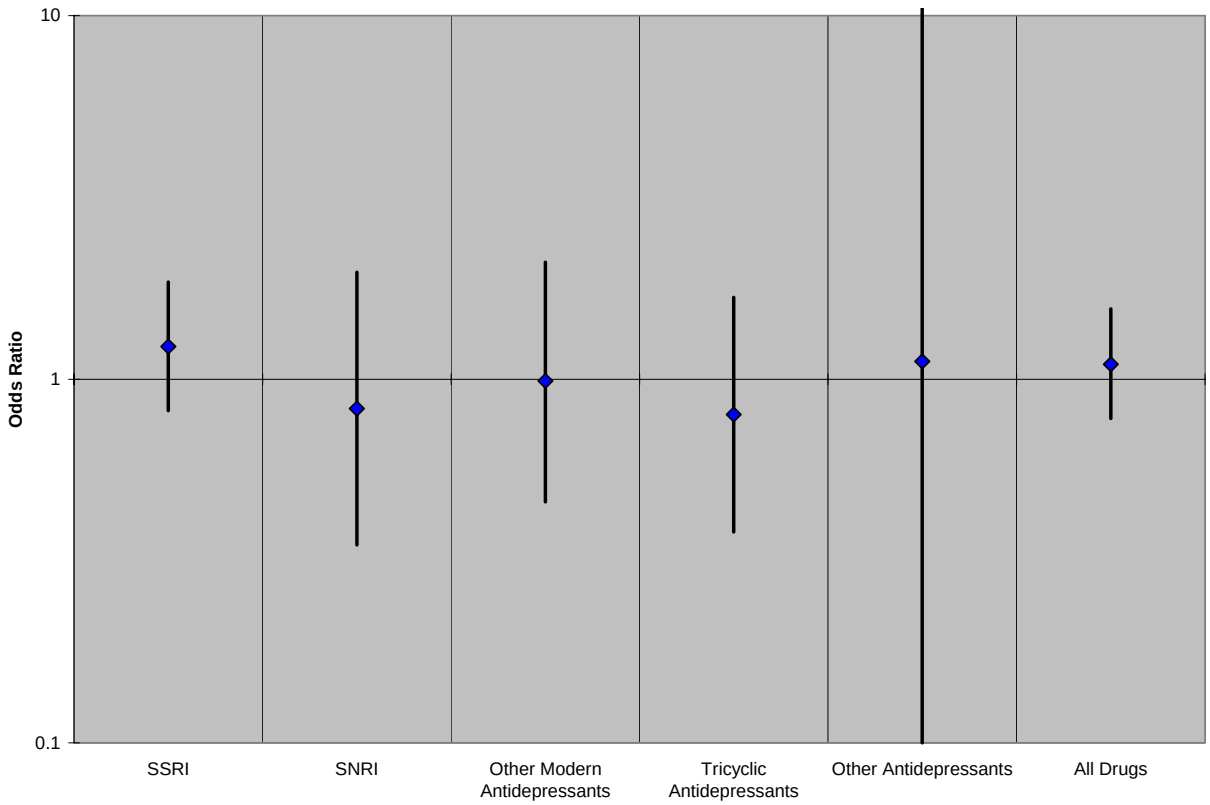

Figure 3: Suicidal Behavior Risk for Active Drug relative to Placebo – Preparation or Worse –Adults with Psychiatric Disorders – By Drug and Drug Class (Bands represent 95% CI)

4.2.4 Effect of Age

Table 17 shows the risks for suicidality associated with assignment to antidepressant treatment for adult subjects with psychiatric disorders broken down by age. The key observation is that suicidality is positively associated with assignment to treatment with antidepressants in subjects under 25 years of age (Odds Ratio 1.62, 95% CI 0.97 – 2.71, p=0.07) but negatively associated (Odds Ratio 0.74, 95% CI 0.60 – 0.90, p=0.003) with suicidality in subjects age 25 and older. There also appears to be a further distinction between a modest protective effect in subjects ages 25 – 64 (Odds Ratio 0.79, 95% CI 0.64 – 0.98, p=0.03) and a stronger protective effect in subjects age 65 and older (Odds Ratio 0.37, 95% CI 0.18 -0.76, p=0.007). Figure 4 shows these age categories graphically as well as displaying risk for suicidality as a continuous function of age.

Table 17: Suicidality Risk for Active Drug relative to Placebo – Ideation or Worse –Adults with Psychiatric Disorders – By Age

Age Range	Odds Ratio	95% Confidence Interval	p value
<25	**1.62**	**0.97 – 2.71**	**0.07**
25 - 34	0.76	0.53 – 1.08	0.13
35 - 44	0.78	0.53 – 1.14	0.20
25 – 44	**0.76**	**0.59 – 0.99**	**0.04**
45 - 54	0.94	0.60 – 1.46	0.78
55 - 64	0.62	0.30 – 1.27	0.19
45 – 64	**0.83**	**0.57 – 1.21**	**0.33**
25 – 64	**0.79**	**0.64 – 0.98**	**0.03**
65 - 74	0.53	0.22 – 1.33	0.18
75 +	0.22	0.06 – 0.79	0.02
65+	**0.37**	**0.18 – 0.76**	**0.007**
>24	**0.74**	**0.60 – 0.90**	**0.003**
Tests for equality of effect across age by			
Deciles			0.19
Quintiles			0.01
Quartiles			0.03
Terciles			0.02
<25 vs. 25+			**0.004**
25 – 34 vs. 35 - 44			0.97
45 – 54 vs. 55 – 64			0.42
65 – 74 vs. 75+			0.29
25 – 44 vs. 45 - 64			0.86
25 – 64 vs. 65+			**0.03**

Note: all estimates were obtained using conditional logistic regression

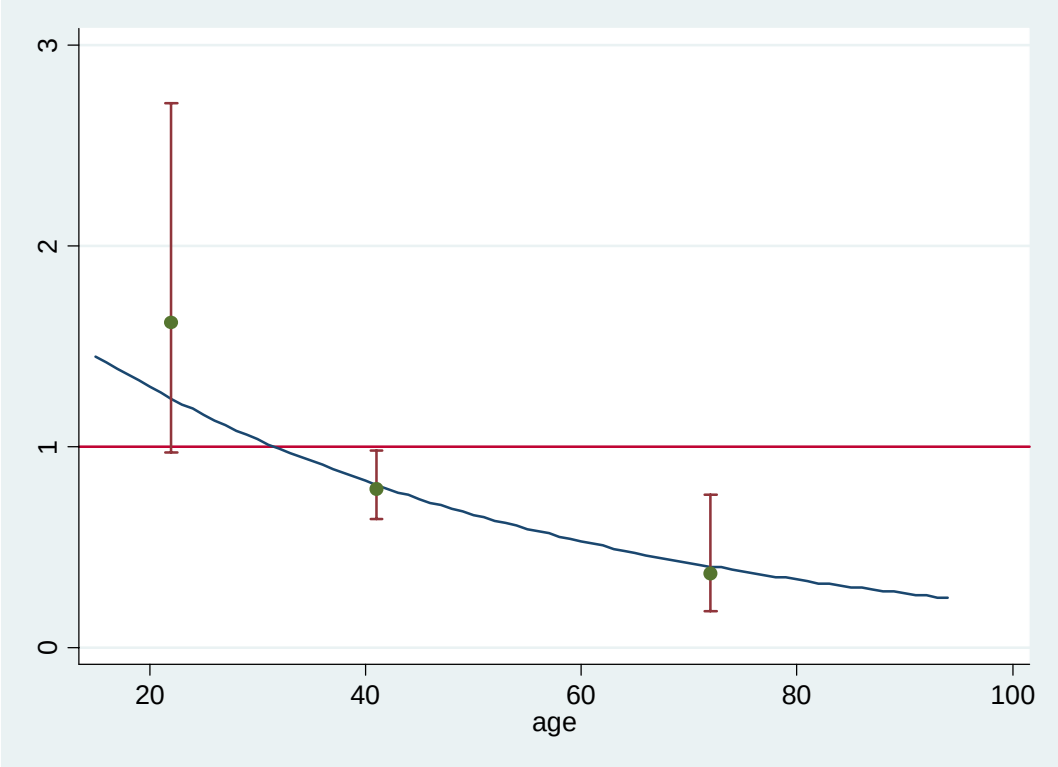

Figure 4: Suicidality Odds Ratio for Active Drug relative to Placebo – Adults with Psychiatric Disorders – By Age

Table 18 shows the risks for suicidal behavior associated with assignment to antidepressant treatment for adult subjects with psychiatric disorders broken down by age. These results also show a significant positive association with assignment to treatment with antidepressants in subjects less than 25 years of age but no overall association with suicidal behavior in subjects age 25 and older. The lack of effect appears to be limited to subjects 25 – 64 as there again appears to be a significant protective effect in subjects age 65 and older.

Table 18: Suicidal Behavior Risk for Active Drug relative to Placebo – Preparation or Worse –Adults with Psychiatric Disorders – By Age

Age Range	Odds Ratio	95% Confidence Interval	p value
<25	**2.30**	**1.04 – 5.09**	**0.04**
25 - 34	0.81	0.43 – 1.52	0.53
35 - 44	0.89	0.42 – 1.87	0.75
25 – 44	***0.88***	***0.54 – 1.42***	***0.59***
45 - 54	2.29	0.73 – 7.14	0.15
55 - 64	0.89	0.17 – 4.73	0.89
45 – 64	***1.75***	***0.68 – 4.48***	***0.24***
25 – 64	***1.03***	***0.68 – 1.58***	***0.88***
65 – 74	0.09	0.01 – 0.95	0.04
75 +	0	0 - inf	1.00
65+	***0.06***	***0.01 – 0.58***	***0.01***
>24	**0.87**	**0.58 – 1.29**	**0.48**
Tests for equality of effect across age by			
Deciles	NA	NA	0.29
Quintiles	NA	NA	0.20
Quartiles	NA	NA	0.43
Terciles	NA	NA	0.86
<25 vs. 25+			**0.04**
25 – 34 vs. 35 – 44			0.97
45 – 54 vs. 55 – 64			0.42
25 – 44 vs. 45 – 64			0.86
25 – 64 vs. 65+			**0.02**

Note: all estimates were obtained using conditional logistic regression
NA – not applicable

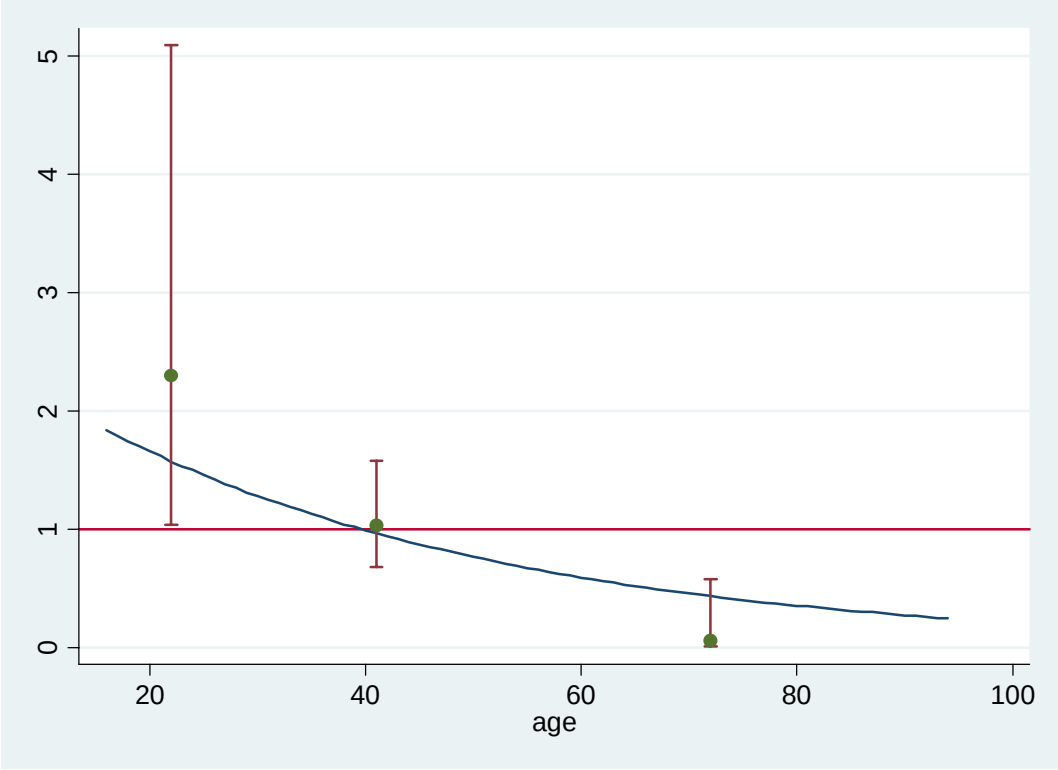

Figure 5: Suicidal Behavior Odds Ratios for Active Drug relative to Placebo – Preparation or Worse –Adults with Psychiatric Disorders – By Age

4.2.5 Impact of Clinical Response

A variable indicating whether a subject was considered a responder to treatment was reported in 189 trials of 53,048 adult subjects with psychiatric disorders. The criteria for response were specific to each trial. Approximately 50% of subjects who received active drug and 40% of subjects who received placebo were designated as responders. Among who were considered to have responded to treatment, 0.26% of all subjects with major depressive disorders and 0.13% of subjects with other psychiatric disorders displayed suicidal ideation or behavior. For subjects considered non-responders, 1.18% with major depressive disorders and 0.55% with other psychiatric disorders displayed suicidal ideation or behavior (Table 19). Table 20 summarizes the suicidality odds ratios for active drug vs. placebo by subject response and age category and Table 21 shows the comparable results for suicidal behavior. The results are consistent with the idea that an increased risk of suicidal behavior in young adults associated with antidepressant treatment may be limited to subjects who do not show a clinical response to treatment but this observation is far from statistically significant and would require a larger sample to make any conclusions.

Table 19: Incidence of Suicidality by Indication and Clinical Response – Adults with Psychiatric Disorders

	MDD	Non-MDD	All Psychiatric
Non-Responders	1.18%	0.55%	1.07%
Responders	0.26%	0.13%	0.23%

Table 20: Suicidality Odds Ratios for Active Drug relative to Placebo by Clinical Response and Age – Adults with Psychiatric Disorders

	Odds Ratio	95% CI	p value
All Ages			
Non-Responders	0.98	0.77 – 1.25	0.89
Response Not Reported	0.80	0.57 – 1.12	0.18
Responders	0.93	0.52 – 1.68	0.81
Equality across classes			0.52
Age <25			
Non-Responders	1.96	0.87 – 4.39	0.10
Response Not Reported	1.62	0.76 – 3.46	0.26
Responders	1.29	0.26 – 6.53	0.76
Responders vs. Non-Responders			0.68
Equality across classes			0.90
Age 25 – 64			
Non-Responders	0.99	0.75 – 1.31	0.93
Response Not Reported	0.63	0.43 – 0.94	0.02
Responders	1.00	0.50 – 2.00	1.00
Equality across classes			0.14
Age 65+			
Non-Responders	0.47	0.22 – 1.00	0.05
Response Not Reported	NA	NA	NA
Responders	0.19	0.02 – 1.91	0.16
Responders vs. Non-Responders			0.47

Note: all estimates were obtained using conditional logistic regression
NA – not applicable

Table 21: Suicidal Behavior Ratios for Active Drug relative to Placebo by Clinical Response and Age – Adults with Psychiatric Disorders

	Odds Ratio	95% CI	p value
All Ages			
Non-Responders	1.43	0.88 – 2.33	0.14
Response Not Reported	1.01	0.54 – 1.89	0.97
Responders	0.75	0.31 – 1.83	0.53
Responders vs. Non-Responders			0.18
Equality across classes			0.34
Age <25			
Non-Responders	3.46	0.88 – 13.6	0.08
Response Not Reported	2.98	0.85 – 10.5	0.09
Responders	0.97	0.18 – 5.29	0.97
Responders vs. Non-Responders			0.24
Equality across classes			0.45
Age 25+			
Non-Responders	1.31	0.77 – 2.21	0.32
Response Not Reported	0.48	0.22 – 1.08	0.08
Responders	0.66	0.23 – 1.90	0.44
Responders vs. Non-Responders			0.24
Equality across classes			0.09

Note: all estimates were obtained using conditional logistic regression

4.2.6 Pediatric Studies

The published analysis[16] of pediatric studies of antidepressants included 25 trials with 4681 subjects ages 6 – 18, all with diagnoses of psychiatric disorders, and reported an overall risk ratio of 1.95 (95% CI 1.28 – 2.98) for suicidality for all drugs and diagnostic categories, a risk ratio for suicidal behavior of 1.90 (1.00 – 3.63) and a risk ratio of 1.66 (1.02 – 2.68) for suicidality in trials of SSRI drugs for the treatment of major depressive disorder with the use of a continuity correction. Because the use of a continuity correction tends to bias the results, the results were recalculated using the Mantel-Haenszel method without a continuity correction and are reported both as risk ratios and odds ratios in Table 22.

Table 22: Results from Pediatric Studies for Active Drug relative to Placebo

	Risk Ratio	RR 95% CI	Odds Ratio	OR 95% CI	Equality Across Trials
Suicidality – All Drugs	2.17	1.38 – 3.42	2.22	1.39 – 3.55	0.70
Suicidal Behavior – All Drugs	2.35	1.11 – 4.98	2.38	1.10 – 5.13	0.99
Suicidality – SSRI in MDD	1.69	1.03 – 2.75	1.72	1.04 – 2.86	0.88

Note: all estimates were obtained using conditional logistic regression

Table 23 compares these results from the pediatric studies with the comparable results in adults. Even within the pediatric studies, risk appears to decline with age and this decline appears to continue in the adult population.

Table 23: Suicidality and Suicidal Behavior Risk for Active Drug relative to Placebo by Population and Age Subgroup

	Odds Ratio	OR 95% CI
Suicidality – All Drugs		
Pediatric studies Age <12	2.88	0.90 – 9.18
Pediatric studies Age 12+	2.11	1.27 – 3.52
Adult studies Age <25	1.62	0.97 – 2.71
Adult studies Age 25 – 64	0.79	0.64 – 0.98
Adult studies Age 65+	0.37	0.18 – 0.76
Suicidal Behavior – All Drugs		
Pediatric studies Age <12	3.68	0.41 – 33.1
Pediatric studies Age 12+	2.22	0.97 – 5.06
Adult studies Age <25	2.30	1.04 – 5.09
Adult studies Age 25 – 64	1.03	0.68 – 1.58
Adult studies Age 65+	0.06	0.01 – 0.58
Suicidality – SSRI in MDD		
Pediatric studies Age <12	2.10	0.62 – 7.11
Pediatric studies Age 12+	1.65	0.94 – 2.88
Adult studies Age <25	1.25	0.48 – 3.27
Adult studies Age 25 – 64	1.02	0.73 – 1.42
Adult studies Age 65+	0.49	0.23 – 1.06

Note: all estimates were obtained using conditional logistic regression

16 Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric subjects treated with antidepressant drugs. Arch General Psychiatry 2006 Mar;63(3):332-9.

4.2.7 Adult and Pediatric Data Combined

The age ranges of the adult and pediatric studies overlap slightly and the results can be considered together to fully assess the interaction of age with antidepressant treatment. Figure 6 shows this interaction for both suicidality and suicidal behavior. The slope of the interaction between antidepressant treatment and age did not differ among drugs (p=0.22 for suicidality and p=0.81 for suicidal behavior) nor did it differ by drug class (p=0.28 for suicidality and p=0.78 for suicidal behavior). Tables 24 and 25 show the breakdown by drug and drug class for suicidality and suicidal behavior, respectively, for subjects under 25 years of age. None of the differences among drugs and drug classes appears significant; the odds ratio for suicidality for SNRI drugs appears a bit higher than the other classes but the confidence intervals are extremely wide. There also do not appear to be any significant differences among diagnostic classes for subjects under age 25 (Tables 26 and 27).

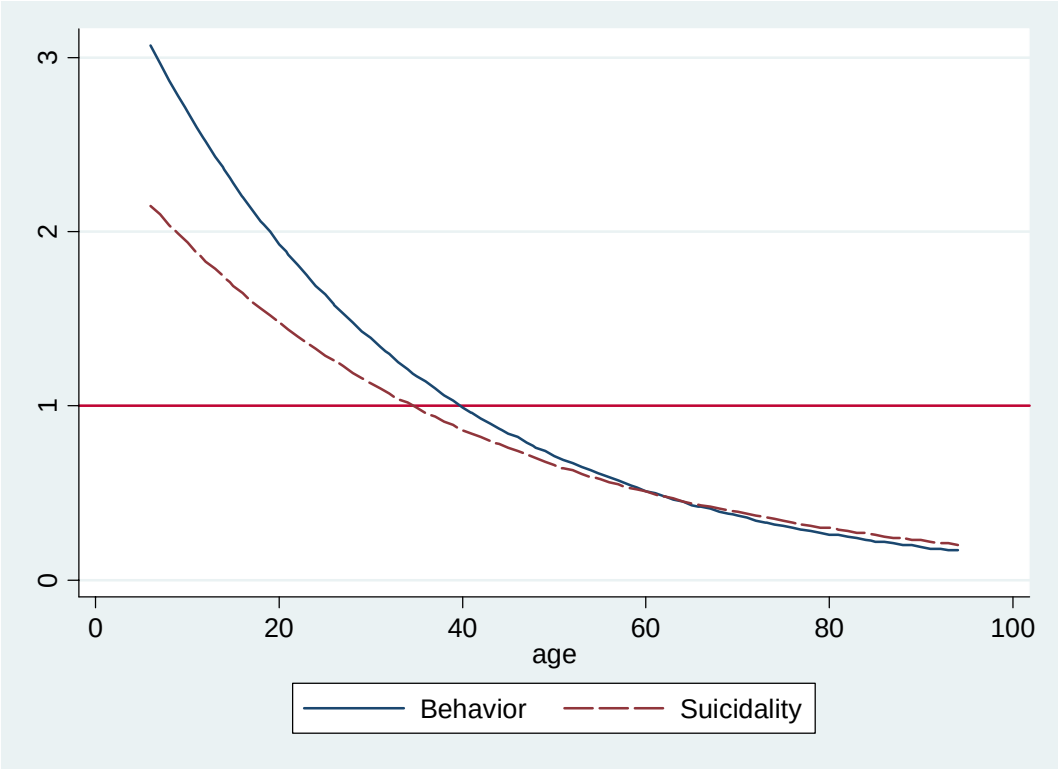

Figure 6: Odds Ratios for Suicidality and Suicidal Behavior for Active Drug relative to Placebo by Age

Table 24: Suicidality Odds Ratios for Active Drug relative to Placebo – Ideation or Worse – Subjects under age 25 with Psychiatric Disorders – By Drug and Drug Class

Drug Class Drug	Odds Ratio	95% Confidence Interval	p value
All Drugs	**1.94**	**1.37 – 2.74**	**0.0002**
SSRI	**1.73**	**1.19 – 2.52**	**0.004**
Citalopram	2.07	0.80 – 5.34	0.13
Escitalopram	2.44	0.30 – 20.2	0.40
Fluoxetine	1.51	0.86 – 2.65	0.15
Fluvoxamine	4.53	0.87 – 23.7	0.07
Paroxetine	2.33	1.10 – 4.96	0.03
Sertraline	0.84	0.30 – 2.29	0.73
Equality within class	NA	NA	0.48
SNRI	**5.13**	**1.80 – 14.6**	**0.002**
Duloxetine	5.37	0.83 – 67.2	0.07
Venlafaxine	4.91	1.50 – 16.1	0.01
Equality within class			0.95
Other Modern Antidepressants	**1.46**	**0.50 – 4.27**	**0.49**
Bupropion	1.30	0.23 – 7.50	0.77
Mirtazapine	1.61	0.25 – 10.4	0.62
Nefazodone	1.94	0.19 – 19.5	0.57
Equality within class	NA	NA	0.96
Equality across “Newer” drugs	NA	NA	0.57
Tricyclic Antidepressants	**2.40**	**0.81 – 7.11**	**0.11**
Clomipramine	1.74	0.14 – 20.9	0.66
Desipramine	inf	0 - inf	0.98
Dothiepin	0	0 - inf	0.99
Imipramine	3.13	0.77 – 12.7	0.11
Equality within class	NA	NA	0.98
Other Antidepressants	**2.95**	**0.17 – 51.8**	**0.46**
Mianserin	2.68	0.15 – 47.8	0.50
Equality across “Older” drugs	NA	NA	1.00
Equality across All Drugs	NA	NA	0.87
Equality across All Classes	NA	NA	0.36

Note: all estimates were obtained using conditional logistic regression
NA – not applicable

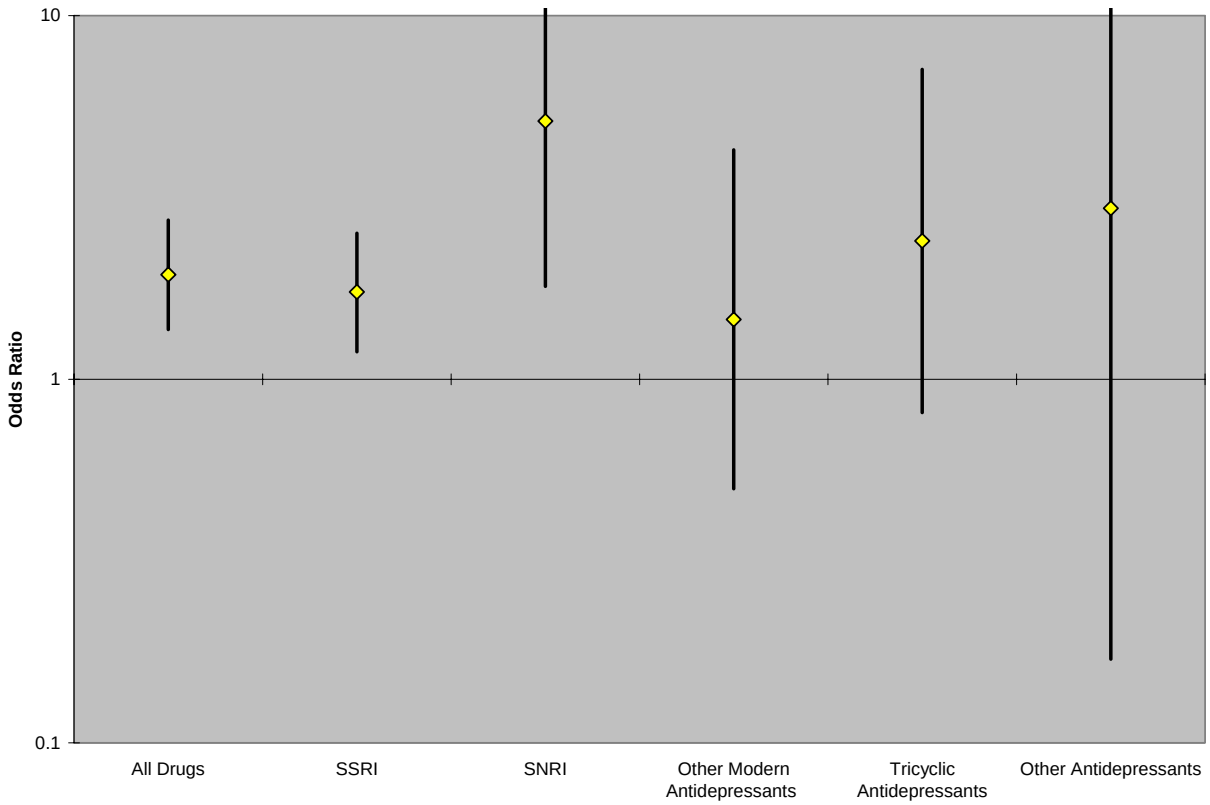

Figure 7: Suicidality Odds Ratios for Active Drug relative to Placebo – Ideation or Worse – Subjects under age 25 with Psychiatric Disorders – By Drug Class

Table 25: Suicidal Behavior Risk for Active Drug relative to Placebo – Preparation or Worse – Subjects under age 25 with Psychiatric Disorders – By Drug and Drug Class

Drug Class Drug	Odds Ratio	95% Confidence Interval	p value
All Drugs	**2.35**	**1.35 – 4.09**	**0.002**
SSRI	**2.29**	**1.27 – 4.13**	**0.006**
Citalopram	3.17	0.81 – 12.4	0.10
Escitalopram	2.35	0.11 – 50.4	0.58
Fluoxetine	2.32	0.78 – 6.87	0.13
Fluvoxamine	3.27	0.19 – 55.8	0.41
Paroxetine	4.36	1.21 – 15.7	0.02
Sertraline	0.61	0.15 – 2.53	0.50
Equality within class	NA	NA	0.48
SNRI	**6.13**	**0.59 – 63.5**	**0.13**
Venlafaxine	6.15	0.59 – 64.6	0.13
Equality within class			NA
Other Modern Antidepressants	**1.62**	**0.43 – 6.08**	**0.48**
Bupropion	1.46	0.17 – 12.4	0.73
Mirtazapine	2.99	0.23 – 39.1	0.40
Nefazodone	1.09	0.07 – 18.1	0.95
Equality within class	NA	NA	0.86
Equality across “Newer” drugs	NA	NA	0.77
Tricyclic Antidepressants	**2.31**	**0.58 – 9.24**	**0.24**
Clomipramine	0	0 - inf	0.99
Desipramine	Inf	0 - inf	0.99
Imipramine	2.73	0.46 – 16.1	0.27
Equality within class	NA	NA	1.00
Other Antidepressants	**3.60**	**0.20 – 64.8**	**0.39**
Mianserin	3.63	0.19 – 70.7	0.40
Equality across “Older” drugs	NA	NA	1.00
Equality across All Drugs	NA	NA	0.96
Equality across All Classes	NA	NA	0.90

Note: all estimates were obtained using conditional logistic regression
NA – not applicable

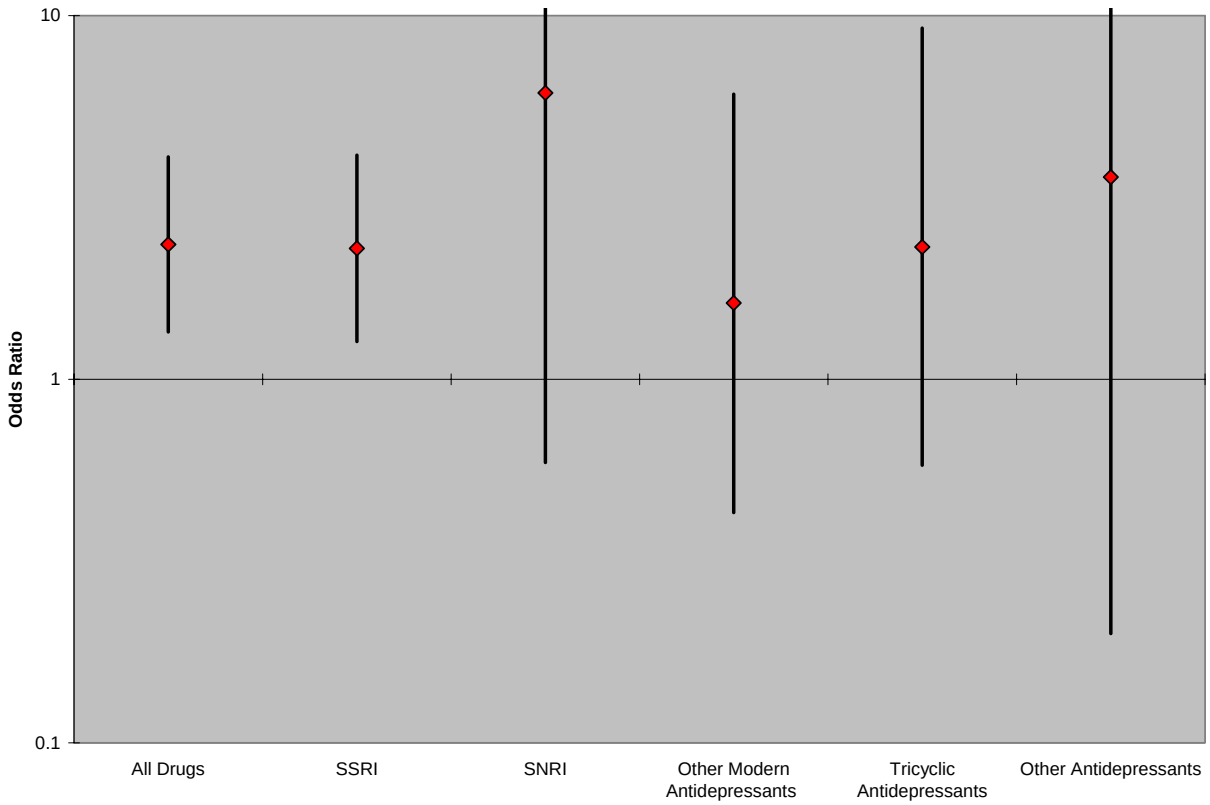

Figure 8: Suicidal Behavior Risk for Active Drug relative to Placebo – Preparation or Worse – Subjects under age 25 with Psychiatric Disorders – By Drug Class

Table 26: Suicidality Risk for Active Drug relative to Placebo – Ideation or Worse – Subjects under age 25 with Psychiatric Disorders – By Diagnostic Class

	Odds Ratio	95% Confidence Interval	p value
Major Depression	1.88	1.25 – 2.84	0.003
Other Depression	1.10	0.18 – 6.56	0.92
Other Psychiatric	2.26	1.13 – 4.54	0.02
All Psychiatric	1.94	1.37 – 2.74	0.0002
Equality across Class	NA	NA	0.74

Note: all estimates were obtained using conditional logistic regression
NA – not applicable

Table 27: Suicidal Behavior Risk for Active Drug relative to Placebo – Preparation or Worse – Subjects under age 25 with Psychiatric Disorders – By Diagnostic Class

	Odds Ratio	95% Confidence Interval	p value
Major Depression	2.04	1.06 – 3.90	0.03
Other Depression	2.07	0.22 – 19.5	0.52
Other Psychiatric	3.77	1.09 – 13.1	0.04
All Psychiatric	2.35	1.35 – 4.09	0.002
Equality across Class	NA	NA	0.69

Note: all estimates were obtained using conditional logistic regression
NA – not applicable

4.2.8 Additional Analyses Involving Sertraline

As noted in Section 4.2.3, the only statistical evidence of a difference in effect upon suicidality or suicidal behavior among drugs was within the class of SSRI drugs. When drug-specific odds ratios for both suicidality and suicidal behavior among adult subjects (Tables 15 and 16) and subjects under age 25 (Tables 24 and 25) are examined the most consistent finding is an odds ratio for sertraline that is lower than for other drugs, both SSRI and non-SSRI. Given the large number of comparisons made in this review, chance is a very plausible explanation for this difference but the consistency of this finding indicates a need to entertain other possibilities.

There were 57 trials, adult and pediatric, for psychiatric disorders involving sertraline. In 19 trials with 6002 subjects, sertraline was directly compared with other antidepressant drugs, including amitriptyline, bupropion, desipramine, dothiepin, escitalopram, fluoxetine, imipramine and venlafaxine. In these trials the odds ratio for suicidality relative to placebo was 0.52 (95% CI 0.17 – 1.64) for sertraline and 1.35 (95% CI 0.56 – 3.27) for other antidepressants. The difference was statistically significant (ratio 0.36, 95% CI 0.13 – 1.00, p=0.05). There were no suicidal behavior events in the 2126 subjects assigned to sertraline but three events among 1733 placebo subjects and six events among the 2143 subjects assigned to other antidepressant drugs.

Table 28: Suicidality and Suicidal Behavior Risk for Sertraline vs. Other Antidepressants relative to Placebo

	Odds Ratio	OR 95% CI
Suicidality		
Sertraline[a]	0.52	0.17 – 1.64
Other Antidepressants[a]	1.35	0.56 – 3.27
Ratio[a]	0.36	0.13 – 1.00
Suicidal Behavior		
Sertraline[b]	0	0 – 1.75
Other Antidepressants[a]	1.72	0.42 – 7.12
Ratio[b]	0	0 – 0.65

[a] By conditional logistic regression

[b] By the exact method

Although suicidality risk may be lower with sertraline, there is still a suggestion of the same interaction of treatment with age category (Table 29) that is far from statistical significance. If age is treated as a continuous variable, however, there is a linear trend of diminishing suicidality risk with age from sertraline treatment relative to placebo that is much closer to statistical significance (p= 0.10 for suicidality and p=0.14 for suicidal behavior).

Table 29: Suicidality and Suicidal Behavior Risk for Sertraline relative to Placebo – By Age

	Odds Ratio	OR 95% CI
Suicidality		
Age <25	0.99	0.34 – 2.87
Age 25+	0.62	0.33 – 1.18
Equality of age groups	p=0.54	
Suicidal Behavior		
Age <25	0.80	0.18 – 3.63
Age 25+	0.29	0.06 – 1.41
Equality of age groups	p=0.37	

Note: all estimates were obtained using conditional logistic regression

4.2.9 Comparison with the Meta-analysis of Gunnell *et al.*

Gunnell *et al.*[17] published a meta-analysis of randomized controlled trials of SSRIs compared with placebo in adults. The data used in the meta-analysis had been submitted by pharmaceutical companies to the safety review of the U.K. Medicines and Healthcare products Regulatory Agency (MHRA). For each SSRI (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline), sponsors provided summed end point data across all trials, for all indications, separately in subjects treated with placebo and with the intervention. These trials were limited to depression for citalopram but included trials for all indications for all other SSRI drugs. The meta-analysis included 477 trials including 52,503 subjects. The three outcomes examined were completed suicide, intentional self-harm and suicidal thoughts.

Table 30 compares the data from Gunnell's study with comparable data from this review – all studies of citalopram for adults with depression and studies for all indications for adults for the other SSRI drugs. Although the reported number of trials in the Gunnell study (477) is greater than the number of trials meeting the same criteria in this review (251), the number of subjects in the Gunnell study is 52,503 compared to 59,502 for this review. This review does not use one of the outcomes in the Gunnell study, intentional self-harm (whether or not the action could be considered a suicide attempt). The most comparable outcome in this study would be to consider either "suicide attempt" or "self-injurious behavior, intent unknown" as being equivalent to outcome used by Gunnell.

The Gunnell paper generally shows a higher incidence of all outcomes both with drug and placebo than were evident in the FDA analysis. It does not clearly indicate whether multiple events for the same subject are included or whether only one event per subject, the most severe event, is considered. This would not explain, however, why there were more completed suicides reported by Gunnell. Even if multiple events per subject were not included, the number of events in this review could be fewer because: 1) studies or events in studies reported to the MHRA were not reported to the FDA, 2) the Gunnell paper includes events that occurred more than one day after study treatment was discontinued or 3) a number of events considered suicide-related by Gunnell were rejected by the adjudication process requested by FDA.

The two studies also have important methodological differences. Gunnell did not have individual or trial level data. This can potentially distort the results because the proportions of subjects allocated to active drug or placebo differ across trials and the trials themselves differ in length and other aspects of protocol. Because results were not stratified by trial and standard errors adjusted for intra-trial correlation, the reported credible intervals will be too narrow. Despite these considerable differences as well as differences in statistical approach (Bayesian random effects meta-analysis in Gunnell's study vs. fixed effects logistic regression in the FDA analysis), the reported odds ratios in the Gunnell study are remarkably similar to those obtained with the FDA data.

17 Gunnell D, Saperia J, Ashby D. Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: meta-analysis of drug company data from placebo controlled, randomized trials submitted to the MHRA's safety review. BMJ 2005; 330 (7488):385.

4.2.10 Comparison with the Meta-analysis of Fegusson *et al.*

Fergusson *et al.*[18] identified 345 randomized controlled trials of SSRI drugs that provided information on fatal or non-fatal suicide attempts using published reports from Medline, the Cochrane registry and trials identified in other systematic reviews. SSRI treatment was compared to placebo in 189 trials and to tricyclic antidepressant drugs in 115 trials. Table 31 compares the results to studies that match comparable criteria in this review. For the comparison of SSRI and placebo, the Fergusson paper includes many fewer subjects than are obtained in this review, probably due to its limitation to public data. The prevalence of events, except for non-fatal suicide attempts in placebo subjects, is higher in the Fergusson report probably because the standards for inclusion were not as restrictive as those used in this review. The number of non-fatal suicide attempts relative to completed suicides in placebo subjects is surprisingly low; this anomaly may explain the higher odds ratio. Fergusson's comparison of SSRIs with tricyclics includes twice as many subjects as are available in this review because the FDA analysis is limited to studies that also contain a placebo arm. Again, the prevalence of events is notably higher in Fergusson's review but the reported odds ratios are very similar.

18 Fergusson D, Douchette S, Glass KC et al. Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomized controlled trials. BMJ 2005;330(7488):396.

Table 30: Comparison of Gunnell Results with Trials Meeting Comparable Criteria in FDA Review

	Gunnell					FDA				
		Active (SSRI) arm		Placebo arm			Active (SSRI) arm		Placebo arm	
SSRI (conditions included in RCTs)	No of trials contributing data	No of subjects	No of episodes	No of subjects	No of episodes	No of trials contributing data	No of subjects	No of episodes	No of subjects	No of episodes
Suicides in placebo controlled trials in adults										
Citalopram (depression)	9	1320	1	622	1	10	1728	0	1025	0
Escitalopram (all indications)	34	2648	1	2088	1	18	3130	0	2604	0
Fluoxetine (all indications)	Not Included									
Fluvoxamine (all indications)	48	4186	2	3396	2	26	2187	0	1828	0
Paroxetine (all indications)	95	8481	1	5808	3	63	9951	1	7005	0
Sertraline (all indications)	156	7169	4	5108	0	66	6950	0	6047	1
			Odds Ratio	95% CI				Odds Ratio	95% CI	
Bayesian random effects meta-analysis			0.85	0.20	3.40	Fixed-effects logistic regression		0.86	0.12	6.30
Non-fatal self harm in placebo controlled trials in adults						**Self harm or suicide attempt**				
Citalopram (depression)	9	1320	11	622	5	10	1728	7	1025	4
Escitalopram (all indications)	34	2648	6	2088	1	18	3130	5	2604	1
Fluoxetine (all indications)	135	7010	17	4667	11	81	11488	18	7645	13
Fluvoxamine (all indications)	48	4186	24	3396	10	26	2187	11	1828	8
Paroxetine (all indications)	95	8481	33	5808	26	63	9951	19	7005	6
Sertraline (all indications)	156	7169	20	5108	8	66	6950	7	6047	6
			Odds Ratio	95% CI				Odds Ratio	95% CI	
Bayesian random effects meta-analysis		Paroxetine included	1.29	0.9	1.91	Fixed-effects logistic regression		1.25	0.84	1.89
		Paroxetine excluded	1.57	0.99	2.55			1.09	0.69	1.71
Suicidal thoughts in placebo controlled trials in adults										
Citalopram (depression)	9	1320	10	622	4	10	1728	11	1025	4
Escitalopram (all indications)	34	2648	1	2088	2	18	3130	5	2604	3
Fluoxetine (all indications)	135	3078	24	1800	31	81	11488	67	7645	58
Fluvoxamine (all indications)	48	4186	23	3396	12	26	2187	12	1828	6

Paroxetine (all indications)	95	8481	32	5808	26	63	9951	31	7005	24	
Sertraline (all indications)	156	7169	6	5108	6	66	6950	15	6047	20	
			Odds Ratio	95% CI				Odds Ratio	95% CI		
Bayesian random effects meta-analysis		Paroxetine included	0.79	0.48	1.28	Fixed-effects logistic regression		0.76	0.59	1	
		Paroxetine excluded	0.77	0.37	1.55			0.79	0.59	1.06	

Table 31: Comparison of Fergusson Results with Trials Meeting Comparable Criteria in FDA Review

			Subjects		Completed Suicides		Non-Fatal Suicide Attempts		All Attempts		Odds Ratio for all attempts	
Comparison	Reviewer	No of trials	SSRI	Control	SSRI	Control	SSRI	Control	SSRI	Control		95%CI
SSRI vs. Placebo	Fergusson	189	10557	7856	4	3	23	6	27	9	2.28	1.14-4.55
	FDA	272	38017	26056	2	2	60	31	62	33	1.31	0.85-2.03
SSRI vs. Tricyclics	Fergusson	115	6126	5401	5	4	29	31	34	35	0.88	0.54-1.42
	FDA	37	3135	2791	0	0	7	5	7	5	1.11	0.62-1.99

5. DISCUSSION AND CONCLUSIONS

5.1 Validity of Cross-Study Comparisons

The essential question regarding the validity of this meta-analysis is the comparability of the observed results across studies. Pooled results cannot be meaningful if there were systematic differences across studies in the identification and classification of suicidality events. These studies were not designed to specifically detect suicidality; uniformity of reporting cannot be assumed. The statistical approach employed to assess comparability among trials, tests of homogeneity or equality of effect, compared the observed differences in results among trials with what would be expected to be observed if these differences were purely random. These tests are not very powerful but the results show no indication of systematic differences. Confidence in the findings is reinforced by the consistency of results obtained whether fixed effects or random effects assumptions are used.

5.1.1 Differences from FDA Pediatric Suicidality Analysis

The current submission of adult data differs from the prior submission of pediatric data in that only one event was submitted per subject and FDA did not attempt to independently verify the adjudication of suicide-related events. The principal methods of analysis also differed. The analysis of pediatric data reported risk ratios calculated from trial-level estimates that often included continuity corrections. This review reports odds ratios derived from individual-level data that do not require the use of continuity corrections. In order to compare and integrate the results of these two analyses, the pediatric data were reanalyzed using the same approach as was used for the adult data. Only the most serious events for each pediatric subject were considered and the same statistical model was used.

5.2 Effect of Antidepressant Treatment on Suicidality and Suicidal Behavior

In contrast with the previous FDA review of pediatric studies, the pooled estimates of studies of the adult population support the null hypothesis of no treatment effect on suicidality. The most obvious explanation for this difference in results is that the effect may be age related. When results are analyzed by age it becomes clear that there is an elevated risk for suicidality and suicidal behavior among adults younger than 25 years of age that approaches that seen in the pediatric population. The net effect appears to be neutral on suicidal behavior but possibly protective for suicidality for adults between the ages of 25 and 64 and to reduce the risk of both suicidality and suicidal behavior in subjects aged 65 years and older.

5.2.1 Suicidal Ideation vs. Suicidal Behavior

The previous FDA review of pediatric suicidality reported a statistically significant increase in suicidality (suicidal ideation or behavior) associated with antidepressant treatment but reported no significant effect on suicidal behavior alone. This led to consideration of the idea that the effect of antidepressant treatment may increase the incidence of suicidal ideation in children but not increase suicidal actions. This raised the possibility that the effect could have an essentially benign explanation: some subjects were so depressed that they could not articulate suicidal thoughts and drug treatment produced sufficient relief that subjects could now articulate these thoughts without increasing the risk that they would act upon them. This idea could be extended to self-reported suicidal behavior by postulating that subjects on antidepressants are more likely than placebo subjects to report suicidal behaviors.

The evidence accumulated in this review is not very consistent with the “improved articulation” theory. In these analyses, the antidepressant drugs appear to have a clear age-dependent effect on

reported suicidal behavior, not just ideation. Even in the initial report of the pediatric data, the reported risk ratio for suicidal behavior (1.78, 95% CI 0.92 – 3.47) was elevated and nearly statistically significant. In order for this finding to be consistent with the "improved articulation" theory, differences between antidepressants and placebo in suicidal behavior would necessarily be limited to self-reported suicidal behavior that was not observed by others. This review reanalyzed the pediatric data using methods that allow the inclusion of drugs used as active controls and the elimination of the distortions created by continuity corrections.

This analysis indicates that increase in suicidal behavior attributable to antidepressant drugs is at least as great as the increase in suicidal ideation. This effect is observable in young adults as well as in the pediatric population. Similarly, although there seems to be a net protective effect of drug treatment among adults 25 – 64 for suicidality, the net effect on suicidal behavior appears to be neutral.

5.2.2 Suicidality and Clinical Response

Although the data are clearly insufficient to reject chance as a plausible explanation, the relationship found between suicidal behavior and reported clinical response is consistent with the expectations of clinicians. Subjects, under age 25 who did not show notable clinical improvement, appeared more likely to engage in suicidal behavior if they were receiving active drug than if they were receiving placebo. It is not possible to ascertain factors that would increase the risk of suicidality such as bipolar disorder or other causes of impulsivity that were not diagnosed. This cannot be explained simply by the theory that response to active drug is a means of separating subjects who have an inherently lower propensity for suicidal behavior from those with stronger proclivities; if that were true there would be no difference between drug and placebo when the responder and non-responder categories are combined. This may be the case in subjects age 25 and older where there is no net effect of drug on suicidal behavior but cannot explain the association in younger adults where the overall risk of suicidal behavior is higher with drug treatment. It is also consistent with the expectations of clinicians that, among responders, there was a suggestion of a protective effect from antidepressant treatment in adults 25 and older. The lack of a protective effect in responders under 25 is an opportunity for further research.

5.2.3 Differences among Drugs and Drug Classes

The observed effects were generally similar among drugs and drug classes. The apparent lower risk of suicidality observed with sertraline is consistent enough to be intriguing but it is difficult to postulate a functional reason why there would be a significant difference in suicidality and suicidal behavior between this drug and other SSRIs when there is so little consistent difference in suicidality and suicidal behavior among other SSRIs. Functional differences ought to be even greater among drug classes than within a single drug class, but there is only a slight suggestion that SNRI drugs may have a greater effect than other classes on subjects under age 25.

A possible alternative to a functional explanation is differences in populations among drugs. The first drugs to be introduced on the market for a new indication or class, such as fluoxetine and sertraline, may be developed using studies of patients who are less complicated and more responsive to treatment than were used in studies for the later entrants to the market. If the interaction between drug treatment and suicidality is negatively related to treatment response, drugs with an earlier entry to the market may appear more protective of suicidality than drugs that were developed later when there were more complicated subjects diagnosed with depression available to study. This, however, would not explain the results of trials where sertraline was directly compared to other antidepressants. In these trials the risk of suicidality or suicidal

behavior was lower than placebo for sertraline. For other antidepressants, the risk observed was not only higher than placebo but also higher than the pooled estimated risk for antidepressants across all studies.

5.2.4 Issues Relevant to an Explanatory Hypothesis

The association of antidepressant treatment with an increased risk of suicidality and suicidal behavior is, on its face, paradoxical. It is commonly believed that suicide is a response to the symptoms of depression and treatments proven to reduce these symptoms ought to reduce the risk of suicide. In the FDA review of pediatric data, antidepressant treatment in trials of subjects with major depressive disorder was associated with a higher risk of developing symptoms of hostility or agitation. The data did not allow for a direct examination of a correlation between the development of these symptoms in individual subjects and the development of suicidality. It is possible that this "activation syndrome" could promote suicidality, counteracting any therapeutic benefit.

Regardless of the exact mechanism, the observations contained in this review support the idea that antidepressant drugs can have two separate effects, one that promotes suicidality or suicidal behavior and one that prevents it. A simpler explanation that denies a preventative effect and assumes only a promoting effect does not explain the protective effect seen in older subjects. The relative susceptibility to these two effects varies with age. In older subjects the preventative effect tends to predominate while in younger subjects the opposite is true. It is likely that these effects also vary among individuals of comparable ages. The preventative effect may correlate with measures of clinical response. If so, the preventative effect should be fairly uniform across ages; clinical response rates were slightly lower in adults under age 25 and those 65 and older. This would then imply that the primary explanation for the observe decline in suicidality risk with age is a decrease in susceptibility to the suicidality-promoting effects with age rather than a strengthening of the protective effects.

The observed relationship between suicidality, age and antidepressant treatment appears to be generalizable beyond subjects with major depressive disorder to all subjects with psychiatric diagnoses. The incidence of suicidality is lower but the relative risk attributable to treatment appears to be much the same. If this is the case, suicidality must be understood in a broader context than depression. This has important implications in the use of these drugs for indications outside of psychiatric disorders: even though the background incidence of suicidality is even lower than in non-MDD psychiatric disorders, the balance between the suicidality-promoting and suicidality-preventing characteristics of these drugs could be very different and of great significance in younger patients.

6. APPENDICES

Appendix 6.1: FDA data request letter to sponsors

ADVICE FOR THE PHARMACEUTICAL INDUSTRY IN EXPLORING THEIR PLACEBO-CONTROLLED CLINICAL TRIALS DATABASES FOR SUICIDALITY AND PREPARING DATA SETS FOR ANALYSIS BY FDA

[Version: 8-2-05]

Given the finding of a signal for an increased risk of suicidality (suicidal ideation and behavior) in pediatric subjects exposed to various antidepressants in placebo-controlled trials, and possible

signals for treatment-emergent suicidality for antidepressants and other drugs in adult trials, including non-psychiatric drugs and indications, there is interest in re-examining data from trials of a broader range of drugs and indications. In exploring these clinical trials databases, we recommend that similar methods to those used in evaluating the pediatric antidepressant data be utilized. We have outlined in this guidance document an approach that we recommend for these exploratory efforts.

Clinical Trials to Include in the Suicidality Exploration

Precisely which trials to include will depend in part on the study designs used in the indications of interest. In general, however, we recommend that the explorations be limited to double-blind, randomized, placebo-controlled trials which have been completed. Duration of the trials should not be a limiting factor, however, we recommend that only trials with at least 20 subjects or subjects per treatment arm be included. Before beginning the exploration, we ask that you provide a list of the trials that you intend to include, and also a list of the RCTs that you have chosen not to include, along with a brief explanation for their exclusion.

Once there is agreement with FDA on which trials to include in the exploration, we ask that you provide certain descriptive information about these trials. We ask that you provide this information in table format at the same time that you submit a dataset with the suicidality data (see later). Attached to this document is the information that should be included in the requested tables.

Search for "Possibly Suicide-Related" Adverse Events and Preparation of Narrative Summaries

Time Frame for "Possibly Suicide-Related" Adverse Events

This search should be strictly limited to adverse events that occurred during the double-blind phase of treatment, or within 1 day of stopping randomized treatment. Adverse events should not be included if they occurred prior to randomization or more than 1 day after discontinuing from randomized treatment. The end of trials with a tapering period should be set to be at the beginning of the tapering period. Events occurring more than 1 day after discontinuing from randomized treatment should be excluded even if discontinuation occurred before the nominal endpoint of the trial. For example, if a subject either discontinued of his or her own volition or was asked to discontinue by the investigator after 2 weeks of randomized treatment in a trial of 8 weeks duration, and the subject then experienced a "possibly suicide related" adverse event 2 days after stopping, that event should not be included.

Generally, events that are preexisting at baseline are not counted as treatment emergent if they recur during the course of a trial. However, in the requested analysis, suicidality-related events that occur during the course of the double-blind phase or within 1 day of beginning taper, switching or stopping treatment should be counted, even if they occur in a subject who had such events at some prior time. The rationale for this rule is that it is generally very difficult to determine for the quality of data available in most of these trials whether suicidality occurring during the context of these trials is new or a continuation of some prior event.

Search Strategies for Possibly Suicide-Related Adverse Events (PSRAEs)

The following search strategies should be employed to identify adverse events of possible interest with regard to suicidality:

- The following text strings should be used in searches of (1) all preferred terms; (2) all verbatim terms; and, (3) any comment fields:

  "accident-", "attempt", "burn", "cut", "drown", "gas", "gun", "hang", "hung", "immolat", "injur-", "jump", "monoxide", "mutilat-", "overdos-", "self damag-", "self harm", "self inflict", "self injur-", "shoot", "slash", "suic-", "poison", "asphyxiation", "suffocation", "firearm" should be included. All events identified by this search should be included among the PSRAEs, unless they can be considered false positives.

  Note: 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"). These terms might be characterized as "false positives" in the sense that the verbatim term was selected because one of the text strings occurred within that term but the term had no relevance to suicidality. Although we request that such terms be excluded, we ask that you prepare a table listing all such false positives, as follows:

Study #	Subject #	Treatment Assignment	Term in Which Text String Occurred

  The subjects in this table will have as many rows as they have potential events.

- All deaths and other serious adverse events (SAEs) should be included among the PSRAEs.

- All PSRAEs identified by these 2 search strategies (and not excluded as "false positives") should have narrative summaries prepared, as described in the following section.

Preparation of Narrative Summaries for "Possibly Suicide-Related" Adverse Events

A complete set of narrative summaries should be prepared and collected for all PSRAEs that were not otherwise excluded as false positives. In some cases, narratives will have already been prepared, e.g., deaths and SAEs. Many of these may be acceptable, however, some may need to be re-written if important information is missing (see below). In other cases, however, sponsors will need to prepare narrative summaries by searching CRFs for any information that might be considered possibly relevant to suicidality. They should also utilize other relevant sources of information, e.g., hospital records, results of consults, questionnaire responses, etc, in preparing these narrative summaries. Depending on how much information is available, narrative summaries may be longer than 1 page, however, in no case, should more than 1 narrative summary be included on a single page. Following is the type of information that should be included in the original narrative summaries:

- Subject ID number
- Trial number
- Treatment group
- Dose at time of event (mg)
- Recent dose change – elaborate on timing and amount of dose change
- Sex

- Age
- Diagnosis
- History of suicidal thoughts
- History of suicide attempt
- History of self harm
- Adverse event Preferred term
- Adverse event Verbatim term
- Serious adverse event (y/n)
- Number of days on drug at time of event
- Treatment was discontinued following event (y/n)
- Subject had an emergency department visit and was discharged (y/n)
- Subject was hospitalized (y/n)
- Subject died (y/n) – if yes, elaborate on cause of death
- Associated treatment emergent adverse events
- Concurrent psychosocial stressors
- Psychiatric comorbidities
- Concomitant medications
- Other pertinent information (e.g., family history of psychiatric disorders)-

Other relevant information for preparing narrative summaries:

-Subjects may be identified as having events of interest in one or more of the above searches, and they may have more than one event of interest. In no case, however, should there be more than one narrative summary per subject. In cases where there is more than one event for a given subject, each different event should be clearly demarcated in the narrative.

-Only events occurring during the "exposure window" defined as during the double-blind phase (including the first day after abrupt discontinuation or the first day of taper, if tapering is utilized) should be included in the narrative summary, i.e., sponsors should not include any prerandomization events or events occurring more than 1 day after stopping randomized treatment or during the tapering period.

-As noted, sponsor should not exclude events of interest on the basis of a judgment that they might not represent "treatment-emergent" events; we feel this judgment is too difficult to make and we prefer to simply include all potentially relevant events, regardless of whether or not similar thoughts or behaviors may have occurred prior to treatment.

The narrative summaries do not need to be submitted to FDA. However, we may at some point request a random sample of the summaries to audit your classification process.

Classification of "Possibly Suicide-Related" Adverse Events

Once the narrative summaries for "possibly suicide-related" adverse events are prepared and collected, we ask that you accomplish a rational classification of these events using the approach that was well-characterized by the Columbia group for the pediatric suicidality narratives. This approach was described in detail by Dr. Kelly Posner at the September 13 and 14, 2004 advisory committee meeting. The details are provided in her slides for that meeting (available on FDA's website), in the transcript for that meeting, and in other reviews, etc. pertinent to pediatric suicidality and available on FDA's website [Slides http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4065S1_06_FDA-Posner.ppt and Briefing

Document, transcripts, etc.
http://www.fda.gov/ohrms/dockets/ac/cder04.html#PsychopharmacologicDrugs

The categories of interest from FDA's standpoint are as follows:

Completed suicide (code 1)
Suicide attempt (code 2)
Preparatory acts toward imminent suicidal behavior (code 3)
Suicidal ideation (code 4)
Self-injurious behavior, intent unknown (code 5)
Not enough information (fatal) (code 6)
Not enough information (nonfatal) (code 9)

Those individuals who classify the narratives must have the appropriate expertise and training to accomplish this task. Thus, this task could be accomplished by seeking the help of an outside contractor who has this expertise. However, it is also possible that a sponsor may have internal expertise to accomplish this classification. Even in the latter instance, you may consider at least obtaining training of your internal staff from an outside contractor. Such training might help to increase the reliability of the classifications for subsequent meta-analyses of the data across programs.

Prior to their rational classification, the narratives must be blinded to details that might bias their assessments. The details of appropriate blinding of the narratives can also be obtained in the transcript from the advisory committee meeting referred to above, and the materials available on FDA's website pertinent to that meeting. We request that you block out the following information that could reveal treatment assignment:

- Identifying subject information, identity of study drug, and subject's randomized drug assignment
- All identifying information regarding the sponsor, the clinical trial number, and the location of the trial
- All years with the exception of years in remote history
- Study drug start and stop dates (month, day, and year)
- All medications, both prescription and non-prescription, whether taken before, during, or after the study; non-pharmaceutical substances (e.g., alcohol, tobacco) should not be blocked out
- Names of medications involved in overdoses; the number of pills consumed should not be blocked out
- Indications for medications started during or after the study
- Indications for study drug

Data Submission

In order to perform additional analyses investigating the relationship between exposure to the drug of interest and PSRAEs among the subjects of interest, we would appreciate your submitting the following variables as outlined in the next table. As noted, we are requesting information from placebo controlled trials only. Please do not submit data from active control only studies, uncontrolled extensions of placebo controlled studies, or combination drug studies.

We would expect that you will provide us with a SAS transport file. We are requesting that you provide this file to the Agency by [insert date].

Variable name	Type	Description	Coding notes
SOURCE	Character	First few letters of your drug name	
TRIAL	Character	Trial ID	
INDICATION	Character	Indication that is focus of the trial	
CTPID	Character	Subject ID within each trial	
UNIQUEID	Character	A unique ID for every subject	
AGE	Numeric	Subject age	In years
AGECAT	Numeric	Age category	1=5-17 y 2=18-24 y 3=25-64 y 4=65 y or more
GENDER	Numeric	Subject gender	1=female 2=male
RACE	Numeric	Subject race	1=White Caucasian 2=African-American 3=Hispanic 4=Asian 5=Other . = Missing
RANTXCAT	Numeric	Treatment category (assuming drugs can be categorized by class)	1= 2= 3= 6=placebo
SETTING	Numeric	Setting of trial	1=insubject 2=outsubject 3=both
LOCATION	Numeric	Location of trial	1=North America 2=Non-North America
TXARM	Numeric	Randomized treatment	1=drug 2=placebo 3=active control No missing values are allowed in this variable.
TXACTIVE	Character	Name of drug used as active control	Leave subjects in other treatment arms blank
SCALE	Character	Primary scale used to rate indication that is focus of the trial (this variable is required only for depression trials)	This should be a text field. As noted, please submit an electronic copy of whatever instrument was used for the primary protocol-specified endpoint(s).
SCOREA	Numeric	Score of primary scale at	No missing values are

Variable name	Type	Description	Coding notes
		baseline (this variable is required only for depression trials)	allowed in this variable.
SCOREB	Numeric	Score of primary scale at end of trial (this variable is required only for depression trials)	No missing values are allowed in this variable.
RESPONSE	Numeric	Response status (this variable is required only for depression trials)	0=non-responder 1=responder[19] . = Missing
EVENT	Numeric	This variable contains the code for the first suicidality event. If a subject had more than one event in the desired "exposure window", then the most severe event should be listed. Severity is decided based on the following order of codes: 1>2>3>4>5>6>9. Every subject in every trial will be classified on this variable. For the majority of subjects who are not identified as having a "possibly suicide-related AE", the classification will be 0 (no event). Similarly, those subjects who have "possibly suicide-related AEs" that are coded as 7 or 8 will also be classified for this variable as 0 (no event), because we will not be using codes 7 or 8 in our analyses. Subjects with event codes 1 through 6 for SRE's will be classified with their most severe event code.	0=no event 1=completed suicide 2=suicide attempt 3=preparatory acts toward imminent suicidal behavior 4=suicidal ideation 5=self-injurious behavior, intent unknown 6= not enough information, fatal 9= not enough information, non-fatal No missing values are allowed in this variable.
EVENTDAY	Numeric	The number of days to the first most severe suicidal event, counting from the day of the first dose.	For subjects without events, this variable should contain days until end of trial or until premature discontinuation For subjects with more than one event, this variable should contain days until the

[19] Please specify the criteria used to define subjects as responders

Variable name	Type	Description	Coding notes
			first most severe event that is listed under the variable "EVENT" No missing values are allowed in this variable.
DISCONT	Numeric	The subject discontinued before the end of the controlled portion of the trial	0=No 1=Yes No missing values are allowed in this variable
HXSUIATT	Numeric	The subject had a history of suicide attempt prior to entering the RCT as defined by: HAMD item 3=4 or relevant screen in other questionnaires used at baseline (this variable is required only for depression trials)	0=No 1=Yes . = Missing or no information available
HXSUIID	Numeric	The subject had a history of suicidal ideation prior to entering the RCT as defined by: HAMD item 3=3, MADRS item 10 >=3, or relevant screen in other questionnaires used at baseline (this variable is required only for depression trials)	0=No 1=Yes . = Missing or no information available

Attachment

For each trial included in the analysis, please provide a summary of important study characteristics in tabular form as shown in Tables 1 and 2 below. Many of the column headings are self-explanatory. However, the following headings merit clarification:

• **Number of Subjects**: number of subjects randomized to the drug and placebo treatment groups.
• **DB TX Duration**: the nominal duration of the analyzed double-blind treatment phase.
• **Protocol Dose**: the protocol-specified daily target dose expressed as a range for flexible dose studies and as individual doses for fixed dose trials.
Note: The following headings apply only to depression trials:

- **Extensive DX Screening**: indicate yes if the study required confirmation of the diagnostic entry criteria by two or more independent raters. Otherwise, indicate no.
- **Exclude TX Resistant**: indicate yes if a study exclusion criterion was a history of treatment resistance or poor response of the index illness to previous treatment. Otherwise, indicate no.
- **Exclude Bipolar D/O**: indicate yes if a study exclusion criterion was a history or presence of bipolar disorder or mania in the subject. Otherwise, indicate no.
- **Exclude Family H/O Bipolar Disorder**: indicate yes if a study exclusion criterion was any family history of bipolar disorder or mania. Otherwise, indicate no.

Drug	Study	Indication	Age Range (years)	Number of Subjects		DB TX Duration (weeks)	Protocol Dose (mg/day)
				Drug	Placebo		
XYZ	123	MDD	18 to 60	120	119	6	120 to 160
	456	MDD	55 to 85	148	148	8	120, 140, 160
	789	OCCURRED	18 to 65	119	110	12	120, 140
	1111	OCCURRED	18 to 70	71	69	13	120 to 160

TABLE 2: SCREENING AND KEY EXCLUSIONARY CRITERIA

Drug	Study	Indication	Extensive DXScreen	Placebo Lead-In	Exclude TX Resistant	Excl. Current Suicide Risk	Excl. H/O Suicide Attempt	Excl. Bipolar D/O	Excl. Family H/O Bipolar Disorder
XYZ	123	MDD	No	Yes	No	Yes	No	Yes	No
	456	MDD	Yes	Yes	No	No	No	Yes	Yes
	789	OCCURRED	Yes	Yes	Yes	Yes	No	Yes	Yes
	1111	OCCURRED	No	No	No	Yes	No	Yes	Yes

Appendix 6.2: Class Labeling Language for Antidepressants based on the FDA Pediatric Suicidality Analysis

Taken from FDA website at: http://www.fda.gov/cder/drug/antidepressants/PI_template.pdf

Class Suicidality Labeling Language for Antidepressants

[This section should be located at the beginning of the package insert with bolded font and enclosed in a black box]

[Insert established name]

Suicidality in Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Insert established name] or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. [Insert established name] is not approved for use in pediatric patients. (See Warnings and Precautions: Pediatric Use) [This sentence would be revised to reflect if a drug were approved for a pediatric indication(s). Such as, [Insert established name] is not approved for use in pediatric patients except for patients with [Insert approved pediatric indication(s)]. (See Warnings and Precautions: Pediatric Use)]

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

[This section should be located under **WARNINGS**. Please note that the title of this section should be bolded, and it should be the first paragraph in this section.]

WARNINGS-Clinical Worsening and Suicide Risk

Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The

average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

[For drugs that have discontinuation language, the following paragraph would be inserted.]

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION—Discontinuation of Treatment with [Insert established name] , for a description of the risks of discontinuation of [Insert established name]).

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for [Insert established name] should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly

advised.

Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that [Insert established name] is not approved for use in treating bipolar depression.

[This section should be located under **PRECAUTIONS, Information for Patients.**]

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with [Insert established name] and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for [Insert established name]. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking [Insert established name].

Clinical Worsening and Suicide Risk: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

[This section should be located under **PRECAUTIONS, Pediatric Use**.]

[For drugs with approved pediatric indications, the section would read as follows.]

Pediatric Use-Safety and effectiveness in the pediatric population other than pediatric patients with [Insert approved pediatric indication] have not been established (see BOX WARNING and WARNINGS—Clinical Worsening and Suicide Risk). Anyone considering the use of [Insert established name] in a child or adolescent must balance the potential risks with the clinical need.

[For drugs with no approved pediatric indications, the section would read as follows.]

Pediatric Use-Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS—Clinical Worsening and Suicide Risk). Anyone considering the use of [Insert established name] in a child or adolescent must balance the potential risks with the clinical need.

Revised 1/26/05

Appendix 6.3: Classification of Possibly Suicide-Related Events in the Analysis of Pediatric Antidepressant Trials

Adapted from “Background Information on the Suicidality Classification Project” at http://www.fda.gov/cder/drug/antidepressants/classificationProject.htm.

Reviewer Note*: The procedure described below was utilized within the FDA’s analysis of pediatric suicide data. Due to the greatly increased number of events, the FDA did not oversee the same procedure in the analysis of the adult suicidality data. Instead, the FDA’s data request letter asked the sponsors of antidepressant drugs to perform a classification procedure similar to that described below and submit the results to the FDA.*

> Research-based definitions, established before the data are reviewed, will be systematically applied to case descriptions. The documents that will be circulated for review will include information that was deemed to be relevant pursuant to requests from the FDA. All narratives will have been de-identified of information on the subjects, the pharmaceutical company, and the drug being studied, prior to the panel's receiving them and before expert review. Panel members will initially participate in a training session and pre-reliability study, to ensure that application of research-supported definitions will be conducted in a consistent way. The expert panel will then systematically review over 400 case descriptions from the 25 pediatric trials, including events that were originally described as possibly suicidal, all events coded as accidental injuries, and all serious adverse events. The review of the additional events that were not originally indicated as possibly suicidal renders the process more meaningful by allowing for a more objective review (i.e., reviewers, in addition to not knowing what treatment the subject received, also will not know the initial classification of any cases). Furthermore, the review of the additional cases will allow for the possibility of the identification of missed suicidal cases, since as mentioned previously, there may be some cases among the accidental injuries that were not classified appropriately. The approximately 400 cases will be randomly assigned to panel members in such a manner that each case will be independently reviewed by multiple raters. If there is non-agreement on any particular event, the case will be reviewed in a consensus procedure. If consensus still cannot be reached, the case will be classified as "indeterminate."

Appendix 6.4: Classification of non-MDD Treatment Indications

OTHER DEPRESSION
Atypical Depression
Bipolar Disorder
Depression (Unspecified)
Depression (Non-MDD)
Dysthymia
Dysthymia or Major Depression
MDD or Bipolar Disorder
Premenstrual Dysphoric Disorder
Post Natal Depression
Seasonal Affective Disorder

OTHER PSYCHIATRIC DISORDERS
ADHD
Adjustment Disorder
Anxiety Disorders
Alzheimer Disease
Bulimia
Generalized Anxiety Disorder
Generalized Social Phobia
Negative Symptoms Of Schizophrenia
Neurasthenia
Non-Depressed OCD
Obsessive Compulsive Disorder
Pain Disorder
Panic Disorder
Post-traumatic Stress Disorder
Social Anxiety Disorder

OTHER BEHAVIORAL DISORDERS
Alcoholism
Insomnia
Insomnia and Anxiety Preceding Surgery
Obesity
Obesity and Hypertension
Obesity and Hypertension / Diabetes
Obesity / Diabetes or Glucose Intolerance
Smoking Cessation
Weight Loss
Weight Maintenance

NON-BEHAVIORAL DISORDERS
Diabetic Neuropathy
Fibromyalgia
Mixed Urinary Incontinence
Migraine Prophylaxis
Neuropathic Pain
Non-Ulcer Dyspepsia
Premature Ejaculation
Stress Urinary Incontinence
Sexual Dysfunction
Sleep in Healthy Volunteers
Urge Urinary Incontinence

Appendix 6.5: Characteristics of the 11 Antidepressant Drugs Studied

Test Drug	Brand Name	Approval Date	Type
Bupropion	Wellbutrin	12/30/1985	Non-SSRI
Citalopram	Celexa	07/17/1998	SSRI
Duloxetine	Cymbalta	08/03/2004	Non-SSRI
Escitalopram	Lexapro	08/14/2002	SSRI
Fluoxetine	Prozac	12/29/1987	SSRI
Fluvoxamine	Luvox	12/05/1994	SSRI
Mirtazapine	Remeron	06/14/1996	Non-SSRI
Nefazodone	Serzone	12/22/1994	Non-SSRI
Paroxetine	Paxil	12/29/1992	SSRI
Sertraline	Zoloft	12/30/1991	SSRI
Venlafaxine	Effexor	12/28/1993	Non-SSRI

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Evaluation of Suicidality in Adults Treated with Antidepressants

Drug Class:	Modern antidepressants
Drug Name(s):	Bupropion, citalopram, escitalopram, duloxetine, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, and venlafaxine
Indication(s):	Major depressive disorder, other depressive disorders, non-depressive disorders
Date of Review:	November 17, 2006
Biometrics Division:	Division of Biometrics 6
Statistical Reviewers:	Mark Levenson, PhD and Chris Holland, MS
Concurring Reviewers:	George Rochester, PhD, RAC
Medical Division:	Division of Psychiatric Products (DPP)
Project Manager:	Renmeet Grewal

Keywords: Antidepressants, suicidality, adults, meta-analysis, odds ratio, exact tests, Mantel-Haenszel

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1. INTRODUCTION

1.1 Overview

Based on the findings of increased risk of suicidality (suicidal behavior and ideation) in pediatric clinical trials of antidepressants,[1] the U.S. Food and Drug Administration (FDA) is interested in whether there exist similar risks in adult populations. In 2005, FDA requested from sponsors of antidepressant drugs data from double-blind, randomized, placebo-controlled trials (RCTs) of adult subjects.[2] The requests provided instructions for the selection of the trials and identification of suicidal outcomes. The trials were separated by indication into two groups: those with major depressive disorder (MDD) indications and those with other indications.

1.2 Objectives

Primary Objective

The primary objective of this review is to estimate the effect of antidepressant drugs versus placebos on suicidal outcomes in adults in double-blind, randomized, placebo-controlled clinical trials.

Secondary Objective

The secondary objective of this review is to examine the effect of antidepressant drugs versus placebos on suicidal outcomes in adults in double-blind, randomized, placebo-controlled clinical trials for various subgroups defined by subject-level and trial-level characteristics and indication groups.

2. STATISTICAL METHODS

2.1 Data Sources

FDA requested that sponsors of 11 antidepressant drugs provide data from completed double-blind, randomized, placebo-controlled trials (RCTs) of adult subjects. The 11 drugs represent the antidepressants approved in the last 25 years. The initial approval dates ranged from 1985 to 2004.

Table 1 provides a list of these drugs and their initial approval dates. The clinical trials for these drugs sometimes included active control drug treatment arms. An advice document was sent to the sponsors describing what data should be included and how it should be prepared.[3] Below is a description of the salient features of the advice document. For further details, refer to the advice document provided in the Appendix 2.

[1] Hammad (2004).
[2] FDA (2005). Provided in Appendix 2.
[3] FDA (2005).

Table 1: Primary Analysis Antidepressant Drugs.

Test Drug	Brand Name	Approval Date	Type
Bupropion	Wellbutrin	12/30/1985	Non-SSRI
Citalopram	Celexa	07/17/1998	SSRI
Duloxetine	Cymbalta	08/03/2004	Non-SSRI
Escitalopram	Lexapro	08/14/2002	SSRI
Fluoxetine	Prozac	12/29/1987	SSRI
Fluvoxamine	Luvox	12/05/1994	SSRI
Mirtazapine	Remeron	06/14/1996	Non-SSRI
Nefazodone	Serzone	12/22/1994	Non-SSRI
Paroxetine	Paxil	12/29/1992	SSRI
Sertraline	Zoloft	12/30/1991	SSRI
Venlafaxine	Effexor	12/28/1993	Non-SSRI

Clinical Trials

Completed double-blind, randomized, placebo-controlled trials (RCTs) of adult subjects were to be considered. Trial duration was not to be a limiting factor for deciding which trials to include in the analysis, but it was recommended that the size of the trial be limited to those with at least 20 subjects per treatment arm. Before beginning the exploration of suicide-related events, sponsors were to provide a list to FDA of all trials under consideration for inclusion and justification for exclusion of any particular trial.

"Possibly Suicide-Related" Adverse Events (PSRAEs)

Sponsors were to follow a pre-specified algorithm to search for "possibly suicide-related" adverse events (PSRAEs). The search for events was to be strictly limited to adverse events that occurred during the double-blind phase of treatment, or within 1 day of stopping randomized treatment. Events were not to be included if they occurred prior to randomization or more than 1 day after discontinuation of randomized treatment.

All deaths and serious adverse events (SAEs) were to be included as PSRAEs. In addition, events of interest were identified through a search of (1) all preferred terms, (2) all verbatim terms, and, (3) any comment fields in the case report forms for the following text strings:

> "accident-", "attempt", "burn", "cut", "drown", "gas", "gun", "hang", "hung", "immolat", "injur-", "jump", "monoxide", "mutilat-", "overdos-", "self damag-", "self harm", "self inflict", "self injur-", "shoot", "slash", "suic-", "poison", "asphyxiation", "suffocation", "firearm".

Terms identified by this search because the text string was a substring of an unrelated word were to be excluded (for example, the text string “cut” might identify the word “acute”). A narrative for each PSRAEs identified was to be prepared as described in the advice document.

Classification of PSRAEs

Once the narrative summaries for “possibly suicide-related” adverse events were prepared, the sponsors were asked to classify the events in a manner similar to the pediatric population analysis. References to the classification performed in the pediatric population analysis were provided. Those individuals who classified the narratives were to have the appropriate expertise and training to accomplish this task. Prior to the classification, the narratives were to be blinded to details that might bias their assessments, such as subject identity information, all administered drug names and indications, treatment group assignment, sponsor name, trial identification location, references to years, and study start and stop dates. The events were classified according to Table 2. The classification outcomes differed from those used in the pediatric population analysis, although events codes 2 through 4 were defined the same, and there were no completed suicides in the pediatric population.

Table 2: Classification Codes of “Possibly Suicide-Related” Adverse Events.

Event	Event Code
Completed suicide	1
Suicide attempt	2
Preparatory acts toward imminent suicidal behavior	3
Suicidal ideation	4
Self-injurious behavior, intent unknown	5
Not enough information (fatal)	6
Self-injurious behavior, no suicidal intent	7
Other: accident; psychiatric; medical	8
Not enough information (nonfatal)	9

Data Submission

The sponsors were asked to submit subject-levels datasets. These datasets included variables for the trial ID, indication, age, gender, race, treatment group, setting of the trial (inpatient, outpatient, both), location of the trial (North America, Non-North America), active control drug name (for subjects in the active-control treatment group), the event code (to be discussed below), the day of the event, (to be discussed below), psychiatric scale values used to rate indication (required for depression trials only), response status (required for depression trials only), history of suicide attempt prior to trial (required for depression trials only), history of suicide ideation prior to trial (required for depression trials only), and trial-discontinuation status.

For subjects without a PSRAE, the event code was assigned the value 0. Events 7 and 8 were not considered a PSRAE in the assignment of the event code. For those subjects with a PSRAE, the event variable was assigned the classification code for the most severe PSRAE within the exposure window, defined as during the double-blind phase of treatment, or within 1 day of stopping randomized treatment. The severity of the events was defined by the order of the classification codes. The day of the event, recorded in a variable called EVENTDAY, was assigned the day of the event for subjects with a non-zero event code. For subjects without events, it was assigned the earlier of the last day in the trial or the day of premature discontinuation.

In addition to the subject-level dataset, the sponsors were asked to submit summary design and protocol information for each trial. This information included the indication, age range of subjects, the number of subjects in each treatment arm, the nominal duration of the trial, the protocol dose, and screening and exclusionary criteria.

Data Processing

The data received from the sponsors underwent quality checks. For each drug, this included verifying the following:

- The number of trials
- The number of subjects within each treatment group for each trial
- The range or set of values for each variable.

The values of the days of the events were compared to the nominal durations of the corresponding trials. Questions arising from the quality checks were sent to the appropriate sponsor for resolution. In some cases, the necessary data were not available. The amount of missing data for the analysis variables was minimal. Except for the variable EVENTDAY, no missing values were imputed.

For the variable EVENTDAY, several special rules were applied. For subjects with events, if the day was beyond 14 days of the nominal duration of the trial, the corresponding event was not counted. If this event was ideation, the event code was assigned the value of 0. For events more severe than ideation, the sponsor was asked to search for events prior to this event. If the variable EVENTDAY was missing and could not be determined by the sponsor, the corresponding event code was assumed to occur during the exposure window of the trial. For subjects without events, the variable EVENTDAY was truncated to the nominal duration of the trial plus 14 days, if necessary.

Data for 404 trials were submitted to the FDA.[4] Of these trials, 32 were excluded from the analysis. Table 3 gives a summary of the 404 trials by exclusion criteria.

[4] Two additional trials were submitted for the combination drug olanzapine/fluoxetine. These trials were not considered in the analysis.

Table 3: Trial Exclusion Summary.

Trial Exclusion Criteria	Number of Trials
Not excluded	372
Fewer than 20 subjects per arm in test-drug or placebo arms	23
Data not available for all subjects	3
Duplicate trials	6
Total	**404**

For three trials, information was only available for subjects who had serious adverse events. These trials were sertraline trials "STL-CR-90-002", “337”, and “STL-JP-94-603”. Four trials, which each evaluated both citalopram and escitalopram, were submitted with the data for both drugs. These trials were citalopram and escitalopram trials “99003”, “SCT-MD-01”, “SCT-MD-02”, and “SCTMD04”. The citalopram data were removed from the primary analysis, which required that the trials be independent. Likewise, two trials, which each evaluated both fluoxetine and duloxetine, were submitted with the data for both drugs. These trials were fluoxetine and duloxetine trials “F1J-MC-HMAQA” and “F1J-MC-HMAQB”. The fluoxetine data were removed from the primary analysis for the same reason as the similar citalopram data were removed. Finally, 23 trials were excluded because they did meet the criterion of having at least 20 subjects in each of the test drug and placebo arms. Among the excluded trials, not considering the duplicating trials, there was one completed suicide.

2.2 Study Indications and Endpoints

Trial indications were classified into one of five groups by medical officers in the Division of Psychiatric Products and the Division of Neurology Products. Four cumulative indication groups were created based on a hierarchical ordering of these five groups, as shown in Table 4. The indications that make up each group can be found in Appendix 1.

Table 4: Cumulative and Non-cumulative Indication Groupings.

All Indications	*Other Disorders*			
	Psychiatric and Behavioral Indications	*Behavioral Disorders*		
		Psychiatric Indications	*Other Psychiatric Disorders*	
			Depression Indications	*Other Depression Disorders*
				Major Depressive Disorder

Notes: Non-cumulative indication groups are italicized.

The primary analysis was performed on the Psychiatric Indications cumulative indication group, which represents the union of major depressive disorder, other depression disorders, and other psychiatric disorders. This decision was based both on medical judgment and a review of the observed rates of events in the various indication groups. A secondary analysis considered other groups of indications.

The primary endpoint was the presence of any of the four events: completed suicide, suicide attempt, preparatory acts toward imminent suicidal behavior, and suicidal ideation. These events are collectively referred to as "Suicidal Behavior and Ideation." The endpoint defined by the first three events, referred to as "Suicidal Behavior" and the endpoint defined by the fourth event, referred to as "Suicidal Ideation", were considered secondary endpoints.

2.3 Statistical Methodologies

2.3.1 Primary Analysis

The primary analysis consisted of estimating the odds ratio for subjects in the test drug arms versus the subjects in the placebo arms. The active control arms were not considered in this analysis for reasons discussed below. The analysis was performed across all drugs and trials, but was stratified by the individual trials. A stratified estimate allows the rates of events for individual trials to differ. Therefore, data from trials with differing durations and intensities of events may be combined.

There are many methods of estimating the odds ratio. Most methods are asymptotic. Asymptotic methods may perform well in a variety of settings. However, their validity may be questionable when the number of trials, the number of subjects per trial, and the rate of events are not high or

when there are imbalances in the sizes of the treatment groups.[5] In the present review, the rate of events is low and may call into question the validity of asymptotic methods. For certain subgroup analyses, the number of subjects per trial may be low as well.

The primary method chosen for the estimation of the odds ratio was the "exact method."[6] The method is valid with low event rates and small numbers of subjects per trial. The exact method is based on trial-level summaries and assumes that each trial is independent. Like other methods based on trial-level summaries, the active control data could not be considered in the same analysis as the primary drug analysis, because the inclusion would violate the independence assumption. The exact method makes use of trials that have events in both treatment arms and trials that have events in only one treatment arm, but does not make use of trials with no events. A sensitivity analysis comparing the exact method with asymptotic and other methods is described in the next section.

The difference in study exposure between the treatment groups was evaluated. The analysis was based on the variable EVENTDAY[7] for subjects who had no events. The mean within-trial treatment group difference was -1.1 days, indicating slightly less exposure in the test drug treatment arm. Because of such a small mean difference in exposure, the odds ratio was based on subjects and not subject-years.

The exact method assumes a common odds ratio across the trials. To test this assumption, a heterogeneity test, known as Zelen's test, was performed.[8] The test is an "exact" test analogous to the exact method used to estimate the common odds ratio.

In addition to the common odds ratio across the trials of all drugs, a common odds ratio across the trials for each drug was estimated. These odds ratios were estimated using the same exact method used to estimate the odds ratio across the trials of all drugs. The odds ratios for individual trials were estimated using the exact method, as well.[9] For each odds ratio estimate,

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[5] Note that different asymptotic methods require different conditions. See Emerson (1994) and Bradburn (2006) for comparisons of methods to estimate an odds ratio, in particular when the event rate is low.

[6] See Agresti (1992). The exact method involves conditioning on the total number of events in each trial. A statistic is formed equal to the number of events in the treatment arms conditional on the total numbers of events in each trial. The distribution of this statistic is the convolution of non-central hypergeometric distributions. The point estimate of the odds ratio is the conditional maximum likelihood estimate based on the statistic. Confidence intervals of the odds ratio are formed by inversion of hypothesis tests.

[7] See the Data Processing section above for processing related to the variable EVENTDAY.

[8] Cytel (2005).

[9] There were no strata in this estimation.

point estimates and 95% confidence intervals were the primary summary statistics.[10] The point estimates and intervals were displayed in forest plots.[11]

The exact methods were applied with the software StatXact 7 PROCs for SAS Users.[12] The exact methods may be computationally intensive. When the calculation of an estimate exceeds the computing resources, a Monte Carlo approximation may be used.[13] In the current analysis, the calculation of Zelen's test was the only method requiring the Monte Carlo approximation.[14]

In addition to the common odds ratio estimation, a common risk difference was estimated using a generalization to risk differences of the Mantel-Haenszel odds ratio method.[15] One important benefit of the risk difference approach is that it makes use of all the trials including trials with no events.

2.3.2 Sensitivity Analysis

A sensitivity analysis was performed to examine the robustness of the exact method for estimating the common odds ratio. The sensitivity analysis was performed on the primary population (Psychiatric Indications) and endpoint (Suicidal Behavior and Ideation). Much of the sensitivity analyses examined the consequences of the low event rate in the data (see Section 3). The low event rate poses several issues. It has already been stated that certain asymptotic methods may not be appropriate when the event rate is low. Moreover, because of the low event rate, many trials either do not have any events or have events in only one of the treatment arms (see Section 3). The exact method makes use of trials that have events in both treatment arms and trials that have events in only one treatment arm, but does not make use of trials with no events.

The sensitivity analysis consisted of comparing the results of the exact method with those from alternative methods. The alternative methods can be grouped into three classes (1) asymptotic and model-based methods, (2) methods that make use of trials with no events, and (3) methods that allow trials to have varying odds ratios. In all the methods considered, there is either implicit or explicit weighting by the number of subjects. Drugs with high numbers of corresponding subjects in the data will have greater influence in the estimates than those drugs with low numbers of subjects.

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[10] The confidence intervals were "mid-p adjusted." See Cytel (2005).
[11] Sutton (2000).
[12] Cytel (2005).
[13] Cytel (2005).
[14] The seed used in the Monte Carlo approximation was "111606".
[15] Greenland and Robins (1985).

Asymptotic and Model-Based Methods

The Mantel-Haenszel method is a common method used to estimate an odds ratio in meta-analysis.[16] Like the exact method, the method does not make use of trials with no events.

Continuity corrections are sometimes used with the method. The common continuity correction involves adding the constant value of 0.5 to each cell of the "2-by-2" table for trials that have events in only one arm.[17] In the antidepressant data, the test-drug group size is often larger than that of the placebo group. Under this condition, the constant continuity correction adds proportionally more events to the placebo group. The result, however, is that the overall odds ratio is slightly reduced.

In the sensitivity analyses, we used the Mantel-Haenszel method with no continuity correction and with the constant continuity correction. Like others, [18] we do not use trials with no events in the Mantel-Haenszel method.

Logistic regression models may be used in meta-analysis.[19] They can be used to model the odds ratio at the subject level and allow for the adjustment and modeling of subject-level characteristics. Also, because the model requires that subjects, not trials, be independent conditional on the model, active-control arms of the trials can be included.

The basic logistic model used in meta-analysis is

$$\text{logit}(p_{ij}) = \mu + \alpha_i + \beta_j,$$

where p_{ij} is the probability of an event for a subject in trial *i* and treatment group *j*, α_i is the effect of trial *i*, and β_j is the effect of treatment group *j*. The subjects are assumed independent conditional on the model. The model allows each trial to have a unique event rate and forces the treatment effect on the rate to be common across trials. To make the model estimable, the parameter β_0 corresponding to the placebo group is fixed at zero. With this restriction, the parameter β_1 represents the log odds ratio for the test drug versus the placebo group. The model does not make use of trials with no events. Subject and trial characteristics can be added to the

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[16] See Sutton (2000). Mantel-Haenszel was designed to estimate an average odds ratio across strata and can be thought of as allowing for some trial heterogeneity.

[17] Sweeting (2004) examines various continuity corrections.

[18] See Sterne et al (2001) and Sweeting (2004). Sterne et al. (2001) describes routines written in the statistical analysis package Stata. The Mantel-Haenszel odds ratio method implemented in these routines uses the constant continuity correction and does not make use of the trial without events.

[19] See Sutton (2002) and Whitehead (2002) for the use of logistic regression in meta-analysis. See Hosmer and Lemeshow (2000) and McCullagh and Nelder (1989) for a general review of logistic regression.

model. For the sensitivity analysis, the model was fit with maximum likelihood with the SAS procedure Logistic.[20]

Maximum likelihood has asymptotic properties that justify its use when the number of subjects relative to the number of parameters is large. In the meta-analysis model, there is a parameter for each trial. If the number of subjects per trial is not high, maximum likelihood estimation may not be valid.[21] An alternative is to use conditional logistic regression, which conditions on the number of events in each trial.[22] The conditioning and the resulting likelihood is the same as in the exact method described in Section 3. However, traditionally and for computational reasons, asymptotic methods are often used rather than exact estimation. For the sensitivity analysis, the conditional logistic model was fit with maximum likelihood with the SAS procedure Logistic using the strata option.[23]

Methods That Make Use of Trials with No Events

There is debate about whether trials that do not have any events provide any information on the odds ratio.[24] However, because of the large number of trials without events in the present review, additional analyses were used that made use of these trials.

As discussed above, the Mantel-Haenszel method for risk differences makes use of trials with no events in the calculation of the overall summary. This method was used as a secondary analysis and sensitivity analysis to examine the effect of the trials without events. Risk difference estimates and confidence intervals of individual trials were calculated based on the normal approximation to the binomial distribution.[25]

Methods that Allow Trials to Have Varying Odds Ratios

Another issue in estimating an overall odds ratio using the exact method is the assumption that the individual trials have a common odds ratio. Models that assume a common odds ratio across trials are known as “fixed effects” models. Models that allow for the odds ratios to vary are

[20] SAS (2003).
[21] See McCullagh and Nelder (1989) p. 266 and Hosmer and Lemeshow (2000) p. 224.
[22] See McCullagh and Nelder (1989) chapter 7 and Hosmer and Lemeshow (2000) chapter 7. The conditional models do not include a parameter for each trial and do not require that the number of subjects per trial be large in order to use asymptotic methods.
[23] SAS (2003).
[24] See Sweeting et al. (2004).
[25] In the calculation of the standard error and the resulting confidence interval of the difference for an individual trial, a continuity correction of 0.5 was added to each cell in the “2x2” table, if either arms had zero events. No continuity correction was used for either the overall Mantel-Haenszel estimate, its confidence interval, or the individual trial difference estimates.

known as “random effects models. The above logit model is an example of a fixed effects model.[26]

A generalization of the above logistic model, known as a “generalized linear mixed model” (GLMM) was used to explore allowing the odds ratios to vary by trial.[27] Continuing with the notation used above, the model is given by

$$\text{logit}(p_{ij}) = \mu + \alpha_i + \beta_j + \tau_j$$
$$\tau_j \sim \text{normal}(0, \sigma_b^2).$$

This model assumes that there is an infinite population of treatment effects and the trials in the data provide a random sample of the treatment effects. The fixed component β_j represents the average treatment effect over the population. The random component τ_j represents a random deviation from the average for a single trial. In this model, the random deviations are assumed normally distributed and independent. The parameter σ_b^2 provides a measure of the between-trial variation in the treatment effect.

The parameters β_1 and σ_b^2 and their standard errors were estimated with maximum likelihood, using the SAS procedure Glimmix.[28] Let $\hat{\beta}_1$ and $\hat{\sigma}_\beta$ be the estimate of β_1 and its associated estimated standard error. Likewise, let $\hat{\sigma}_b^2$ and $\hat{\sigma}_{sb}$ be the estimate of σ_b^2 and its associated estimated standard error.

A 95% approximate confidence interval for the population average log odds ratio β_1 was calculated as

$$\hat{\beta}_1 \pm 1.96\hat{\sigma}_\beta .$$

If there is between-trial variation in the treatment effect, the interval will be larger than the comparable interval from the fixed effect model, because σ_β accounts for the additional variation in estimating β_1 due to the presence of the random treatment effect. However, as the number of trials increases, the standard errors of $\hat{\beta}_1$ in both the fixed and the random effects models will decrease. In effect, the variance components are averaged out.

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[26] See Whitehead (2002) and Senn (2000) for discussion of fixed and random effect models in meta-analysis.
[27] McCulloch and Searle (2001).
[28] SAS (2005).

The method of DerSimonian and Laird is a traditional meta-analysis random effect method.[29] The method generalizes the inverse-weighting method to allow for a variance component due to trial effect heterogeneity. For meta-analysis with low event rates, the method is not recommended because like the inverse-weighting method, it makes use of the within-trial variance estimates, which may be imprecise in the low event setting.[30] The DerSimonian and Laird method was applied with the metan routines in Stata.[31]

2.3.3 Subgroup Analyses

Subgroups based on trial-level and subject-level characteristics were analyzed. Table 5 provides the characteristics defining the subgroups and the definition of the subgroups.

Table 5: Subgroup Definitions.

Characteristic	Scope	Group Definition
Drug Type	Trial-Level	Selective Serotonin Reuptake Inhibitor (SSRI)
		Other Drugs (Non-SSRI)
Trial Location	Trial-Level	North America
		Other Locations
Trial Setting	Trial-Level	In-Patient and Combined In- and Out-Patient
		Out-Patient
Age	Subject-Level	Age 18 – 24
		Age 25 – 30
		Age 31 – 64
		Age 65 and up
Gender	Subject-Level	Male
		Female
Race	Subject-Level	White
		Non-white

The analysis of the subgroups was performed with the primary indication group, endpoint, and analysis method. Note that for some subgroups, there were trials that had subjects only in one treatment arm. The stratified estimate and confidence intervals do not make use of these trials.

[29] Whitehead (2002).
[30] Bradburn (2006).
[31] Sterne et al (2001).

For comparison purposes, the pediatric data for subjects under the age of 18 analyzed in Hammad (2004) were also analyzed using the primary analysis method of this review.

Subjects with missing values for a characteristic defining a subgroup were removed from that subgroup analysis. There were no missing values for the trial-level characteristics.

2.3.4 Joint Primary and Active Control Drug Analysis

The effect on suicidality of all antidepressants including both the primary analysis drugs and the active control drugs was analyzed. Overall, including the primary analysis and the active-control drugs, there were data for 24 drugs. Some of the primary analysis drugs were used as active controls in the trials of other drugs. Data from all antidepressants from both the test drug and active control arms were used in this analysis. Of these drugs, 18 were antidepressants. A medical officer from the Division of Neurology Products classified the 18 antidepressants drugs into 5 classes:

1. Selective serotonin reuptake inhibitors (SSRIs)
2. Serotonin-norephrine reuptake inhibitors (SNRIs)
3. Other modern antidepressants
4. Tricyclic antidepressants
5. Other antidepressants.

Table 6 gives the classification of the 18 drugs into the five classes.

Table 6: Primary and Active Control Drugs by Drug Class.

SSRI	SNRI	Other New Drugs	Tricyclics	Other Drugs
Citalopram	Duloxetine	Bupropion	Amitriptyline	Mianserin
Escitalopram	Venlafaxine	Mirtazapine	Clomipramine	Trazodone
Fluoxetine		Nefazodone	Desipramine	
Fluvoxamine			Dothiepin	
Paroxetine			Imipramine	
Sertraline				

Statistical Model

Subject-level multivariate-logistic models were fit with the data from all the antidepressant drugs to estimate the effect on suicidality for the drugs. The first model was

$$\text{logit}(p_{ij}) = \mu + \alpha_i + \beta_j,$$

where p_{ij} is the probability of an event for a subject in trial *i* and drug class *j*, α_i is the effect of trial *i*, and β_j is the effect of the drug class *j*. The subjects are assumed independent conditional on the model. In the second model, which is nested in the first, the factor β_j is replaced by a two-level factor representing the effect of any drug versus the placebo. Only data from trials with events can be included in the model.

The primary endpoint (Suicidal Behavior and Ideation) and indication groups (Psychiatric Indications group) were used. The odds ratios and 95% confidence intervals of the effect of each drug class versus the placebo, for the first model, and the effect of any drug versus the placebo, for the second model, were estimated with maximum likelihood using the SAS procedure Logistic.[32] The second model was also fit with the all the indication groups.

Note that the estimates of the drug class and the overall effects from the logistic model reflect the mix of drugs of the subjects in the data. Drugs with high numbers of corresponding subjects in the data will have greater influence in the estimates than those drugs with a low number of subjects.

3. TRIAL AND SUBJECT CHARACTERISTICS

3.1 Trial Characteristics

Table 7 displays the number of trials and subjects by indication group. The largest indication group was for the MDD trials (162 trials, placebo N=14,728, test drug N=22,309), followed by Other Psychiatric Disorders (108 trials, placebo N=10,573, test drug N=15,061). The smallest indication group was that for Other Depression Disorders (25 trials, placebo N=1,863, test drug N=2,359).

[32] SAS (2003).

Table 7: Trial and Subject Counts by Indication Group and Treatment Group.

			Treatment Groups		
Drug	Indication	Trials n (cumulative)	Placebo n (cumulative)	Test Drug n (cumulative)	Active Control n (cumulative)
All Drugs	Major Depressive Disorder	162 (162)	14728 (14728)	22309 (22309)	8176 (8176)
	Other Depression Disorders	25 (187)	1863 (16591)	2359 (24668)	385 (8561)
	Other Psychiatric Disorders	108 (295)	10573 (27164)	15061 (39729)	1928 (10489)
	Behavioral Disorders	43 (338)	5218 (32382)	8144 (47873)	433 (10922)
	Other Disorders	34 (372)	3522 (35904)	5087 (52960)	53 (10975)

Table 8 displays the number of trials by indication group for each of the 11 investigated test drugs. The number of submitted MDD trials ranged from 6 (Citalopram, 3.7% of all MDD trials) to 22 (Venlafaxine, 13.6% of all MDD trials). For non-MDD indications, the number of submitted trials varied by drug and indication group.

Table 8: Test Drug Trials by Indication Group (Non-Cumulative).

	Indication Group					
Test Drugs	MDD n (%)	Other Depression n (%)	Other Psychiatric Disorders n (%)	Behavioral Disorders n (%)	Other Disorders n (%)	All Trials n (%)
Bupropion	18 (11.1)	0 (0)	1 (0.9)	13 (30.2)	2 (5.9)	34 (9.1)
Citalopram	6 (3.7)	0 (0)	3 (2.8)	0 (0)	0 (0)	9 (2.4)
Duloxetine	15 (9.3)	0 (0)	0 (0)	0 (0)	20 (58.8)	35 (9.4)
Escitalopram	8 (4.9)	0 (0)	7 (6.5)	0 (0)	0 (0)	15 (4.0)
Fluoxetine	14 (8.6)	7 (28.0)	19 (17.6)	22 (51.2)	0 (0)	62 (16.7)
Fluvoxamine	16 (9.9)	0 (0)	10 (9.3)	0 (0)	0 (0)	26 (7.0)
Mirtazapine	12 (7.4)	0 (0)	1 (0.9)	2 (4.7)	0 (0)	15 (4.0)
Nefazodone	16 (9.9)	0 (0)	5 (4.6)	0 (0)	4 (11.8)	25 (6.7)
Paroxetine	18 (11.1)	8 (32.0)	26 (24.1)	0 (0)	0 (0)	52 (14.0)
Venlafaxine	22 (13.6)	1 (4.0)	14 (13.0)	0 (0)	2 (5.9)	39 (10.5)
Sertraline	17 (10.5)	9 (36.0)	22 (20.4)	6 (14.0)	6 (17.6)	60 (16.1)

Table 9 displays trial characteristics for each indication group. For each indication group, the most studied class of antidepressants was the SSRIs, with the exception of Other Disorders where SNRIs were studied more often. Most studies were conducted in North America and in an outpatient setting. On average, MDD trials were shorter (median duration=8 weeks) than trials in the other indication groups (median durations=10-12 weeks).

Table 9: Trial Characteristics by Indication Group (Non-Cumulative).

		Indication Group				
Characteristic	**Statistic/ Category**	**MDD**	**Other Depression**	**Other Psychiatric Disorders**	**Behavioral Disorders**	**Other Disorders**
Total Number of Trials		162	25	108	43	34
Test Drug Sub-Class [n (%)]	SSRI[1]	79 (48.8)	24 (96.0)	87 (80.6)	28 (65.1)	6 (17.6)
	SNRI[2]	37 (22.8)	1 (4.0)	14 (13.0)	0 (0.0)	22 (64.7)
	Other[3]	46 (28.4)	0 (0.0)	7 (6.5)	15 (34.9)	6 (17.6)
Location [n (%)]	North America	138 (85.2)	16 (64.0)	65 (60.2)	26 (60.5)	18 (52.9)
	Non-North America	22 (13.6)	9 (36.0)	42 (38.9)	17 (39.5)	7 (20.6)
	Both	2 (1.2)	0 (0.0)	1 (0.9)	0 (0.0)	9 (26.5)
Setting [n (%)]	Inpatient	13 (8.0)	0 (0.0)	1 (1.0)	1 (2.3)	0 (0.0)
	Outpatient	139 (85.8)	22 (88.0)	97 (94.2)	42 (97.7)	33 (97.1)
	In- and out-patient	10 (6.2)	3 (12.0)	5 (4.9)	0 (0.0)	1 (2.9)
Duration (weeks)	N	162	24	108	43	34
	Mean	7.5	26.5	10.8	10.3	10.0
	SD	2.33	28.24	2.75	4.25	4.25
	Median	8.0	12.0	12.0	10.0	12.0
	Min	4.0	6.0	4.0	0.0	3.0
	Max	16.0	84.0	26.0	17.0	24.0
Duration Category [n (%)]	1-4 Weeks	14 (8.6)	1 (4.0)	1 (0.9)	3 (7.0)	4 (11.8)
	5-8 Weeks	118 (72.8)	5 (20.0)	30 (27.8)	15 (34.9)	12 (35.3)
	9-12 Weeks	26 (16.0)	10 (40.0)	69 (63.9)	14 (32.6)	15 (44.1)
	13-18 Weeks	4 (2.5)	3 (12.0)	7 (6.5)	9 (20.9)	2 (5.9)
	>18 Weeks	0 (0.0)	6 (24.0)	1 (0.9)	2 (4.7)	1 (2.9)

[1] Includes citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline
[2] Includes duloxetine and venlafaxine
[3] Includes bupropion, nefazodone, and mirtazapine

3.2 Subject Characteristics

Table 10 displays subject demographics, baseline characteristics, and study drug exposure for the Psychiatric Indications group. Treatment groups were very similar with respect to all measures.

Table 10: Subject Demographics, Baseline Characteristics, and Treatment Exposure (Psychiatric Indications).

		Treatment Group	
Characteristic	**Statistic/ Category**	**Placebo**	**Test Drug**
Total Number of Subjects		27164	39729
Age (years)	Mean±SD (N) Median (Range)	42.0 ± 14.48 (27144) 40.0 (15.8 - 100.0)	41.8 ± 14.28 (39709) 40.0 (15.0 - 95.4)
Age Group [% (n/N)]	18-24 Years	9.6% (2604/27127)	9.6% (3810/39681)
	25-30 Years	13.9% (3772/27127)	14.0% (5558/39681)
	31-64 Years	67.7% (18354/27127)	68.3% (27086/39681)
	>=65 Years	8.8% (2397/27127)	8.1% (3227/39681)
	<18 or missing	37	48
Gender [% (n/N)]	Female	60.8% (16515/27158)	61.2% (24325/39719)
	Male	39.2% (10643/27158)	38.8% (15394/39719)
Race [% (n/N)]	White Caucasian	85.8% (21371/24910)	85.9% (31575/36738)
	African-American	5.4% (1346/24910)	5.4% (1972/36738)
	Hispanic	3.6% (888/24910)	3.6% (1309/36738)
	Asian	3.6% (898/24910)	3.2% (1162/36738)
	Other	1.6% (407/24910)	2.0% (720/36738)
	missing	2254	2991
Treatment Exposure[1] (days)	Mean±SD (N) Median (Range)	55.5 ± 25.42 (26910) 56.0 (1.0 - 183.0)	54.5 ± 27.38 (39399) 56.0 (1.0 - 183.0)
Baseline history of suicide attempts[2] [% (n/N)]	No	98.7% (14533/14731)	98.7% (22043/22326)
	Yes	1.3% (198/14731)	1.3% (283/22326)
	missing	12433	17403
Baseline history of suicide ideation[2] [% (n/N)]	No	90.9% (16592/18262)	90.5% (25033/27661)
	Yes	9.1% (1670/18262)	9.5% (2628/27661)
	missing	8902	12068

[1] Only includes subjects who did not experience suicidal events. Duration was capped at 14 days after the nominal trial duration.
[2] Not collected for most non-depressive trials.

Trial-by-trial comparisons were performed between the placebo and test drug treatment groups with respect to subject demographics (age and gender), baseline characteristics (history of suicide attempts and history of suicide ideation), and treatment exposure (exposure in days and exposure as a percent of the nominal trial duration). For the Psychiatric Indications group, fewer than 8% of the trials had significant differences with respect to demographics and baseline characteristics. For treatment exposure, as measured both in days and as a percent of trial duration, there was a statistically significant difference in 14.9% of the trials (44/295). Of these 44 trials, placebo exposure was longer in 34 of them (77.3%). The average treatment group difference among all trials with statistically significant differences was -4.2 days, indicating slightly longer exposure in the placebo groups.

4. STATISTICAL EVALUATION AND FINDINGS

4.1 Overall Drug Class Evaluation

Table 11 displays the number and percent of trials with at least one event of suicidal behavior and ideation in either the test drug or placebo arms and the percent of trials with at least one event of suicidal behavior and ideation in both arms. The percent of trials with at least one event was highest for the MDD (64.0%) and Other Psychiatric Disorders (56.5%) indication groups. The percent was substantially lower in the All Other Disorders group (5.9%). Cumulatively, 59.4% of trials in the Psychiatric Indications group have at least one event.

Table 11: Suicidal Behavior and Ideation Events by Indication Group and Treatment Group (Placebo and Test Drug Only).

		Trials With At Least One Event		Trials With Events in Both Treatment Groups	
Drug	**Indication Group**	**% (n/N)**	**Cumulative % (n/N)**	**% (n/N)**	**Cumulative % (n/N)**
All Drugs	Major Depressive Disorder	63.6% (103/162)	63.6% (103/162)	22.8% (37/162)	22.8% (37/162)
	Other Depression Disorders	40.0% (10/ 25)	60.4% (113/187)	16.0% (4/ 25)	21.9% (41/187)
	Other Psychiatric Disorders	56.5% (61/108)	59.0% (174/295)	22.2% (24/108)	22.0% (65/295)
	Behavioral Disorders	18.6% (8/ 43)	53.8% (182/338)	2.3% (1/ 43)	19.5% (66/338)
	Other Disorders	5.9% (2/ 34)	49.5% (184/372)	2.9% (1/ 34)	18.0% (67/372)

[1] Any event of suicidal behavior or ideation.

Table 12 displays the percent of subjects with any event of completed suicide, attempted suicide, preparatory suicidal acts, or suicidal ideation by indication group. Table 13 displays similar information cumulatively for both the event and indication group. The most common events in all treatment groups and indication groups were suicidal ideation and suicide attempts. Event rates for all events were greatest in the MDD indication group, followed by the Other Psychiatric Disorders group. Compared to the three indication groups that make up the Psychiatric Indications group, event rates are substantially lower in the Behavioral Disorders and Other Disorders indication groups. In the Psychiatric Indications group, as shown in Table 13, events of suicidal behavior and ideation occurred in 0.72% of placebo subjects vs. 0.62% of subjects on the test therapy.

Table 12: Suicidal Behavior and Ideation Events by Indication Group and Treatment Group.

		Treatment Group		
Indication Group	**Event**	**Placebo % (n/N)**	**Test Drug % (n/N)**	**Active Control % (n/N)**
Major Depressive Disorder	Completed suicide	0.01% (1/14873)	0.02% (4/22379)	0.01% (1/8328)
	Suicide attempt	0.19% (29/14873)	0.21% (46/22379)	0.18% (15/8328)
	Preparatory acts	0.01% (2/14873)	0.01% (2/22379)	0.04% (3/8328)
	Suicidal ideation	0.61% (91/14873)	0.50% (111/22379)	0.44% (37/8328)
Other Depression Disorders	Completed suicide	0.00% (0/1863)	0.00% (0/2359)	0.00% (0/385)
	Suicide attempt	0.16% (3/1863)	0.08% (2/2359)	0.52% (2/385)
	Preparatory acts	0.00% (0/1863)	0.00% (0/2359)	0.26% (1/385)
	Suicidal ideation	0.32% (6/1863)	0.25% (6/2359)	0.52% (2/385)
Other Psychiatric Disorders	Completed suicide	0.01% (1/10573)	0.01% (1/15061)	0.00% (0/1928)
	Suicide attempt	0.11% (12/10573)	0.15% (23/15061)	0.05% (1/1928)
	Preparatory acts	0.01% (1/10573)	0.01% (1/15061)	0.00% (0/1928)
	Suicidal ideation	0.48% (51/10573)	0.35% (52/15061)	0.26% (5/1928)
Behavioral Disorders	Completed suicide	0.00% (0/5218)	0.00% (0/8144)	0.00% (0/433)
	Suicide attempt	0.00% (0/5218)	0.01% (1/8144)	0.00% (0/433)
	Preparatory acts	0.00% (0/5218)	0.00% (0/8144)	0.00% (0/433)
	Suicidal ideation	0.06% (3/5218)	0.06% (5/8144)	0.00% (0/433)
All Other Disorders	Completed suicide	0.00% (0/3522)	0.00% (0/5087)	0.00% (0/53)
	Suicide attempt	0.00% (0/3522)	0.00% (0/5087)	0.00% (0/53)
	Preparatory acts	0.00% (0/3522)	0.00% (0/5087)	0.00% (0/53)
	Suicidal ideation	0.11% (4/3522)	0.12% (6/5087)	0.00% (0/53)

Table 13: Cumulative Suicidal Behavior and Ideation Events by Indication Group and Treatment Group.

		Treatment Group		
Indication Group	**Event**	**Placebo % (n/N)**	**Test Drug % (n/N)**	**Active Control % (n/N)**
Depression Indications	Completed suicide	0.01% (1/16591)	0.02% (4/24668)	0.01% (1/8561)
	Completed or attempted suicide	0.20% (33/16591)	0.21% (52/24668)	0.21% (18/8561)
	Suicidal behavior	0.21% (35/16591)	0.22% (54/24668)	0.26% (22/8561)
	Suicidal behavior and ideation	0.80% (132/16591)	0.69% (171/24668)	0.69% (59/8561)
Psychiatric Indications	Completed suicide	0.01% (2/27164)	0.01% (5/39729)	0.01% (1/10489)
	Completed or attempted suicide	0.17% (46/27164)	0.19% (76/39729)	0.18% (19/10489)
	Suicidal behavior	0.18% (49/27164)	0.20% (79/39729)	0.22% (23/10489)
	Suicidal behavior and ideation	0.72% (196/27164)	0.62% (248/39729)	0.62% (65/10489)
Psychiatric and Behavioral Indications	Completed suicide	0.01% (2/32382)	0.01% (5/47873)	0.01% (1/10922)
	Completed or attempted suicide	0.14% (46/32382)	0.16% (77/47873)	0.17% (19/10922)
	Suicidal behavior	0.15% (49/32382)	0.17% (80/47873)	0.21% (23/10922)
	Suicidal behavior and ideation	0.61% (199/32382)	0.53% (254/47873)	0.60% (65/10922)
All Indications	Completed suicide	0.01% (2/35904)	0.01% (5/52960)	0.01% (1/10975)
	Completed or attempted suicide	0.13% (46/35904)	0.15% (77/52960)	0.17% (19/10975)
	Suicidal behavior	0.14% (49/35904)	0.15% (80/52960)	0.21% (23/10975)
	Suicidal behavior and ideation	0.57% (203/35904)	0.49% (260/52960)	0.59% (65/10975)

Rates for suicidal behavior and ideation for the Psychiatric Indications group for each individual drug are shown in Table 14.

Table 14: Suicidal Behavior and Ideation Events by Drug (Psychiatric Indications).

		Treatment Group		
Event	**Drug**	**Placebo % (n/N)**	**Test Drug % (n/N)**	**Active Control % (n/N)**
Suicidal behavior and ideation	Bupropion	0.22% (4/1800)	0.26% (7/2659)	0.45% (4/881)
	Citalopram	0.54% (4/744)	1.04% (20/1928)	0.00% (0/98)
	Duloxetine	1.23% (18/1460)	1.07% (25/2327)	0.36% (3/835)
	Escitalopram	0.14% (3/2189)	0.23% (6/2567)	0.27% (3/1096)
	Fluoxetine	1.86% (53/2857)	1.21% (58/4783)	0.69% (3/434)
	Fluvoxamine	0.71% (13/1828)	1.01% (22/2187)	0.99% (8/805)
	Mirtazapine	0.93% (6/644)	0.79% (8/1016)	0.22% (1/452)
	Nefazodone	0.79% (14/1781)	0.42% (12/2836)	0.68% (4/592)
	Paroxetine	0.49% (28/5763)	0.53% (46/8728)	1.13% (17/1506)
	Sertraline	0.53% (23/4330)	0.29% (15/5234)	0.49% (5/1013)
	Venlafaxine	0.80% (30/3768)	0.53% (29/5464)	0.61% (17/2777)
	All Drugs	0.72% (196/27164)	0.62% (248/39729)	0.62% (65/10489)

4.2 Test Drug versus Placebo Estimates

Figure 1 displays the odds ratio estimates of the test drug versus placebo by drug and overall for events of suicidal behavior and ideation using data from clinical trials for the Psychiatric Indications group.[33] The overall odds ratio estimate is less than one. The 95% confidence interval for overall odds ratio slightly overlaps the value of one. The odds ratio estimates for the 11 drugs are scattered around the value of one. The intervals for all but one of the 11 drugs (fluoxetine) overlap the value of one. The p-value for Zelen's test of the homogeneity of the odds ratios across all trials is 0.34. This result does not provide evidence for heterogeneity of the odds ratios.

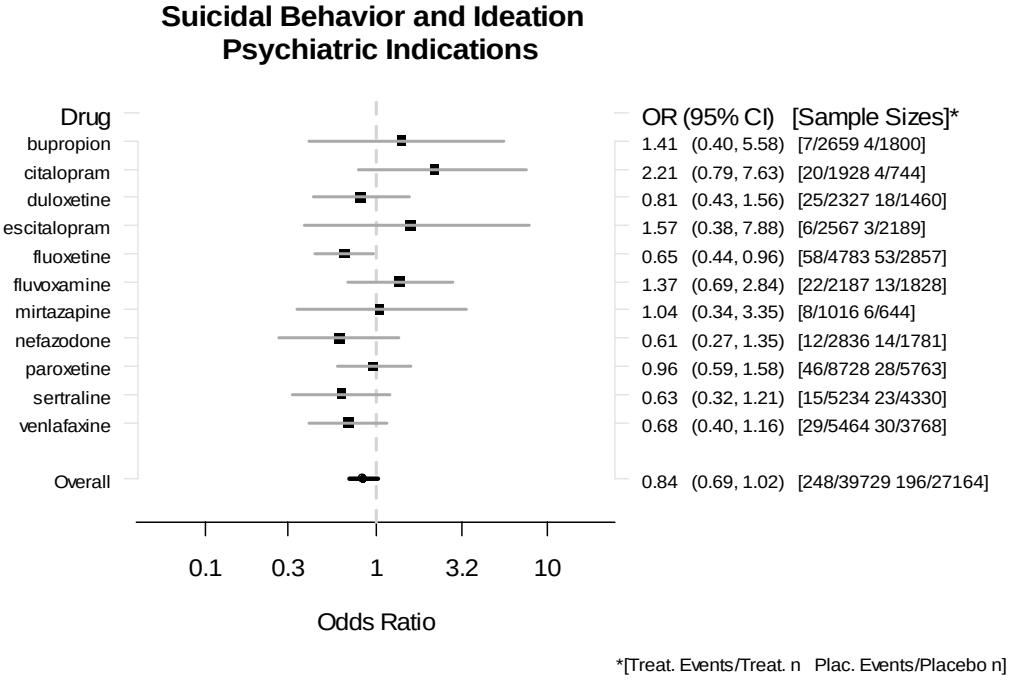

Figure 1: Odds Ratios by Drug for Suicidal Behavior and Ideation (Psychiatric Indications).

[33] Refer to the statistical methodology section for background to the results of this section, in particular Section 2.1 on the definition of the study population and endpoints and Section 2.3.1 on the primary analysis method.

Figure 2 displays the risk difference estimates of the test drug and placebo by drug and overall for events of suicidal behavior and ideation using data from clinical trials for Psychiatric Indications group. The overall risk difference estimate is less than zero. The 95% confidence interval for the overall difference slightly overlaps the value of zero. The risk difference estimates for the 11 drugs are scattered around the value of zero. The intervals for all but one of the 11 drugs overlap the value of zero.

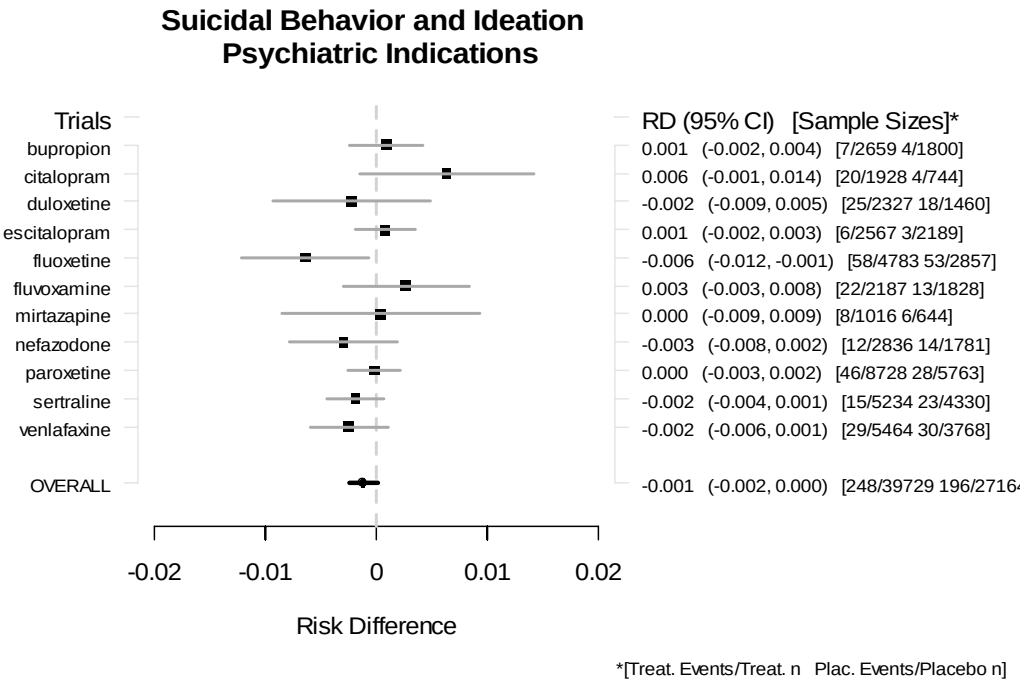

Figure 2: Risk Differences by Drug for Suicidal Behavior and Ideation (Psychiatric Indications).

Figure 3 displays the odds ratio estimates of the test drug versus placebo by indication group for events of suicidal behavior and ideation. The estimates for the first three indications groups (Major Depressive Disorders, Other Depressive Disorders, and Other Psychiatric Disorders) are all less than one. The estimates for the final two indications groups (Behavior Disorders and Other Disorders) are greater than one. For all the indication groups, the 95% intervals overlap the value of one.

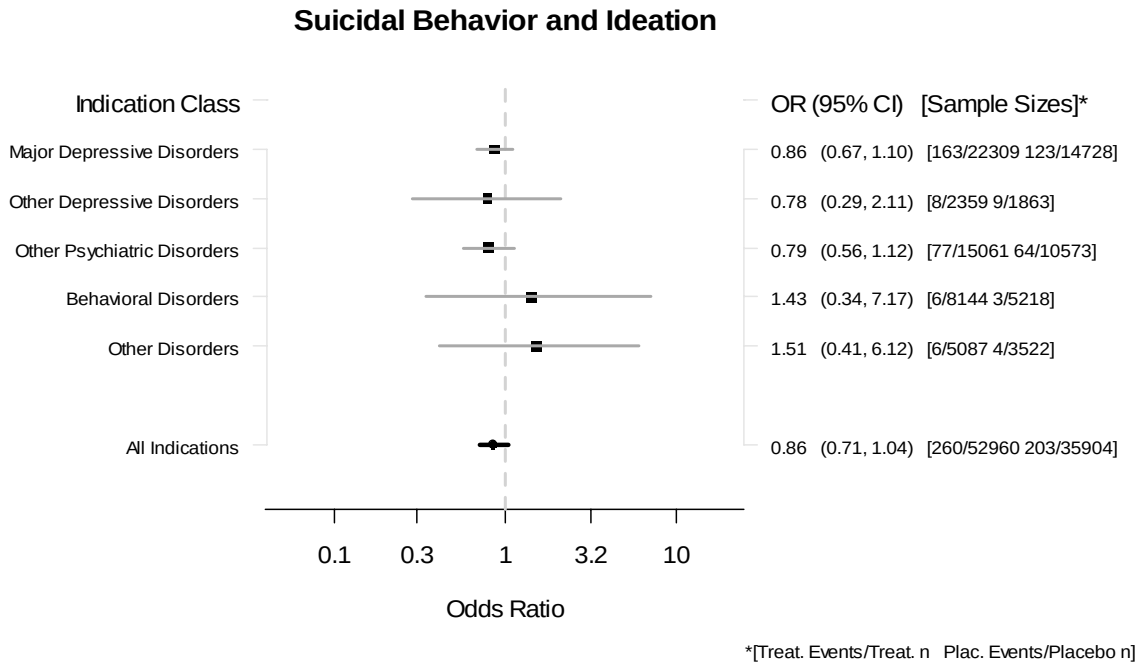

Figure 3: Odds Ratios by Indication for Suicidal Behavior and Ideation.

Figure 4 displays odds ratio estimates of the test drug versus placebo by outcome for all drugs from clinical trials for psychiatric indications. The odds ratio estimate for Suicidal Behavior is greater than one and the corresponding 95% interval overlaps the value of one. The odds ratio estimates for suicidal ideation is less than one and the corresponding 95% interval does not contain the value of one.

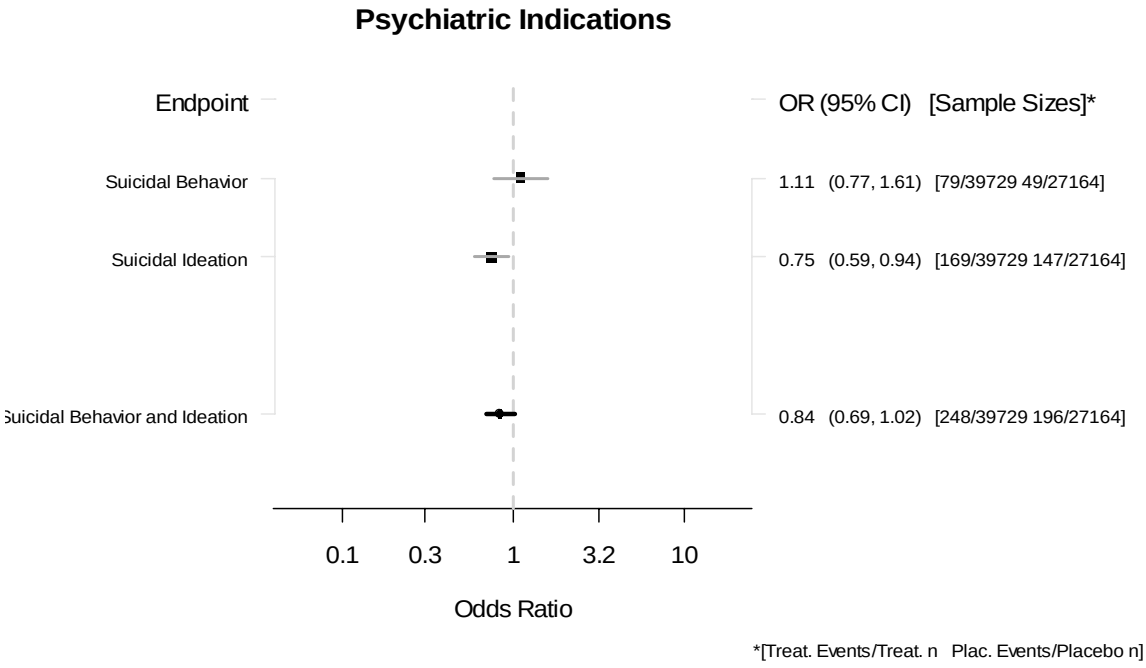

Figure 4: Odds Ratios by Outcome (Psychiatric Indications).

4.3 Sensitivity Analysis Results

Figure 5 displays the results from the methods used in the sensitivity analysis.[34] All the methods employed in the sensitivity analysis produce similar odds ratio estimates ranging from 0.81 to 0.84. As expected, the Mantel-Haenszel method with the continuity correction gives the lowest odds ratio estimate, because, as described in Section 2.3.2, proportionally more events are added to the placebo arm than the test drug arm. All the 95% intervals, except that of the Mantel-Haenszel method with the continuity correction, slightly overlap the value of one. The interval for the Mantel-Haenszel method with the continuity correction is slightly below the value of one and is not qualitatively different from the other intervals.

The variance component of the inter-trial variability of the log odds ratio from the GLMM model described in Section 2.3.2 is 0.060 with a standard error of 0.171. This result does not provide evidence for heterogeneity of the odds ratios across the trials. The heterogeneity estimate from the DerSimonian-Laird method is zero, again failing to provide evidence for heterogeneity of the odds ratios across the trials.

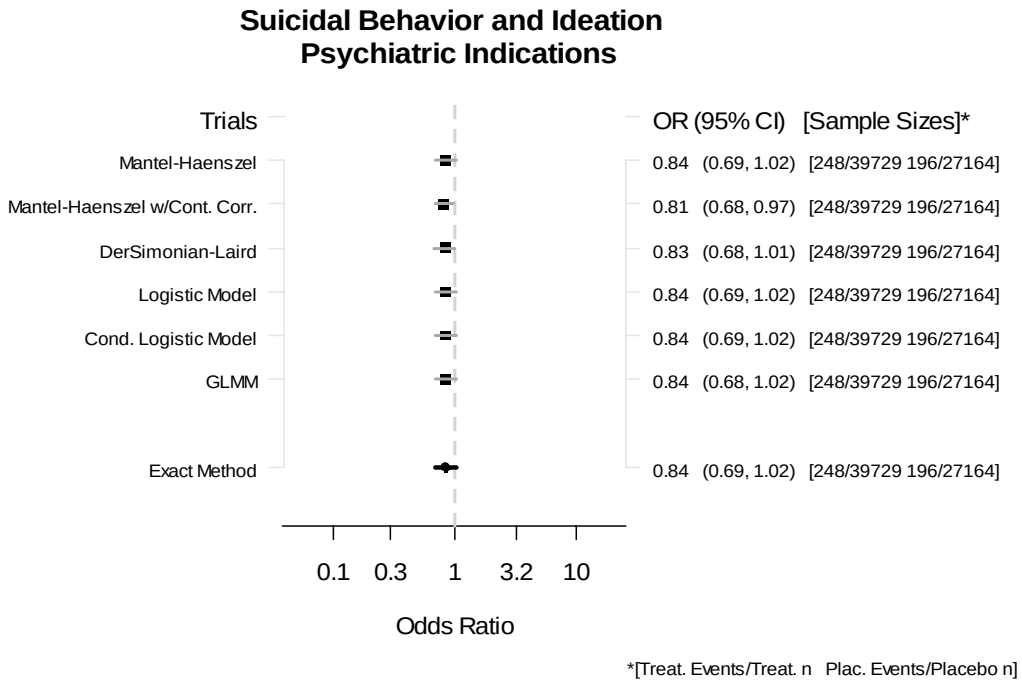

Figure 5: Sensitivity of Odds Ratios by Analysis Method for Suicidal Behavior and Ideation (Psychiatric Indications).

[34] Refer to the Section 2.3.2 on the statistical methodology used for the sensitivity analysis.

5. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

5.1 Age Groups

Because of the finding of increased risk of suicidality in pediatric clinical trials,[35] special attention is given to the age subgroups. Age subgroups were created as shown in Table 5. Table 15 displays the number of trials and subjects represented by each age group.

Table 15: Summary of Trials and Subjects by Age Group and Treatment Group (Psychiatric Indications).

			Treatment Groups		
Drug	**Age Group**	**Trials**	**Placebo n (n/trial)**	**Test Drug n (n/trial)**	**Active Control n (n/trial)**
All Drugs	18-24 Years	272	2604 (9.6)	3810 (14.0)	957 (3.5)
	25-30 Years	273	3772 (13.8)	5558 (20.4)	1482 (5.4)
	31-64 Years	289	18354 (63.5)	27086 (93.7)	7356 (25.5)
	>=65 Years	233	2397 (10.3)	3227 (13.8)	684 (2.9)
	All Non-missing Ages	295	27127 (92.0)	39681 (134.5)	10479 (35.5)

[35] Hammad (2004).

Table 16 displays, by age group, the number of trials with at least one event of suicidal behavior and ideation and at least one event of suicidal behavior and ideation in both treatment groups. Compared to the overall analysis, the number of trials with events in at least one treatment group was considerably lower for all age groups.

Table 16: Summary of Suicidal Behavior and Ideation Events by Age Group and Treatment Group (Psychiatric Indications).

Drug	Age Group	Trials[1] with At Least One Event	Trials[2] with Events in Both Treatment Groups
All Drugs	18-24 Years	19.9% (54/ 272)	2.2% (6/ 272)
	25-30 Years	17.9% (49/ 273)	2.2% (6/ 273)
	31-64 Years	44.8% (129/ 288)	13.5% (39/ 288)
	>=65 Years	7.0% (16/ 228)	0.9% (2/ 228)

[1] Denominator is the number of trials with at least one subject in the subgroup in both treatment groups.

Table 17 displays overall event rates by age group. For all events, the differences between treatment groups were greatest in the 18-24 Years and ≥65 Years age groups. In the 18-24 Years group, rates were higher among the test drug group. In the ≥65 Years age group, rates were lower in the test drug group.

Table 17: Suicidal Behavior and Ideation Events by Age Group and Treatment Group (Psychiatric Indications).

		Treatment Group		
Age Group	**Event**	**Placebo % (n/N)**	**Test Drug % (n/N)**	**Active Control % (n/N)**
18-24 Years	Completed suicide	0.00% (0/2604)	0.03% (1/3810)	0.00% (0/957)
	Suicide attempt	0.27% (7/2604)	0.55% (21/3810)	0.63% (6/957)
	Preparatory acts	0.04% (1/2604)	0.03% (1/3810)	0.21% (2/957)
	Suicidal ideation	0.50% (13/2604)	0.63% (24/3810)	0.84% (8/957)
25-30 Years	Completed suicide	0.03% (1/3772)	0.00% (0/5558)	0.00% (0/1482)
	Suicide attempt	0.11% (4/3772)	0.23% (13/5558)	0.20% (3/1482)
	Preparatory acts	0.03% (1/3772)	0.02% (1/5558)	0.07% (1/1482)
	Suicidal ideation	0.56% (21/3772)	0.49% (27/5558)	0.40% (6/1482)
31-64 Years	Completed suicide	0.00% (0/18354)	0.01% (4/27086)	0.01% (1/7356)
	Suicide attempt	0.15% (27/18354)	0.13% (35/27086)	0.12% (9/7356)
	Preparatory acts	0.01% (1/18354)	0.00% (1/27086)	0.01% (1/7356)
	Suicidal ideation	0.52% (96/18354)	0.40% (107/27086)	0.38% (28/7356)
>=65 Years	Completed suicide	0.04% (1/2397)	0.00% (0/3227)	0.00% (0/684)
	Suicide attempt	0.25% (6/2397)	0.03% (1/3227)	0.00% (0/684)
	Preparatory acts	0.00% (0/2397)	0.00% (0/3227)	0.00% (0/684)
	Suicidal ideation	0.71% (17/2397)	0.34% (11/3227)	0.00% (0/684)

Figure 6 displays odds ratio estimates of the test drug versus placebo by age group, including pediatric data taken from Hammad (2004), for events of suicidal behavior and ideation in psychiatric indications.[36] There is a clear pattern of decreasing odds ratio estimates and 95% intervals in the younger age groups compared to the older age groups. As concluded in the Hammad et al. (2006), the interval for the pediatric age group lies above the value of one. The only other age group whose interval does not contain the value of one is the 65 and up group, whose interval lies below the value of one. The interval for the 18 to 24 age group overlaps the value of one but generally lies above the value of one.

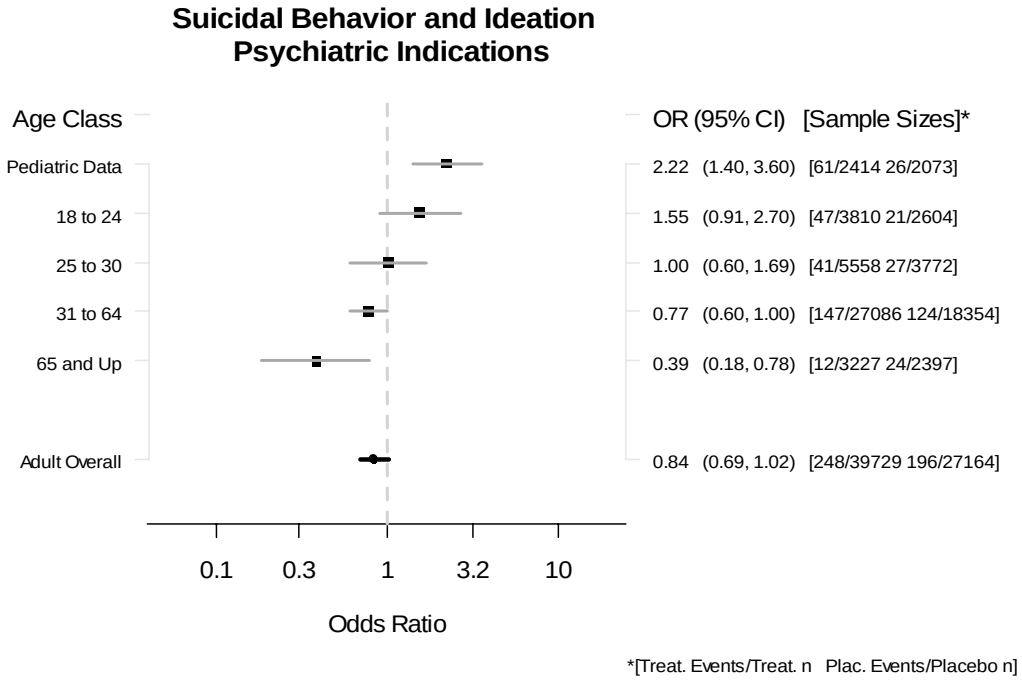

Figure 6: Odds Ratios by Age Group for Suicidal Behavior and Ideation (Psychiatric Indications).

[36] The estimate presented here for the pediatric data differs slightly from that presented in Hammad et al. (2006), because of differences in methodology. Hammad used a risk ratio summary measure estimated by Mantel-Haenszel. The estimate given in this review used the methodology described in Sections 2.3.1 and 2.3.3.

Figure 7 displays odds ratio estimates of the test drug versus placebo by outcome for the 18 to 24 age group. The estimate for the Suicide Behavior outcome is higher than the estimate for the outcome Suicidal Ideation. The 95% interval for the Suicide Behavior outcome lies slightly above the value of one.

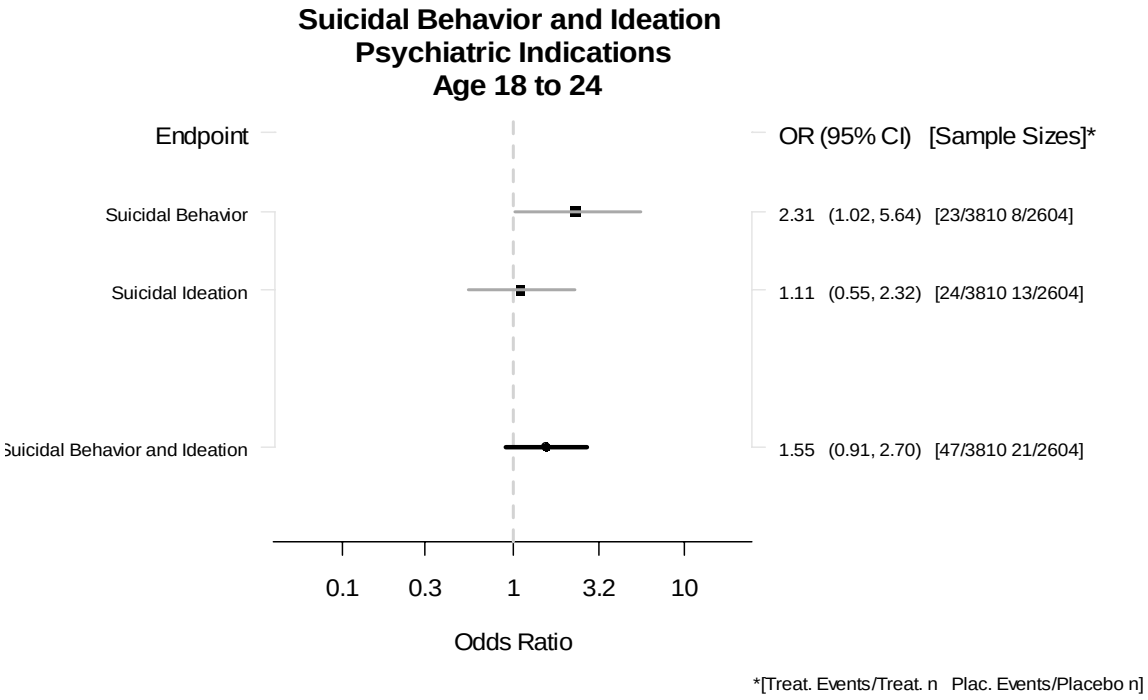

Figure 7: Odds Ratios by Outcome for the 18 to 24 Age Group (Psychiatric Indications).

5.2 Gender

Figure 8 displays odds ratio estimates of the test drug versus placebo by gender for events of suicidal behavior and ideation in psychiatric indications. There are no notable observed differences between genders.

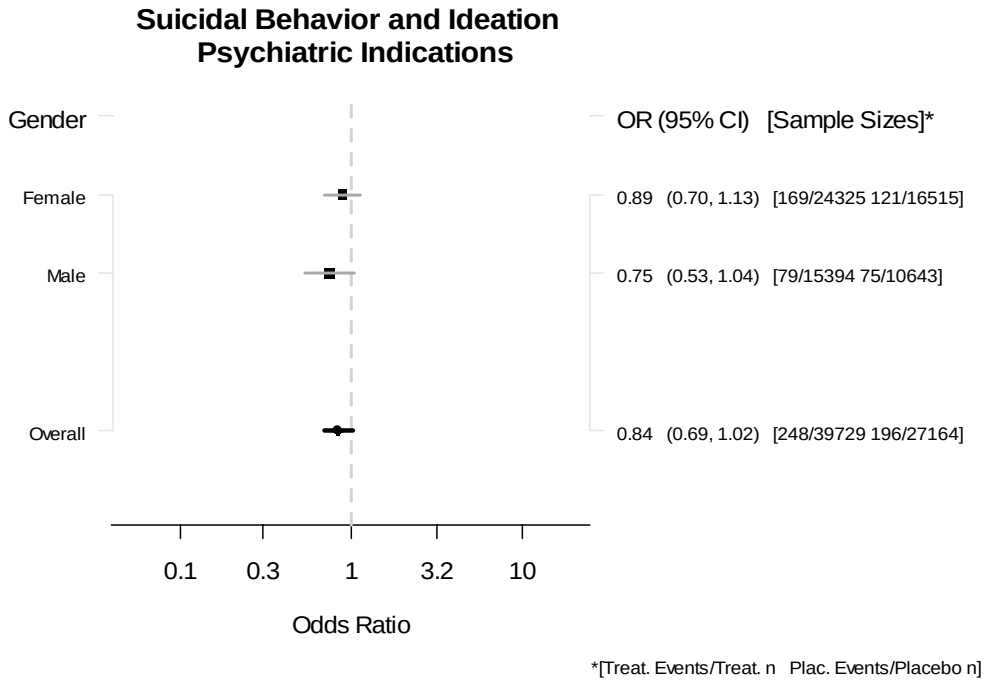

Figure 8: Odds Ratios by Gender for Suicidal Behavior and Ideation (Psychiatric Indications).

5.3 Race

Figure 9 displays odds ratio estimates of the test drug versus placebo by race for events of suicidal behavior and ideation in psychiatric indications. Note that the sample sizes for the non-white subgroup are substantially smaller than those of the white subgroup. There are no notable observed differences between races.

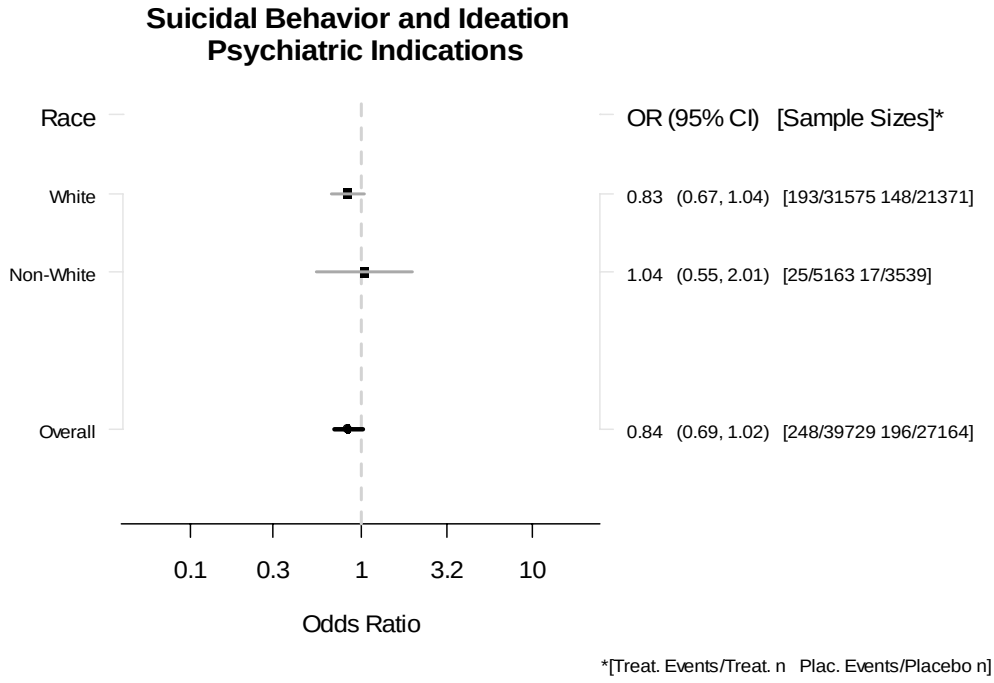

Figure 9: Odds Ratios by Race for Suicidal Behavior and Ideation (Psychiatric Indications).

5.4 Geographic Location

Figure 10 displays odds ratio estimates of the test drug versus placebo by geographic location for events of suicidal behavior and ideation in psychiatric indications. There are no notable observed differences between locations.

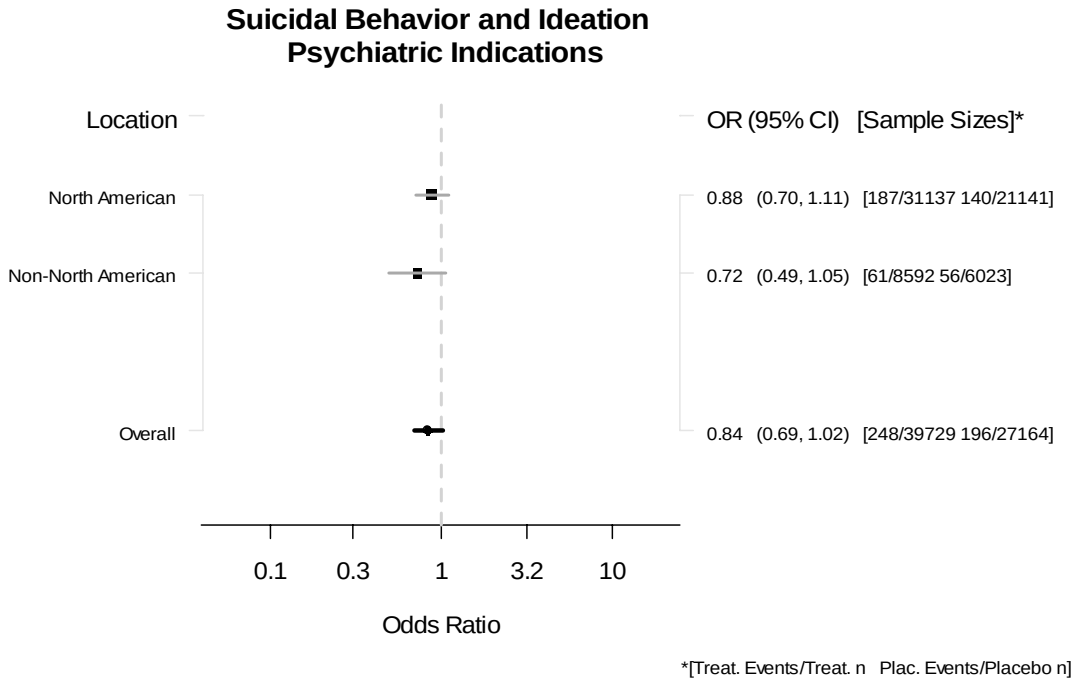

Figure 10: Odds Ratios by Geographic Location for Suicidal Behavior and Ideation (Psychiatric Indications).

5.5 Trial Setting

Figure 11 displays odds ratio estimates of the test drug versus placebo by trial setting (outpatient *vs* inpatient or both in- and out-patient) for events of suicidal behavior and ideation in psychiatric indications. Note that the sample sizes for the inpatient or both subgroup are substantially smaller than those of the outpatient subgroup. There are no notable observed differences between trial settings.

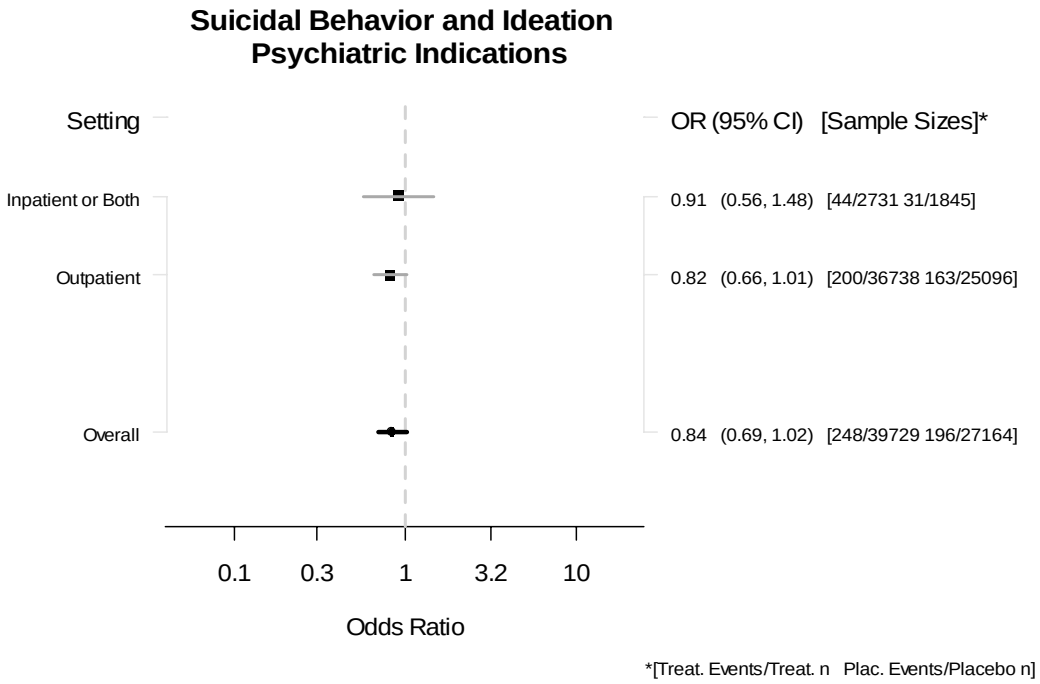

Figure 11: Odds Ratios by Trial Setting for Suicidal Behavior and Ideation (Psychiatric Indications).

5.6 Antidepressant Sub-Class

Figure 12 displays odds ratios of the test drug versus placebo estimates by antidepressant drug class for events of suicidal behavior and ideation in psychiatric indications. There are no notable observed differences between drug classes.

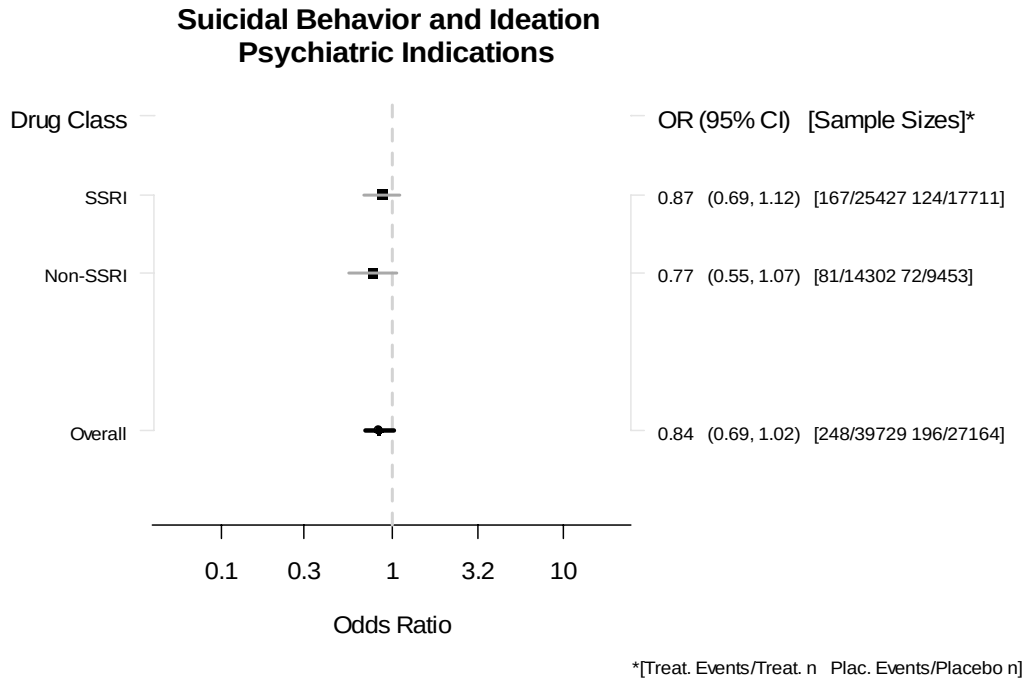

Figure 12: Odds Ratios by Drug Class for Suicidal Behavior and Ideation (Psychiatric Indications).

5.7 Joint Primary and Active Control Drug Results

Table 18 presents the numbers of suicidal behavior and ideation events and subjects for all the primary and active control drugs. Some of the 11 primary drugs were used as active controls in the trials of other primary drugs. The event and subjects counts reflect the totals counts for a drug including data from both trials in which it was the primary test drug and in which it was an active control.

Table 18: Suicidal Behavior and Ideation Events and Subjects for Primary and Active Control Drugs.

		Indication Group		
Drug Class	**Drug**	**Psychiatric**	**Other**	**Total**
Placebo	Placebo	196/27164	7/8740	203/35904
SSRI	Citalopram	24/2661	0/0	24/2661
	Escitalopram	10/3130	0/0	10/3130
	Fluoxetine	80/7180	4/4308	84/11488
	Fluvoxamine	22/2187	0/0	22/2187
	Paroxetine	50/9919	0/32	50/9951
	Sertraline	18/6363	1/587	19/6950
	Total	204/31440	5/4927	209/36367
SNRI	Duloxetine	25/2327	6/4034	31/6361
	Venlafaxine	29/5593	0/229	29/5822
	Total	54/7920	6/4263	60/12183
Other New Drugs	Bupropion	7/2659	1/3359	8/6018
	Mirtazapine	8/1016	0/252	8/1268
	Nefazodone	12/2836	0/483	12/3319
	Total	27/6511	1/4094	28/10605
Tricyclics	Amitriptyline	0/625	0/0	0/625
	Clomipramine	5/632	0/0	5/632
	Desipramine	1/315	0/0	1/315
	Dothiepin	0/106	0/0	0/106
	Imipramine	21/2345	0/0	21/2345
	Total	27/4023	0/0	27/4023
Other Drugs	Mianserin	1/28	0/0	1/28
	Trazodone	0/121	0/0	0/121
	Total	1/149	0/0	1/149
Total		509/77207	19/22024	528/99231

Figure 13 displays odds ratio estimates of drug versus placebo by the five drug classes versus placebo and the overall estimate of antidepressant drugs versus placebo class for events of suicidal behavior and ideation in psychiatric indications.[37] There are large overlaps in the 95% intervals of the drug classes. The overall odds ratio estimate for an antidepressant drug versus placebo was less than one and the corresponding 95% confidence interval marginally overlaps the value of one. This would indicate, overall, that antidepressant drugs might diminish suicidal behavior and ideation. Note that the overall estimate reflects the mix of drugs and the subjects in the data. Drugs with trials that have more subjects have more influence in the estimate than drugs with trials that have fewer subjects. The primary drugs and in particular, the SSRI and SNRI drugs, account for the vast majority of subjects.

For all indications, the odds ratio estimate for an antidepressant drug versus placebo was 0.85 (95% CI: 0.71, 1.02). The estimate and interval are very similar to those for the primary indication groups, Psychiatric Indications. This is not surprising since there are very few events and only 10 additional trials with events in the Other Disorders indications.

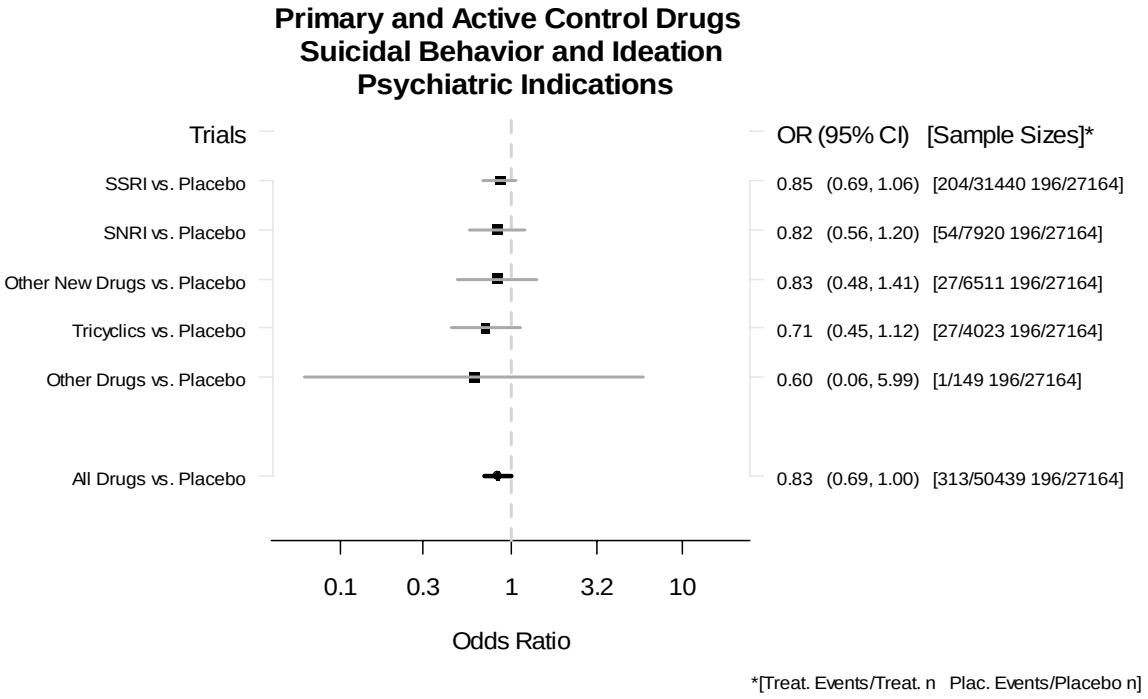

Figure 13: Odds Ratios by Drug Class for Suicidal Behavior and Ideation (Psychiatric Indications) Including Active Controls.

[37] Refer to the Section 2.3.4 on the statistical methodology used for this analysis.

6. SUMMARY AND CONCLUSIONS

The review considered 372 trials of adult subjects from 11 modern antidepressants to estimate the effect of the antidepressant drugs versus placebos on suicidal outcomes in double-blind, randomized, placebo-controlled clinical trials. These trials were divided into five indication classes. The primary analysis considered major depressive disorder, other depressive disorder, and other psychiatric disorder indications, collectively referred to as Psychiatric Indications. The primary endpoint consisted of the presence of any of the events: completed suicide, suicide attempt, preparatory acts toward imminent suicidal behavior, and suicidal ideation. These events were referred to as Suicidal Behavior and Ideation.

There were 295 trials with indications in the Psychiatric Indications group. This resulted in 27,164 subjects in the placebo arms and 39,729 subjects in the test drug arms. Of the 295 trials, 174 (59.0%) trials had a Suicidal Behavior and Ideation event in either the test-drug or the placebo arms. Table 19 summarizes the suicidality events by treatment group for the Psychiatric Indication group. There were 196 subjects with events in the placebo arms representing 0.72% of the subjects. There were 248 subjects with events in the test-drug arms representing 0.62% of the subjects. Overall, for the Psychiatric Indication group, there were 8 completed suicides with one of these suicides in an active control group. [38] There were no suicides from trials not in the Psychiatric Indication group. The rate of other events for trials not in the Psychiatric Indication group was substantially lower than the rate of events in the Psychiatric Indication group.

Table 19: Suicidal Behavior and Ideation Events by Treatment Group for Psychiatric Indications.

Event	Treatment Group			Total
	Placebo	Test Drug	Active Control	
	N=27164	N=39729	N=10489	N=77382
Completed suicide	2	5	1	8
Suicide attempt	44	71	18	133
Preparatory acts	3	3	4	10
Suicidal ideation	147	169	42	358
Total Events	196	248	65	509

Overall, the odds ratio estimate of Suicidal Behavior and Ideation of the test drug versus placebo for the Psychiatric Indications was 0.84 (95% CI: 0.69, 1.02). The comparable risk difference

[38] There was one completed suicide in a trial not considered, because the trial did not have data available for all the subjects. See Table 3.

between the test drug and placebo was -0.001 (95% CI: -0.002, 0.000). The odds ratio estimate makes use of only the trials with an event, where as the risk difference estimate makes use of all the trials.

An odds ratio less than one or risk difference less than zero would imply that drugs have a protective effect relative to placebo. There appears to be marginal support that the drugs might have a protective effect on the overall adult population.

There appears to be an age effect of the drugs. Younger age groups had higher odds ratio estimates than older age groups. The youngest age group considered, the 18 to 24 age group, had an odds ratio estimate of 1.55 (95% CI: 0.91, 2.70).

Other subgroups based on gender, race, trial location, treatment setting did not show notable differences in the odds ratio estimates. Likewise, a comparison between trials with SSRI and non-SSRI drugs, when the drug was the primary test drug, did not show notable differences in the odds ratio estimates.

An analysis that included both the primary test drug and active control drug arms of the trials compared the odds ratio across five classes of antidepressants. There were no notable differences in the odds ratio estimates among the five classes. Overall, considering both the primary test drugs and active control drugs, the odds ratio estimate of Suicidal Behavior and Ideation of drug versus placebo for the Psychiatric Indications was 0.83 (95% CI: 0.69, 1.00).

A sensitivity analysis was performed to evaluate the robustness of the primary statistical analysis method. Several alternative methods were compared to the exact method used in the primary statistical analysis including the Mantel-Haenszel odds ratio method with and without continuity corrections, the DerSimonian and Laird method, a logistic regression model, a conditional logistic regression model, and a generalized linear mixed model. All methods produced very similar results.

There are limitations to the generalizability of this review. Hammad et al. (2006) contains a discussion of limitations in the context of the analysis of the pediatric antidepressant trials that is relevant in this review. We emphasize here those of a statistical nature. The trials were not designed to address the objectives of this review. All the results are thus post hoc and may suffer from the usual concerns of post hoc analyses such as statistical multiplicity. The outcome events were not collected explicitly in the trials. They were created based on FDA advice using the available data. Therefore, there may be measurement error. Finally, the trials were conducted over a large time period. Subjects in the trials and objectives of the trials may have varied over time. The relevance to today’s patient population should be considered.

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APPENDIX 1: INDICATION FIELD BY INDICATION GROUP

This appendix provides the text found in the indication field from the data submission and the grouping of the text into the five indication groups

Indication Group	Indication Text
Major Depressive Disorder	MDD
Other Depression Disorders	Atypical Depression
	BIPOLAR DISORDER
	DEPRESSION
	DYSTHYMIA
	Depression (Non-MDD)
	Dysthymia
	Dysthymia, Major Depression
	MDD or Bipolar Disorder
	Major Depression, Bipolar Disorder
	PMDD
	POST NATAL DEPRESSION
	Premenstrual Dysphoric Disorder
	SEASONAL AFFECTIVE DISORDER
	SSD
	Seasonal Affective Disorder / Recurrent MDD
Other Psychiatric Disorders	ADHD
	ADJUSTMENT DISORDER
	ANXIETY
	ANXIETY DISORDERS
	Alzheimer disease
	BULIMIA
	BULIMIA NERVOSA
	Dementia Alzheimer
	GAD
	GAD/SAD
	Generalized Anxiety Disorder

Indication Group	Indication Text
	Generalized Social Phobia
	Negative Symptoms of Schizophrenia
	Neurasthenia
	Non-Depressed OCD
	OCD
	Obsessive Compulsive Disorder
	PAIN DISORDER
	PANIC
	PANIC DISORDER
	PTSD
	Panic
	Panic Dis.
	Panic Disorder
	Post-traumatic Stress Disorder
	SAD
	SOCIAL PHOBIA
	Social Anxiety Disorder
Behavioral Disorders	ALCOHOL ABUSE (NONDEPENDENT), OTHER AND UNSPECIFIE
	ALCOHOLISM
	Cessation of Smoking in Healthy Male Volunteers
	Cessation of Smoking in Healthy Volunteers
	Exogenous Obesity
	INSOMNIA
	INSOMNIA & ANXIETY PRECEDING SURGERY
	OBESE NIDD
	OBESITY
	OBESITY + HYPERTENSION
	OBESITY + HYPERTENSION / DIABETES
	OBESITY + NIDD
	OBESITY + NIDDM
	OBESITY + TYPE II DM / GLUCOSE INTOLERANCE
	OBESITY / DIABETES + GLUCOSE INTOLERANCE

Indication Group	Indication Text
	Obesity
	SMOKING CESSATION
	SMOKING WITHDRAWAL
	Smoking Cessation
	WEIGHT LOSS
	WEIGHT MAINTENANCE
All Other Disorders	DN
	FIBRO
	Fibromyalgia
	MUI
	Migraine Prophyl.
	Neuropathic Pain
	Non-Ulcer Dyspepsia
	Premature Ejaculation
	SUI
	Sexual Dysfunction
	Sexual Function in Sexually Active, Healthy Hetero
	Sleep in Healthy Volunteers
	UUI

APPENDIX 2: REQUEST TO SPONSORS

ADVICE FOR THE PHARMACEUTICAL INDUSTRY IN EXPLORING THEIR PLACEBO-CONTROLLED CLINICAL TRIALS DATABASES FOR SUICIDALITY AND PREPARING DATA SETS FOR ANALYSIS BY FDA

[Draft: 8-2-05]

Given the finding of a signal for an increased risk of suicidality (suicidal ideation and behavior) in pediatric patients exposed to various antidepressants in placebo-controlled trials, and possible signals for treatment-emergent suicidality for antidepressants and other drugs in adult trials, including nonpsychiatric drugs and indications, there is interest in re-examining data from trials of a broader range of drugs and indications. In exploring these clinical trials databases, we recommend that similar methods to those used in evaluating the pediatric antidepressant data be utilized. We have outlined in this guidance document an approach that we recommend for these exploratory efforts.

Clinical Trials to Include in the Suicidality Exploration

Precisely which trials to include will depend in part on the study designs used in the indications of interest. In general, however, we recommend that the explorations be limited to double-blind, randomized, placebo-controlled trials which have been completed. Duration of the trials should not be a limiting factor, however, we recommend that only trials with at least 20 patients or subjects per treatment arm be included. Before beginning the exploration, we ask that you provide a list of the trials that you intend to include, and also a list of the RCTs that you have chosen not to include, along with a brief explanation for their exclusion.

Once there is agreement with FDA on which trials to include in the exploration, we ask that you provide certain descriptive information about these trials. We ask that you provide this information in table format at the same time that you submit a dataset with the suicidality data (see later). Attached to this document is the information that should be included in the requested tables.

Search for "Possibly Suicide-Related" Adverse Events and Preparation of Narrative Summaries

<u>Time Frame for "Possibly Suicide-Related" Adverse Events</u>

This search should be strictly limited to adverse events that occurred during the double-blind phase of treatment, or within 1 day of stopping randomized treatment. Adverse events should not be included if they occurred prior to randomization or more than 1 day after discontinuing from randomized treatment. The end of trials with a tapering period should be set to be at the beginning of the tapering period. Events occurring more than 1 day after discontinuing from randomized treatment should be excluded even if discontinuation occurred before the nominal endpoint of the trial. For example, if a patient either discontinued of his or her own volition or

was asked to discontinue by the investigator after 2 weeks of randomized treatment in a trial of 8 weeks duration, and the patient then experienced a "possibly suicide related" adverse event 2 days after stopping, that event should not be included.

Generally, events that are preexisting at baseline are not counted as treatment emergent if they recur during the course of a trial. However, in the requested analysis, suicidality-related events that occur during the course of the double-blind phase or within 1 day of beginning taper, switching or stopping treatment should be counted, even if they occur in a patient who had such events at some prior time. The rationale for this rule is that it is generally very difficult to determine for the quality of data available in most of these trials whether suicidality occurring during the context of these trials is new or a continuation of some prior event.

Search Strategies for Possibly Suicide-Related Adverse Events (PSRAEs)

The following search strategies should be employed to identify adverse events of possible interest with regard to suicidality:

- The following text strings should be used in searches of (1) all preferred terms; (2) all verbatim terms; and, (3) any comment fields:

  "accident-", "attempt", "burn", "cut", "drown", "gas", "gun", "hang", "hung", "immolat", "injur-", "jump", "monoxide", "mutilat-", "overdos-", "self damag-", "self harm", "self inflict", "self injur-", "shoot", "slash", "suic-", "poison", "asphyxiation", "suffocation", "firearm" should be included. All events identified by this search should be included among the PSRAEs, unless they can be considered false positives.

  Note: 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"). These terms might be characterized as "false positives" in the sense that the verbatim term was selected because one of the text strings occurred within that term but the term had no relevance to suicidality. Although we request that such terms be excluded, we ask that you prepare a table listing all such false positives, as follows:

Study #	Patient #	Treatment Assignment	Term in Which Text String Occurred

  The patients in this table will have as many rows as they have potential events.

- All deaths and other serious adverse events (SAEs) should be included among the PSRAEs.

- All PSRAEs identified by these 2 search strategies (and not excluded as "false positives") should have narrative summaries prepared, as described in the following section.

Preparation of Narrative Summaries for "Possibly Suicide-Related" Adverse Events

A complete set of narrative summaries should be prepared and collected for all PSRAEs that were not otherwise excluded as false positives. In some cases, narratives will have already been prepared, e.g., deaths and SAEs. Many of these may be acceptable, however, some may need to be re-written if important information is missing (see below). In other cases, however, sponsors will need to prepare narrative summaries by searching CRFs for any information that might be considered possibly relevant to suicidality. They should also utilize other relevant sources of information, e.g., hospital records, results of consults, questionnaire responses, etc, in preparing these narrative summaries. Depending on how much information is available, narrative summaries may be longer than 1 page, however, in no case, should more than 1 narrative summary be included on a single page. Following is the type of information that should be included in the original narrative summaries:

- Patient ID number
- Trial number
- Treatment group
- Dose at time of event (mg)
- Recent dose change – elaborate on timing and amount of dose change
- Sex
- Age
- Diagnosis
- History of suicidal thoughts
- History of suicide attempt
- History of self harm
- Adverse event Preferred term
- Adverse event Verbatim term
- Serious adverse event (y/n)
- Number of days on drug at time of event
- Treatment was discontinued following event (y/n)
- Patient had an emergency department visit and was discharged (y/n)
- Patient was hospitalized (y/n)
- Patient died (y/n) – if yes, elaborate on cause of death
- Associated treatment emergent adverse events
- Concurrent psychosocial stressors
- Psychiatric comorbidities
- Concomitant medications
- Other pertinent information (e.g., family history of psychiatric disorders)-

Other relevant information for preparing narrative summaries:

-Patients may be identified as having events of interest in one or more of the above searches, and they may have more than one event of interest. In no case, however, should

there be more than one narrative summary per patient. In cases where there is more than one event for a given patient, each different event should be clearly demarcated in the narrative.
-Only events occurring during the "exposure window" defined as during the double-blind phase (including the first day after abrupt discontinuation or the first day of taper, if tapering is utilized) should be included in the narrative summary, i.e., sponsors should not include any prerandomization events or events occurring more than 1 day after stopping randomized treatment or during the tapering period.
-As noted, sponsor should not exclude events of interest on the basis of a judgment that they might not represent "treatment-emergent" events; we feel this judgment is too difficult to make and we prefer to simply include all potentially relevant events, regardless of whether or not similar thoughts or behaviors may have occurred prior to treatment.

The narrative summaries do not need to be submitted to FDA. However, we may at some point request a random sample of the summaries to audit your classification process.

Classification of "Possibly Suicide-Related" Adverse Events

Once the narrative summaries for "possibly suicide-related" adverse events are prepared and collected, we ask that you accomplish a rational classification of these events using the approach that was well-characterized by the Columbia group for the pediatric suicidality narratives. This approach was described in detail by Dr. Kelly Posner at the September 13 and 14, 2004 advisory committee meeting. The details are provided in her slides for that meeting (available on FDA's website), in the transcript for that meeting, and in other reviews, etc. pertinent to pediatric suicidality and available on FDA's website [Slides http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4065S1_06_FDA-Posner.ppt and Briefing Document, transcripts, etc. http://www.fda.gov/ohrms/dockets/ac/cder04.html#PsychopharmacologicDrugs

The categories of interest from FDA's standpoint are as follows:

Completed suicide (code 1)
Suicide attempt (code 2)
Preparatory acts toward imminent suicidal behavior (code 3)
Suicidal ideation (code 4)
Self-injurious behavior, intent unknown (code 5)
Not enough information (fatal) (code 6)
Self-injurious behavior, no suicidal intent (code 7)
Other: accident; psychiatric; medical (code 8)
Not enough information (nonfatal) (code 9)

Those individuals who classify the narratives must have the appropriate expertise and training to accomplish this task. Thus, this task could be accomplished by seeking the help of an outside contractor who has this expertise. However, it is also possible that a sponsor may have internal expertise to accomplish this classification. Even in the latter instance, you may consider at least obtaining training of your internal staff from an outside contractor. Such training might help to increase the reliability of the classifications for subsequent meta-analyses of the data across programs.

Prior to their rational classification, the narratives must be blinded to details that might bias their assessments. The details of appropriate blinding of the narratives can also be obtained in the transcript from the advisory committee meeting referred to above, and the materials available on FDA's website pertinent to that meeting. We request that you block out the following information that could reveal treatment assignment:

- Identifying patient information, identity of study drug, and patient's randomized drug assignment
- All identifying information regarding the sponsor, the clinical trial number, and the location of the trial

- All years with the exception of years in remote history
- Study drug start and stop dates (month, day, and year)
- All medications, both prescription and non-prescription, whether taken before, during, or after the study; non-pharmaceutical substances (e.g., alcohol, tobacco) should not be blocked out
- Names of medications involved in overdoses; the number of pills consumed should not be blocked out
- Indications for medications started during or after the study
- Indications for study drug

Data Submission

In order to perform additional analyses investigating the relationship between exposure to the drug of interest and PSRAEs among the patients of interest, we would appreciate your submitting the following variables as outlined in the next table. As noted, we are requesting information from placebo controlled trials only. Please do not submit data from active control only studies, uncontrolled extensions of placebo controlled studies, or combination drug studies. We would expect that you will provide us with a SAS transport file. We are requesting that you provide this file to the Agency by [insert date].

Variable name	Type	Description	Coding notes
SOURCE	Character	First few letters of your drug name	
TRIAL	Character	Trial ID	
INDICATION	Character	Indication that is focus of the trial	
CTPID	Character	Patient ID within each trial	
UNIQUEID	Character	A unique ID for every patient	
AGE	Numeric	Patient age	In years
AGECAT	Numeric	Age category	1=5-17 y 2=18-24 y 3=25-64 y 4=65 y or more
GENDER	Numeric	Patient gender	1=female 2=male
RACE	Numeric	Patient race	1=White Caucasian 2=African-American 3=Hispanic 4=Asian 5=Other . = Missing
RANTXCAT	Numeric	Treatment category	1=

Variable name	Type	Description	Coding notes
		(assuming drugs can be categorized by class)	2= 3= 6=placebo
SETTING	Numeric	Setting of trial	1=inpatient 2=outpatient 3=both
LOCATION	Numeric	Location of trial	1=North America 2=Non-North America
TXARM	Numeric	Randomized treatment	1=drug 2=placebo 3=active control No missing values are allowed in this variable.
TXACTIVE	Character	Name of drug used as active control	Leave patients in other treatment arms blank
SCALE	Character	Primary scale used to rate indication that is focus of the trial (this variable is required only for depression trials)	This should be a text field. As noted, please submit an electronic copy of whatever instrument was used for the primary protocol-specified endpoint(s).
SCOREA	Numeric	Score of primary scale at baseline (this variable is required only for depression trials)	No missing values are allowed in this variable.
SCOREB	Numeric	Score of primary scale at end of trial (this variable is required only for depression trials)	No missing values are allowed in this variable.
RESPONSE	Numeric	Response status (this variable is required only for depression trials)	0=non-responder 1=responder[39] . = Missing
EVENT	Numeric	This variable contains the code for the first suicidality event. If a patient had more than one event in the desired "exposure window", then the most severe event should be	0=no event 1=completed suicide 2=suicide attempt 3=preparatory acts toward imminent suicidal behavior 4=suicidal ideation

[39] Please specify the criteria used to define patients as responders

Variable name	Type	Description	Coding notes
		listed. Severity is decided based on the following order of codes: 1>2>3>4>5>6>9. Every patient in every trial will be classified on this variable. For the majority of patients who are not identified as having a "possibly suicide-related AE", the classification will be 0 (no event). Similarly, those patients who have "possibly suicide-related AEs" that are coded as 7 or 8 will also be classified for this variable as 0 (no event), because we will not be using codes 7 or 8 in our analyses. Patients with event codes 1 through 6 for SRE's will be classified with their most severe event code.	5=self-injurious behavior, intent unknown 6= not enough information, fatal 9= not enough information, non-fatal No missing values are allowed in this variable.
EVENTDAY	Numeric	The number of days to the first most severe suicidal event, counting from the day of the first dose.	For patients without events, this variable should contain days until end of trial or until premature discontinuation For patients with more than one event, this variable should contain days until the first most severe event that is listed under the variable "EVENT" No missing values are allowed in this variable.
DISCONT	Numeric	The patient discontinued before the end of the controlled portion of the trial	0=No 1=Yes No missing values are allowed in this variable
HXSUIATT	Numeric	The subject had a history of	0=No

Variable name	Type	Description	Coding notes
		suicide attempt prior to entering the RCT as defined by: HAMD item 3=4 or relevant screen in other questionnaires used at baseline (this variable is required only for depression trials)	1=Yes . = Missing or no information available
HXSUIID	Numeric	The subject had a history of suicidal ideation prior to entering the RCT as defined by: HAMD item 3=3, MADRS item 10 >=3, or relevant screen in other questionnaires used at baseline (this variable is required only for depression trials)	0=No 1=Yes . = Missing or no information available

Attachment

For each trial included in the analysis, please provide a summary of important study characteristics in tabular form as shown in Tables 1 and 2 below. Many of the column headings are self-explanatory. However, the following headings merit clarification:

• **Number of Patients**: number of patients randomized to the drug and placebo treatment groups.
• **DB TX Duration**: the nominal duration of the analyzed double-blind treatment phase.
• **Protocol Dose**: the protocol-specified daily target dose expressed as a range for flexible dose studies and as individual doses for fixed dose trials.

Note: The following headings apply only to depression trials:

- **Extensive DX Screening**: indicate yes if the study required confirmation of the diagnostic entry criteria by two or more independent raters. Otherwise, indicate no.
- **Exclude TX Resistant**: indicate yes if a study exclusion criterion was a history of treatment resistance or poor response of the index illness to previous treatment. Otherwise, indicate no.
- **Exclude Bipolar D/O**: indicate yes if a study exclusion criterion was a history or presence of bipolar disorder or mania in the patient. Otherwise, indicate no.
- **Exclude Family H/O Bipolar Disorder**: indicate yes if a study exclusion criterion was any family history of bipolar disorder or mania. Otherwise, indicate no.

TABLE 1: BASIC STUDY DESIGN							
Drug	**Study**	**Indication**	**Age Range (years)**	**Number of Patients**		**DB TX Duration (weeks)**	**Protocol Dose (mg/day)**
				Drug	**Placebo**		
XYZ	123	MDD	18 to 60	120	119	6	120 to 160
	456	MDD	55 to 85	148	148	8	120, 140, 160
	789	OCD	18 to 65	119	110	12	120, 140
	1111	OCD	18 to 70	71	69	13	120 to 160

TABLE 2: SCREENING AND KEY EXCLUSIONARY CRITERIA									
Drug	**Study**	**Indication**	**Extensive**	**Placebo**	**Exclude TX**	**Excl. Current**	**Excl. H/O Suicide**	**Excl. Bipolar**	**Excl. Family H/O**
XYZ	123	MDD	No	Yes	No	Yes	No	Yes	No
	456	MDD	Yes	Yes	No	No	No	Yes	Yes
	789	OCD	Yes	Yes	Yes	Yes	No	Yes	Yes
	1111	OCD	No	No	No	Yes	No	Yes	Yes

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/s/

Mark Levenson
11/17/2006 10:51:40 AM
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Stella Machado
11/17/2006 10:59:58 AM
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