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

TABLE OF CONTENTS

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]

---

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

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]

---

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

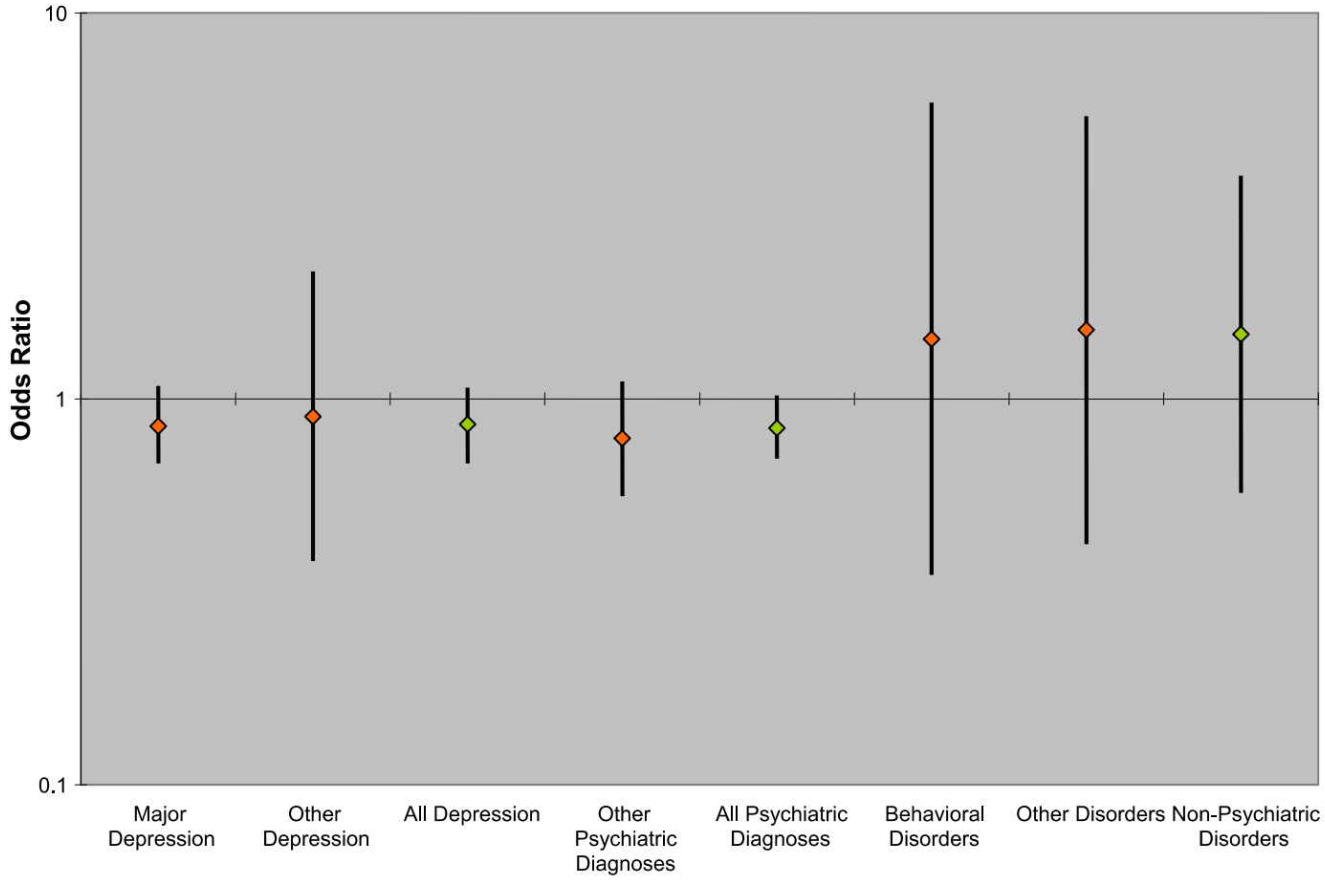

Figure 1: Suicidality Risk for Active Drug relative to Placebo – Ideation or Worse – All Adults – By Diagnostic Category (Bands represent 95% CI)

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

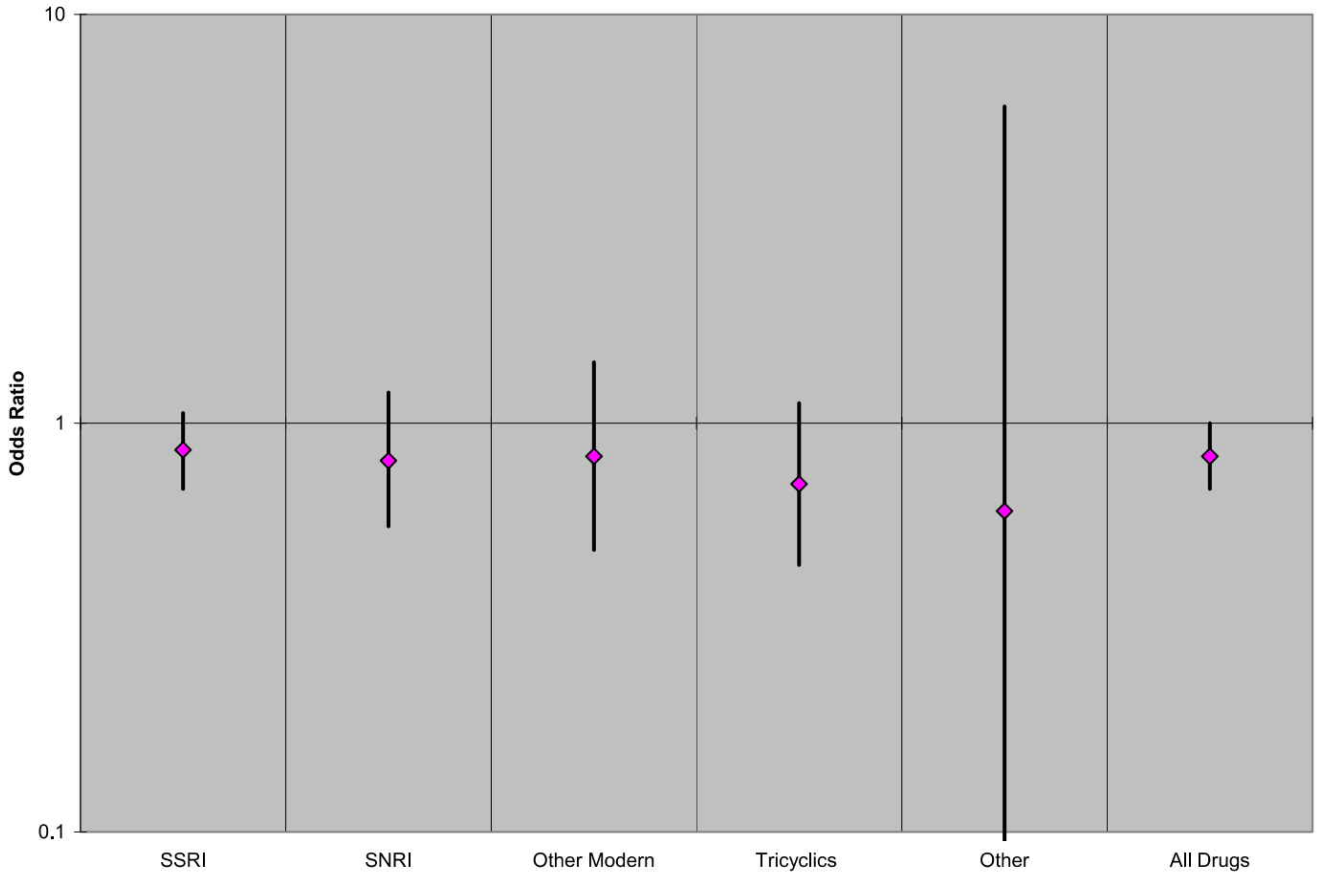

Figure 2: Suicidality Risk for Active Drug relative to Placebo – Ideation or Worse –Adults with Psychiatric Disorders – By Drug Class (Bands represent 95% CI)

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

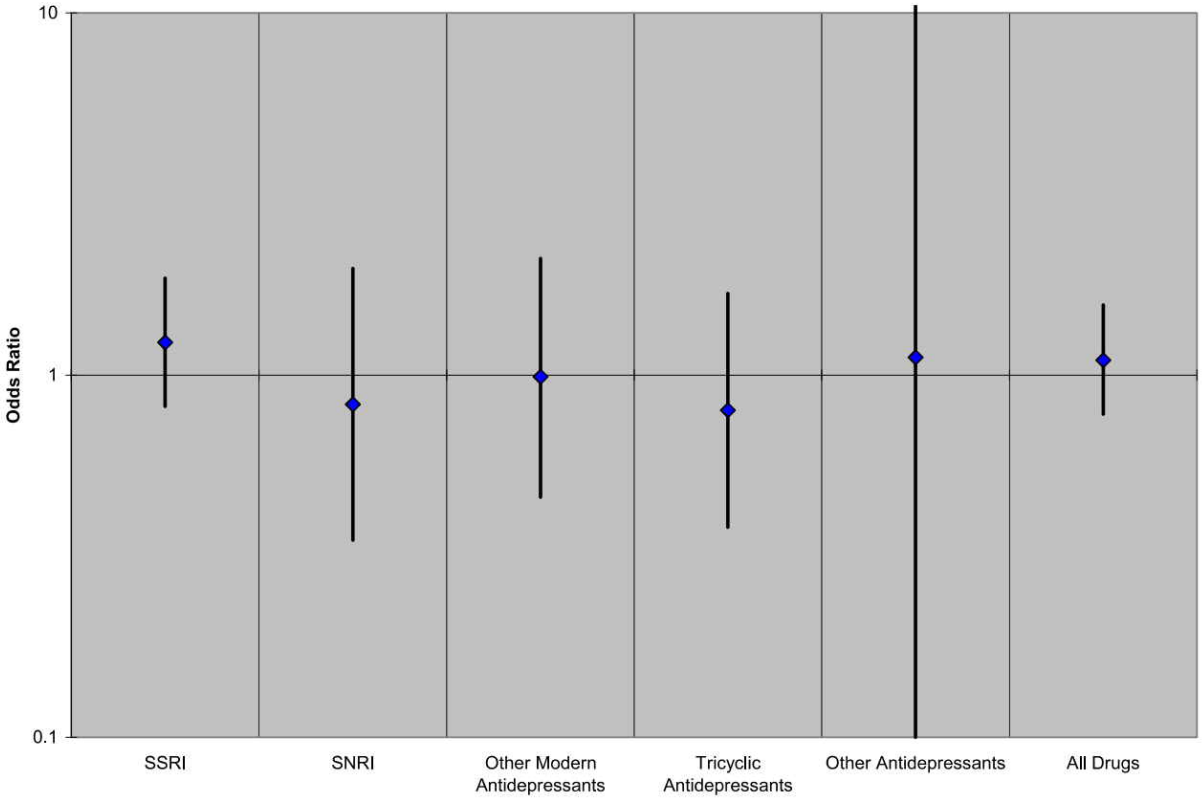

Figure 3: Suicidal Behavior Risk for Active Drug relative to Placebo – Preparation or Worse –Adults with Psychiatric Disorders – By Drug and Drug Class (Bands represent 95% CI)

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

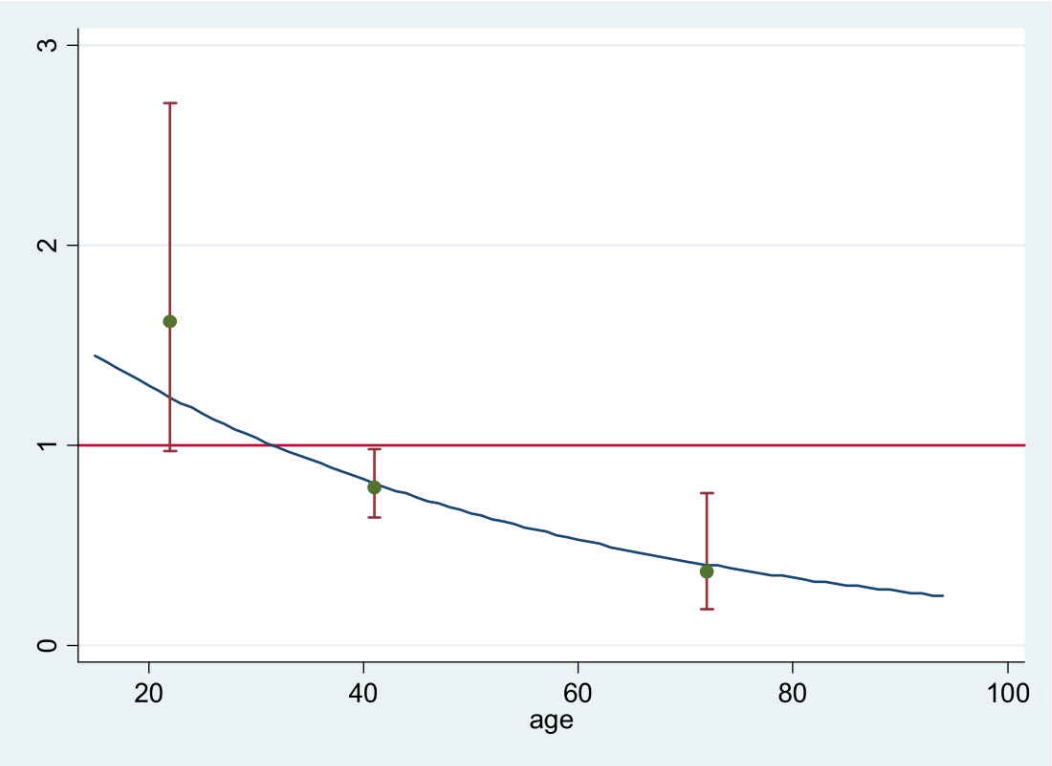

Figure 4: Suicidality Odds Ratio for Active Drug relative to Placebo – Adults with Psychiatric Disorders – By Age

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

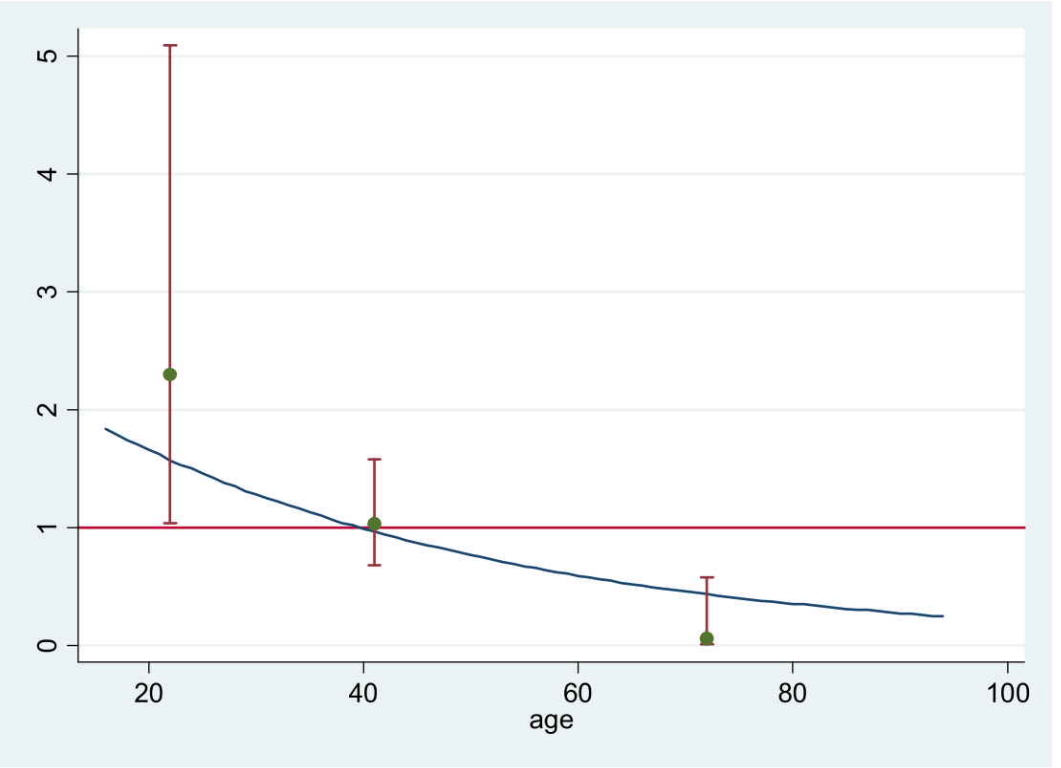

Figure 5: Suicidal Behavior Odds Ratios for Active Drug relative to Placebo – Preparation or Worse –Adults with Psychiatric Disorders – By Age

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).

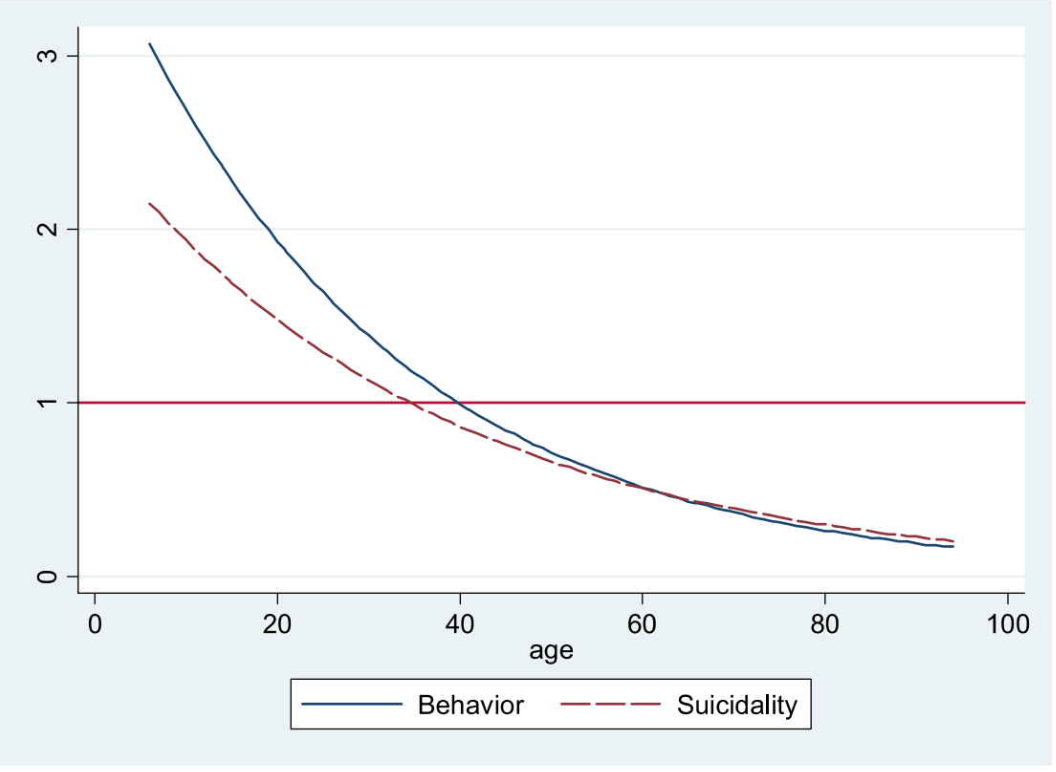

Figure 6: Odds Ratios for Suicidality and Suicidal Behavior for Active Drug relative to Placebo by Age

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

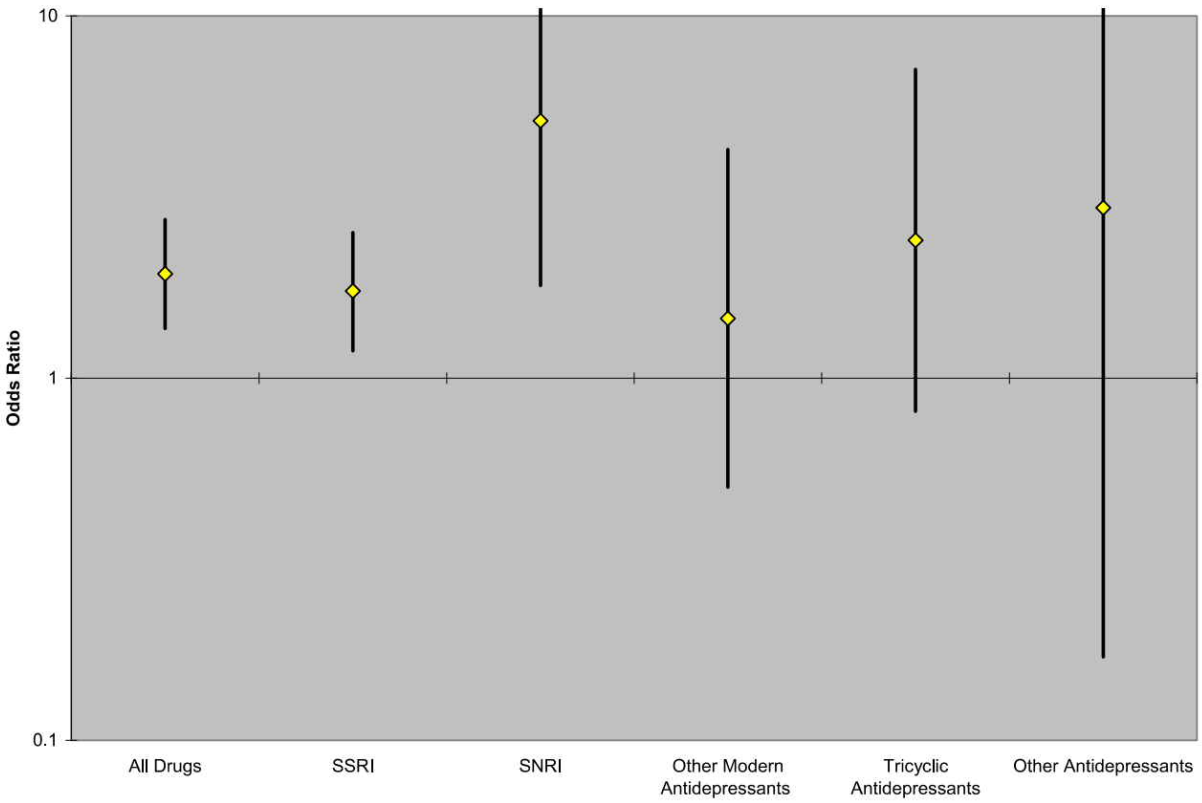

Figure 7: Suicidality Odds Ratios for Active Drug relative to Placebo – Ideation or Worse – Subjects under age 25 with Psychiatric Disorders – By Drug Class

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

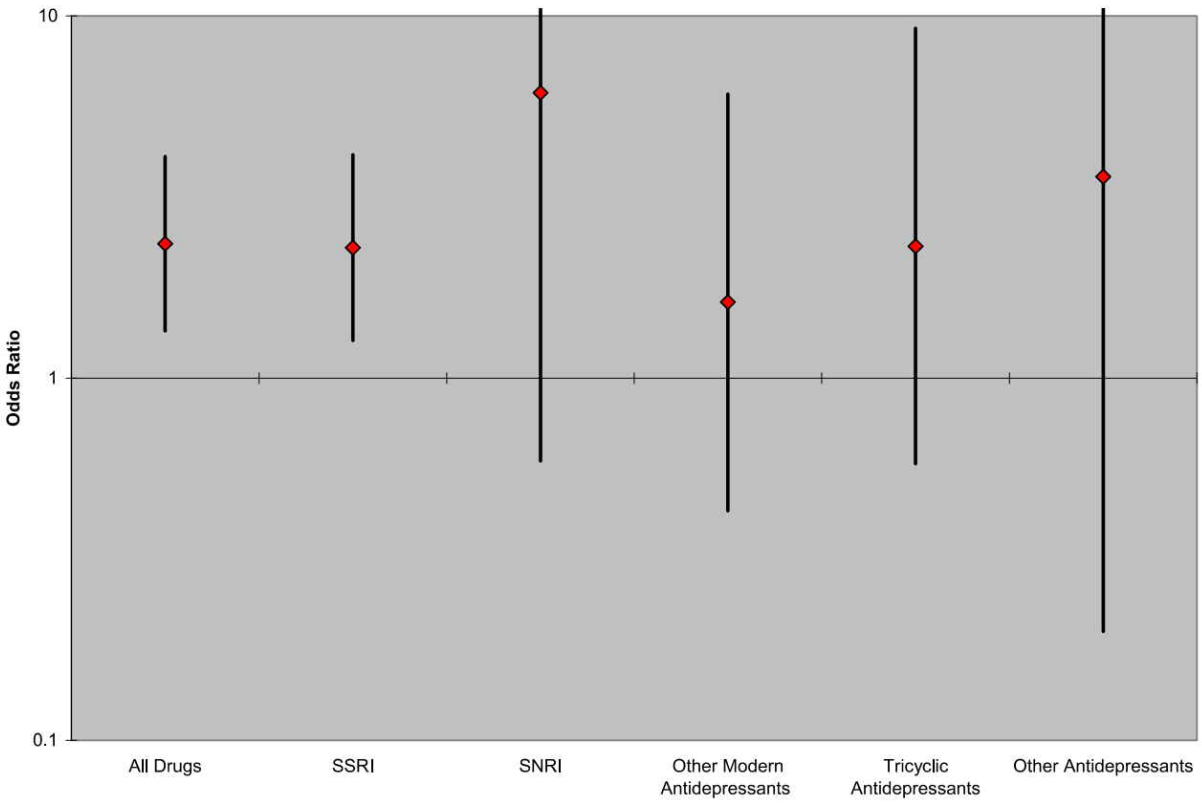

Figure 8: Suicidal Behavior Risk for Active Drug relative to Placebo – Preparation or Worse – Subjects under age 25 with Psychiatric Disorders – By Drug Class

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