Review and Evaluation of Clinical Data

Drugs, NDAs, sponsors, and date of submissions:

1. Wellbutrin (Bupropion), NDA 18-644, GlaxoSmithKline, submissions dated 11/04/03, 4/15/04, 5/18/04
2. Remeron (mirtazapine), NDA 20-415, Organon, submissions dated 11/10/03 & 4/15/04
3. Luvox (fluvoxamine), NDA 21-519, Solvay, submissions dated 11/10/03 & 4/13/04
4. Effexor and Effexor XR (venlafaxine), NDAs 20-151 and 20-699, Wyeth, submissions dated 11/19/03 & 5/14/04
5. Zoloft (sertraline), NDA 19-839, Pfizer, submissions dated 11/21/03 & 4/15/04
6. Celexa (citalopram), NDA 20-822, Forest, submissions dated 11/21/03 & 4/15/04
7. Paxil (paroxetine), NDA 20-031, GlaxoSmithKline, submissions dated 11/24/03, 4/15/04, & 5/17/04
8. Prozac (fluoxetine), NDA 18-936, Lilly, submissions dated 12/4/03 & 4/20/04
9. Serzone (nefazodone), NDA 20-152, Bristol Myers Squibb, submissions dated 1/14/04 & 4/20/04

Subject: Relationship between psychotropic drugs and pediatric suicidality
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Date Review Completed: 8/16/04

This document analyzes and evaluates data submitted by sponsors of several psychotropic drugs in response to FDA requests regarding data pertinent to pediatric suicidality.

Several hyperlinks (seen underlined in blue color) were put in place to facilitate navigating through the document.

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1 Background

On May 22, 2003, GlaxoSmithKline submitted an analysis of suicide-related[1] adverse events in pediatric trials of paroxetine. This analysis showed a statistically significant increase in such behavior with paroxetine treatment, compared to placebo. In order to provide a meaningful comparison to the paroxetine findings, the Division of Neuropharmacological Drug Products (DNDP) requested that the sponsors of eight other psychotropic drugs tested in children and adolescents conduct searches of their databases similar to the search performed by GlaxoSmithKline. The initial letters requesting these searches were issued on 7/22/03. Follow up requests to obtain additional information were issued on 11/24/03 & 12/9/03 (Appendix I). The latter requests were issued in part to cast an even broader net for events, since there was concern that event-finding by sponsors may not have been complete.[2]

Based on our initial assessments of the responses to our 7/22/03 letters, we decided that it may be useful to obtain patient-level datasets to permit an exploration for covariates to assess for possible imbalances among treatment groups. Requests for these data sets were issued on 10/3/03 & 10/28/03 (Appendix II).

Because of a very wide diversity in the events the sponsors had subsumed under the broad category of "possibly suicide-related," concerns were raised within the Division that not all captured events could be considered to reasonably represent suicidal thinking and behavior. At a joint meeting of the Psychopharmacological Drug Products Advisory Committee and Pediatric Subcommittee of the Infectious Diseases Advisory Committee held on February 2, 2004[3], 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 adverse events (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.

On 3/17/04, while the AEs were being classified, DNDP requested additional data (Appendix III) on treatment-emergent suicidality among study patients as measured by the suicidality item(s) in various depression questionnaires (the questionnaires are provided in Appendix IV).

The purpose of this document is to evaluate and to analyze the suicide-related adverse

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[1] The sponsor used an algorithm based on selected preferred terms to identify "suicide-related" adverse events.

[2] See Dr. Thomas P. Laughren memo to the PDAC meeting held on February 2, 2004. The memo was dated December 30, 2003.

[3] http://www.fda.gov/cder/drug/antidepressants/default.htm; http://cdernet.cder.fda.gov/ACS/Flash%20Minutes/Psychopharmacologic/psycho-Minutes_Quick_feb2.pdf

events identified by the blinded adjudication process described above in order to investigate the relationship between pediatric suicidality and psychotropic drugs.

2 Objectives

1- To investigate the relationship between psychotropic drugs and pediatric suicidality reported as AEs (AEs included in the analysis were the ones blindly classified by a group of suicidology experts assembled by Columbia University).

2- To investigate the relationship between psychotropic drugs and pediatric suicidality as suggested by scores on the suicidality item(s) reported in pertinent depression questionnaires.

3- To understand the sources of inconsistency - in any of the above outcomes - between trials and/or between drugs by investigating possible sources of variation or imbalance in the data e.g. trial design, duration of exposure, patient population, and other potential confounders.

3 Sources of data

In total, eight sponsors of nine psychotropic drugs provided datasets to DNDP culled from all the randomized controlled trials of their respective drug products conducted in the pediatric population as electronic files (in SAS transport file format). The variables included in these data provided detailed information about the individual patients. The variables are listed in the data requests in Appendix II and Appendix III.

The studied drugs included fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox), citalopram (Celexa), bupropion (Wellbutrin), venlafaxine (Effexor), nefazodone (Serzone), and mirtazapine (Remeron).

A total of 25 pediatric trials from all drugs were submitted. The trials were conducted over a nearly 20 year period from 1983 to 2001; trial duration ranged from 4 to 16 weeks. The indications included Major Depressive Disorder [15 trials], Anxiety Disorders (Obsessive Compulsive Disorder [five trials], Generalized Anxiety Disorder [two trials], and Social Anxiety Disorder/Social Phobia [one trial]), and Attention Deficit Hyperactivity Disorder (two trials). Descriptive information for all trials included in this review is provided in Appendix V.

Only 23 of the trials were evaluable. Wellbutrin trial number "41" was excluded from the analysis because it was uncontrolled. Paxil trial number "453" was also excluded because its randomized withdrawal design did not allow direct comparison to the other 23 parallel arm trials[4].

[4] Trial 453 included two phases, an open-label phase (Phase I) in which patients received paroxetine for 16 weeks, and a 16 week double-blind placebo-controlled phase (Phase II) in which responders were eligible to participate. Although only data from the 16-week double-blind phase was included in the submitted

4 Operational Definitions

4.1 Outcome variables

4.1.1 Outcome variables under "objective 1"

AEs were captured on Case Report Forms (CRFs) during the course of these trials. Information in these CRFs (and possibly from other sources, e.g., hospital records) was used by the sponsor to write narratives for AEs that led to discontinuation from the trial or were categorized as "serious" by the regulatory definition[5]. As described above, narratives for AEs that were identified by the algorithm for suicide-related events, all serious AEs, all accidental injury AEs, and all accidental overdoses underwent blinded classification by an independent group of experts in suicidology assembled by Columbia University. The coordinating team at Columbia University, led by Dr. Kelly Posner, conducted a training session with the expert panel prior to their application of the coding scheme. The following listing shows the coding scheme used by the expert panel and the number of events that were classified to each type.

1: suicide attempt (n=27)
2: preparatory actions towards imminent suicidal behavior (n=6)
3: self-injurious behavior, intent unknown (n=24)
4: self-injurious behavior, no intent, primarily to affect circumstance (n=2)
5: self-injurious behavior, no intent, primarily to affect internal state (n=5)
6: suicidal ideation (n=45)
7: other: accident*
8: other: psychiatric*
9: other: medical*
10: not enough information (n=7)
11: self-injurious behavior, no suicidal intent (unspecified type, i.e. rater not sure if it is 4 or 5 [n=4])
12: "other" (some combination of 7, 8, and 9) *

* The total of codes 7, 8, 9, & 12 is 261 events.

For the purpose of investigating the data to fulfill objective number 1, codes of AEs were grouped into five outcomes as listed in the following table:

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dataset, there was a concern that patients in this trial might not be comparable to patients in other trials because only patients who were already shown to tolerate and respond to the drug were randomized.

[5] An adverse event is categorized as "serious" if it results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/ incapacity, or a congenital anomaly/birth defect. Also other important medical events requiring interventions to prevent one of the outcomes listed above [21 CFR Ch. 1, 314.80].

Table 1: Outcomes investigated under objective number 1.

Outcomes	Description	Columbia codes
Outcome 1 (n=33)	Definitive suicidal behavior	1, 2
Outcome 2 (n=45)	Suicidal ideation (without behavior)	6
The primary outcome (outcome 3) (n=78)	Definitive suicidal behavior/ideation	1, 2, 6
Outcome 4 (n=109)	Possible suicidal behavior/ideation	1, 2, 3, 6, 10
Outcome 5 (n=11)	Self-injurious behavior, non-suicidal	4, 5, 11

The primary focus of the analysis was outcome 3. For the purpose of "casting the broadest net" to identify potentially suicide-related events, "serious" adverse events were included among the AEs sent for adjudication. Beyond that, the "serious" status of AEs was not utilized in this review because it is a regulatory definition that has no impact on the characterization of an event as suicidal or not (i.e., suicidal ideation or suicide attempt would not qualify as a serious adverse event if it did not meet the regulatory definition mentioned above in footnote. Instead, we relied on the classification resulting from the blinded adjudication process.

4.1.1.1 PHASE DEFINITIONS

Based on the timing of these events, they were grouped in six "phases" as defined in the table below:

Table 2: Definition of "phases" based on the timing of events.

Phases	Description
Phase 1	Event occurred in double-blind acute treatment phase or within one day of the end of this phase[6]. The end of trials with a tapering period was set to be at the beginning of the tapering period.
Phase 2	Event occurred during a taper phase following the end of the double-blind period
Phase 3	Event occurred during the discontinuation phase--this phase was defined as 2 to 8 days after the cessation of medication for all drugs except Prozac where it was 2 to 31 days after the cessation of medication because it has a long half life and active metabolites. For an event to be classified in this phase, the patient must not have been taking drug at the time of the event
Phase 4	Event occurred between 2 and 8 days (2 and 31 days for Prozac) after the cessation of double-blind acute phase study medication *and* the patient had continued in an extension phase or started on a prescription anti-depressant
Phase 5	Event occurred between 9 and 31 days after the cessation of double-blind acute phase study medication *and* the patient had continued in an extension phase or started on a prescription anti-depressant (this category would not apply to Prozac patients)

[6] One day was added onto the end of the exposure because if a patient took the last dose of study drug at night, the drug exposure would continue into the next day.

Phases	Description
Phase 6	Event occurred more than 30 days after the cessation of double-blind medication in the acute phase

The primary analysis focused on the 120 events occurring during the double-blind (i.e. during "phase 1"). Those events are provided in Appendix VII.

Excluding events that occurred in the post-double-blind period (events provided in Appendix VII) avoids the uncontrollable confounding stemming from the array of scenarios that could have happened after the end of a given trial. For example, some trials did not offer patients pharmacotherapy after the end of the double-blind period, whereas others offered the same trial drug or a different drug, or placebo.

Although this approach reduces the probability of including patients who might have had the event of interest because of discontinuation rather than as a consequence of administration of the drug, this is also a limitation.

4.1.1.2 DISPOSITION OF EVENTS

A total of 426 AEs' narratives were accumulated for all trials. It should be noted that there were no events of completed suicides in any of the trials.

All narratives were blinded with regard to drug program and treatment assignment, and were sent to the expert panel assembled by Columbia University. A total of 261 events were coded as "other" (codes 7, 8, 9, and 12 as defined above) and were excluded from any further analysis. As mentioned above, the Division had cast a wide net in the requests to sponsors (see Appendix II) to get all potential events, and this explains the large number of events that were eventually excluded in the analysis after the expert classification.

A total of 165 events were considered for the analysis. Among those, 45 events occurred in 20 patients who had more than one event (provided in Appendix VII). For those patients, the most severe event was used according to the following ranking of the Columbia University codes (definition of codes provided in a previous section): 1 or 2 > 6 > 3 > 4 or 5 > 10. Only one patient had an event of suicidal behavior and a second one of suicidal ideation occurring in phase 1.

This left a total of 140 unique patients with an event for all trials in the various phases as provided in the next table:

Table 3: Distribution of the 140 unique events by phases.

Phase	Number of events
Phase 1 (double-blind acute treatment)	120
Phase 2	1
Phase 3	8

Phase 4	4
Phase 5	4
Phase 6	3
Total	140

As mentioned previously, only 120 events occurring in phase 1 were used in the primary analysis. The following table shows the overall relationship between sponsors' and the expert panel classifications of AEs for those 120 events in phase 1:

Table 4: Relationship between sponsors' and expert panel's classifications.

Expert Panel Events	Sponsor Events		Total
	No	Yes	
No event	4418	17	4435
Definitive suicidal behavior (outcome 1: codes 1 and 2)	1	32	33
Suicidal ideation (outcome 2: code 6)	10	35	45
Definitive suicidal behavior /ideation (outcome 3: codes 1, 2, and 6)	11	67	78
Possible suicidal behavior/ideation (outcome 4: codes 1, 2, 3, 6, and 10)	22	87	109
Self-injurious behavior, non-suicidal (outcome 5: codes 4, 5, and 11)	2	9	11

The highlighted numbers represent the discrepancy between the two classifications. In effect, for the purpose of the primary analysis, 22 new events were added (note that there is an overlap between outcomes 1, 2, 3, and 4) and 26 old events were removed from the pool of evaluable AEs. Among these 26 events, nine were classified as self-injury (non-suicidal) by the expert panel, two were classified as "other: psychiatric" (code 8), and 15 occurred after the double-blind period. The detailed cross-tabulation between the two classifications is provided in Appendix X.

4.1.2 Outcome variables under "objective 2"

For the purpose of investigating the data to fulfill objective number 2, information was collected about the "worsening of suicidality score" and "emergence of suicidality" using the following depression scales: Children's Depression Rating Scale-Revised (CDRS-R), Hamilton Psychiatric Rating Scale for Depression (HAM-D), Schedule for Affective Disorders and Schizophrenia for School Aged Children (K-SADS), and Montgomery and Asberg Depression Rating Scale (MADRS). Those depression scales, except the K-SADS, are provided in Appendix IV. The outcome variables based on changes in pertinent depression scales are defined in the following table:

Table 5: Definition of outcome 6 and outcome 7.

Outcomes	Description	Definition
Outcome 6 (n=434)	Worsening of suicidality score	Patient reached the threshold for "worsening of suicidality" at any time during the controlled portion of the trial based on an increase of **one point or more** on the HAM-D item 3 or **two points or more** on the suicidality item 13 in CDRS-R or on the suicidality item 10 in MADRS, regardless of subsequent change. The definition of this variable is intended to capture only patients that exhibit the listed changes in their suicidality items in relation to their respective **baseline values**.
Outcome 7	Emergence of	Definition of patient reaching the threshold of "emergence of suicidality" under the variable

Outcomes	Description	Definition
(n=349)	suicidality (a subset of outcome 6)	named "SUITHRESH" depends on the scale used to rate suicidality: HAM-D The patient is assigned a value of "1" if there is a change in rating of "suicide" item (item number 3) from 0 at baseline to 1 or more, or from 1 at baseline to 2 or more, at any time during the controlled phase of the trial. The variable should reflect the first time such a change occurs regardless of subsequent changes. CDRS-R The patient is assigned a value of "1" if there is a change in rating of "suicidal ideation" item (item number 13) from 1 or 2 at baseline to 3 or more at any time during the controlled phase of the trial. The variable should reflect the first time such a change occurs regardless of subsequent changes. MADRS The patient is assigned a value of "1" if there is a change in rating of "suicidal thoughts" item (item number 10) from 0 or 1 at baseline to 2 or more at any time during the controlled phase of the trial. The variable should reflect the first time such a change occurs regardless of subsequent changes.

4.2 Variables used to investigate potential effect modification (interaction) and confounding (objective 3)

For the purpose of investigating the data to fulfill objective number 3, the following list of variables were investigated to discern the presence of effect modification (interaction) and for their role as potential confounders:

- Demographics variables
  - Age
  - Gender
  - Race
  - BMI

- Trial-related variables
  - Trial location (North America vs. not)
  - Trial setting (inpatient vs. outpatient vs. both)

- Disease-related variables
  - Baseline severity score
  - Suicidality score at baseline
  - Duration of illness prior to treatment

- Drug-related variables
  - Duration of treatment (exposure)
  - Discontinuation
  - Erratic compliance

- Prior history of:
  - Suicide attempt
  - Suicide ideation
  - Psychiatric hospitalization
  - Substance abuse

- Hostility or aggressive behavior
- Irritability or agitation
- Insomnia

It is worth noting that sources for the psychiatric histories of interest, in addition to documentation of non-compliance during the trial period, varied from trial to trial and from sponsor to sponsor. This variability diminished the utility of these variables in the analysis, and limited their use to within trial adjustment. Details about theses sources are provided in Appendix V by drug, trial, and indication.

5 Statistical Analysis and Findings

5.1 Software used in the analysis

Data were analyzed using the statistical software packages JMP (version 4.0.4), SAS (version 8.2 for Windows)[7], and STATA/SE (version 8.2 for Windows)[8].

5.2 The primary outcome

The primary outcome that was the focus of the investigation was set *a priori* to be outcome 3 (Definitive suicidal behavior/ideation) because it is the most relevant and the one least likely to be susceptible to misclassification and dilution bias.

Although outcomes 6 and 7 (changes in suicidality scale scores) were collected in a systematic and complete manner at each visit as part of the efficacy measures, the scores constituting the outcomes might not have been collected at the time of an event for logistical reasons or, for example, in patients who discontinued because of an event. Therefore, these outcomes were not chosen to be the primary ones.

5.3 Trial as the unit of analysis

In concept, pooling data from different trials and treating them as one large trial fails to preserve the randomization effect and might introduce bias and confounding. Maintaining the randomization guards against the foreseen (e.g. age and gender) and the unforeseen (e.g. differences in medical practices or event ascertainment) sources of imbalance between treatment groups.

In addition, the issue of trial similarity is not only pertinent to having the same protocol, but is also pertinent to the implementation of those protocols (implementation of inclusion and exclusion criteria, quality of patient care, etc).

Therefore, this review, unless otherwise specified, used "trial" as the unit of investigation and analysis as the primary analytical approach. Using patient as the unit of analysis, i.e. pooling more than one trial together, was carried out only in the time-to-event sub-

[7] JMP and Statistical Analysis System, SAS Institute Inc., Cary, NC, USA.
[8] STATACorp, College Station, TX, USA

analysis. Similar trials in the same indication for the same drug were pooled to get enough events together to enable the evaluation of time-to-event and observation of how the hazard function changes over time.

5.4 Person vs. person-time as the unit of analysis within trials

In order to decide whether to use the number of persons or the person-time as the unit of analysis within trials, the average exposure time was compared between the drug and the placebo groups for every trial. The averages of exposure time and 95% confidence intervals are provided by drug, trial, and indication in Appendix IX.

Most trials did not show a meaningful difference in the exposure time between the drug and placebo groups. Eight trials had a potential imbalance in exposure time (at p-value <=0.1). These are trials # HCCJ, X065, HCJE, HCJW, 1001, 329, 704, 141. The following table summarizes the average exposure time (and 95% CI) for those trials by treatment.

Table 6: Trials with potential imbalance in exposure between the drug and placebo groups

Drug	Trial	Treatment	Average exposure time (95% CI)	p-value
Prozac	HCCJ	Drug	36.6 (31.4 , 41.4)	0.11
		Placebo	40.6 (37.5 , 43.7)	
	X065	Drug	51.0 (47.7 , 54.4)	0.03
		Placebo	44.3 (39.6 , 49.1)	
	HCJE	Drug	59.0 (57.0, 61.0)	0.01
		Placebo	53.5 (50.2, 56.9)	
	HCJW	Drug	77.8 (71.8 , 83.8)	0.11
		Placebo	68.3 (57.7 , 78.8)	
Zoloft	A0501001	Drug	58.6 (54.4 , 62.9)	0.02
		Placebo	65.2 (62.1 , 68.3)	
Paxil	329	Drug	49.2 (45.5 , 53.0)	0.06
		Placebo	54.3 (50.5 , 58.2)	
	704	Drug	68.9 (63.5 , 74.4)	0.11
		Placebo	75.2 (69.8 , 80.6)	
Serzone	CN104-141	Drug	52.3 (49.4 , 55.3)	0.06
		Placebo	47.9 (44.5 , 51.4)	

As an example, a trial with a large number of events is Prozac trial number HCJE. This trial had six events of outcome 3 in each of the drug and placebo groups.
To show the little impact the differences in exposure had on risk estimates, both the risk ratio (using person as the unit of analysis) and the rate ratio (using person-time as the unit of the analysis) were calculated. The risk ratio was 1.0 and the rate ratio was 0.9.

In general, using person-time as the unit of the analysis is not as readily interpretable as using persons. This is because one year of person time can be accumulated from 12

patients followed for one month each, or from two patients followed six months each. Therefore, using person-time should be only used when warranted. Because of lack of an evidence of a meaningful imbalance that might have had an impact on the risk estimates of interest, this reviewer decided on using persons as the unit of analysis for the primary analysis.

5.5 Examining and handling missing data for explanatory variables

The frequency of missing data was explored and reported for every explanatory variable for every trial provided to the Division in response to various data requests. Explanatory variables that were completely reported in all trials were age, gender, race, setting of trial, location of trial, baseline severity score, and all outcomes. Variables that were notably missing in many trials were duration of illness prior to randomization (in 10 trials), and history of psychiatric hospitalization (in 21 trials), substance abuse (in 9 trials), and hostility or aggressive behavior (in 8 trials). Details of the frequency of missing data for all variables are provided in Appendix V by drug, trial, and indication.

Variables with missing information of more than 10% in a given trial were not considered further when investigating potential confounders for that particular trial. Note that variables with missing information of more than 10% in one trial were not necessarily missing for other trials.

For binary variables (e.g., history of insomnia), if a trial was missing information on 10% or less in the "history of insomnia" variable, the missing patients' data were replaced with "zero", which translates to no history of insomnia. For continuous variables with missing data of 10% or less, data were imputed using the average value of that variable in the particular trial where the data were missing.

5.6 Preliminary analysis

Count, percent, and rate of all outcomes (1 through 7) by drug, trial, and indication are provided in Appendix IX. There was variability in the number of events and corresponding risk estimates within drug development programs and between drug development programs. For the primary outcome (outcome 3), four trials did not have any events (namely trials # 75 [Wellbutrin, ADHD], 141 & 187 [Serzone, MDD], and 396 [Effexor, GAD]). The remainder of the trials had at least one event. Ten trials had no events in one of the treatment groups (namely, trials HCCJ & HCJW [Prozac], 114 [Luvox], 676 & 704 [Paxil], 045 [Remeron], 1001 & 0498 [Zoloft], and 382 & 394 [Effexor]). The incidence of the primary outcome (outcome 3) varied from 0% up to 7% in various trials.

The association between the primary outcome (outcome 3) ("definitive suicidal behavior/ideation") and outcome 6 ("worsening of suicidality score") by drug, trial, and indication was investigated. There were statistically significant associations between the primary outcome (outcome 3) and outcome 6 in some trials, i.e., patients who had an

event under outcome 6 were more likely to have an event under the primary outcome (outcome 3), regardless of the treatment group. These trials are # 94404 & CIT-MD-18 (Citalopram), HCJE & HCJW (Prozac), 377 (Paxil), 1001 & 1017 (Zoloft), and 382 (Effexor). The detailed cross-tabulations of the primary outcome (outcome 3) and outcome 6 by drug, trial, and indication are provided in Appendix X.

Description of the studied patient population characteristics and other variables, by drug, trial, and indication was done for continuous and categorical variables and are provided in Appendix VIII.

The crude associations between continuous and categorical explanatory variables and both the exposure (drug vs. placebo) and the primary outcome (outcome 3, suicidal behavior or ideation vs. not) were evaluated using Mantel-Haenszel chi-square test (or Fisher exact test if 25% or more of the cells have expected counts less than 5), t-test (or Wilcoxon Rank Sum test for small groups of < 30), or ANOVA test (used in study 329 with three arms) as appropriate. A variable that was associated with both exposure and outcome at a p-value of 0.1 or less was considered further in the modeling stage as a potential confounder. The detailed results of these investigations for all variables by drug, trial, and indication are provided in Appendix VI.

In short, few variables showed evidence of a potential imbalance between the drug and the placebo groups. The following table shows a summary of these findings by drug, trial, and indication. Most of the variables did not reach the traditional statistical significance threshold of 0.05. This suggests that randomization largely succeeded in creating a reasonably similar profile as far as the distribution of baseline and treatment-related variables across the drug and the placebo groups. Evidence of similar distribution of variables is reassuring when considering that some trials were missing information on some of these variables. In other words, it would be reasonable to assume that these variables will not exhibit major imbalances in those trials.

Table 7: Summary of variables showing potential (p-value <=0.1) randomization failure or imbalances between the placebo and the drug groups by drug, trial, and indication

Drug	Trial	Indication	Variables showing potential randomization failure or imbalances (p-values)
Selective serotonin re-uptake inhibitors (SSRI) anti-depressant group			
Prozac	HCCJ	MDD	Age (0.13), exposure (0.11)
	X065	MDD	Exposure (0.03), Hx irritability (0.08)
	HCJE	MDD	Exposure (0.03), Hx substance abuse (0.12), suicidality item score at baseline (0.13), race (0.03)
	HCJW	OCD	Exposure (0.11)
Zoloft	90CE21-0498	OCD	None
	A0501001	MDD	Discontinuation (0.005), exposure (0.02), Hx suicidal ideation (0.14)
	A0501017	MDD	Gender (0.02), Hx insomnia (0.03)
Paxil	329	MDD	Discontinuation (0.09), exposure (0.09), Hx erratic compliance (0.13), suicidality item score at baseline (0.06)
	377	MDD	Age (0.1)
	701	MDD	Baseline severity (0.14), Discontinuation (0.11), suicidality

Drug	Trial	Indication	Variables showing potential randomization failure or imbalances (p-values)
			item score at baseline (0.07)
	704	OCD	Exposure (0.11)
	453	OCD	Exposure (0.09)
	676	SAD	Discontinuation (0.1), gender (0.01), Hx insomnia (0.08)
Luvox	RH_114_02_01	OCD	None
Celexa	CIT-MD-18	MDD	None
	94404	MDD	Age (0.07), Hx psychiatric hospitalization (0.13),
Atypical anti-depressants group			
Wellbutrin	75	ADHD	BMI (0.03)
Effexor	382	MDD	None
	394	MDD	Discontinuation (0.12)
	396	GAD	Gender (0.01), Hx irritability (0.04), Hx suicidal ideation (0.04), suicidality item score at baseline (0.14)
	397	GAD	Hx irritability (0.09), Hx suicidal ideation (0.09)
Serzone	CN104-141	MDD	Discontinuation (0.06), exposure (0.06), gender (0.1)
	CN104-187	MDD	Baseline severity (0.007), duration of illness (0.11), Hx substance abuse (0.03), suicidality item score at baseline (0.11)
Remeron	003-045	MDD	Hx psychiatric hospitalization (0.05)

5.7 Stratified analysis

Stratified analysis of the primary outcome (outcome 3) was used to rule out interactions (effect modification) between exposure to drug and other pertinent variables in the data. Investigating effect modification was difficult because of the inherent data separation associated with rare outcomes. By definition, a few events in a given trial will have to fall by chance in some of the examined subgroups, but it does not necessary translate to an actual effect modification. In addition, there is an inherent lack of statistical power in situations with few events observed during the course of the trial.

Therefore, this reviewer's approach was to investigate if there is a "consistent" change in the signal (effect of exposure to drug as compared to placebo) in most trials when patients are stratified by the variables of interest. For this investigation, the variables that were used are well known to have an impact on risk of suicidality, and they are age, gender, and history of suicide attempt or ideation.

Additionally, stratifying trials by premature discontinuation was implemented to examine the possibility of having an informed censoring due to discontinuation.

5.7.1 Age group

Stratification of data by age group (6-11 vs. 12-18 years) did not point to a particular age group where the risk of the primary outcome (outcome 3) was more pronounced. In some trials the signal was coming from the 6-11 age group and in others it was coming from the 12-18 age group (details of the results of this analysis are not included in this review).

5.7.2 Gender

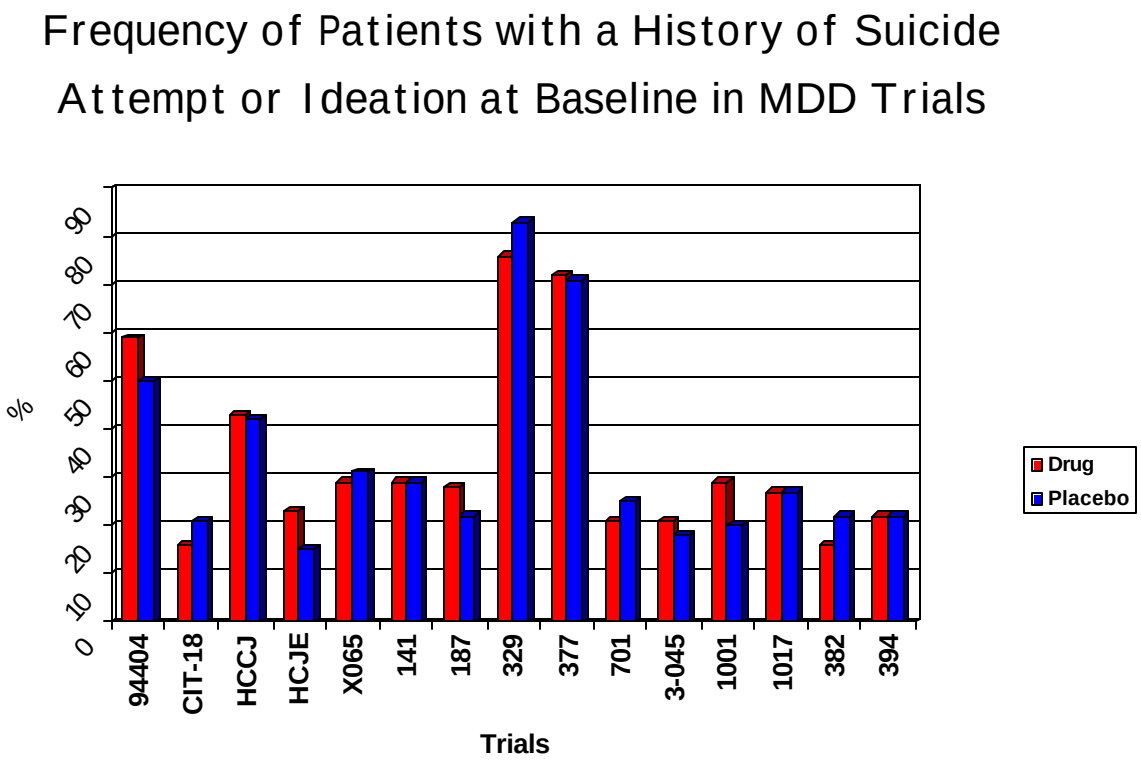
Stratification of data by gender did not point to a particular gender where the risk of the primary outcome (outcome 3) was more pronounced. In some trials the signal was coming from the males group and in others it was coming from the females group (details of the results of this analysis are not included in this review).

5.7.3 History of suicide attempt or ideation

Six trials used history of suicide attempt as an exclusion criterion (namely, trials # CIT-18 [Celexa], 141 & 187 [Serzone], 045 [Remeron], and 1001 & 1017 [Zoloft]). However, no trial used history of ideation as an exclusion criterion. For the purpose of this analysis, the two histories were combined.

No significant difference was found in any of the MDD trials between the drug and placebo groups in the rates of patients with history of suicide attempt or ideation at baseline.

Interestingly, The majority of the primary outcome (outcome 3) events in the MDD trials (39/66=59%) were in the four trials that had the highest rate of patients with history of suicide attempt or ideation at baseline, namely trials # 94404 [Celexa], HCCJ [Prozac], and 329 & 377 [Paxil]. The following graph shows the frequency of this variable at baseline in all MDD trials by treatment group.



The following table summarizes the overall risk estimates of the primary outcome (outcome 3) in patients in MDD trials with and without history of suicide attempt or ideation at baseline by drug.

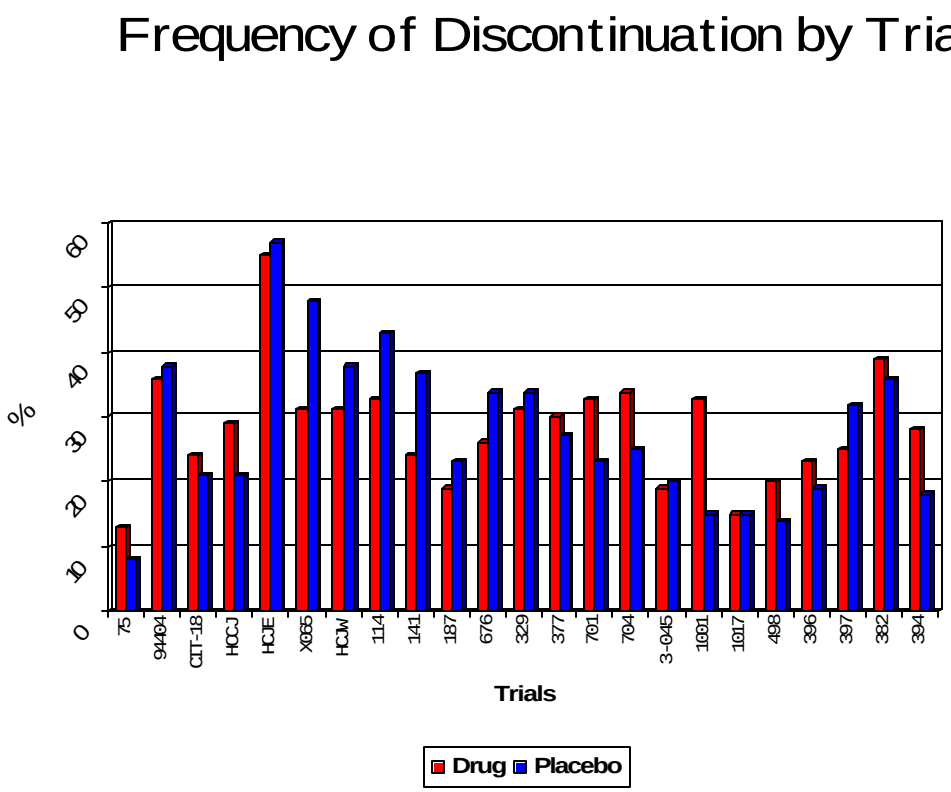
Table 8: Summary of the overall risk estimates (relative risks [RR]) of the primary outcome (outcome 3) in patients with and without history of suicide attempt at baseline in MDD trials

Drug	RR and 95% CI in patients with **no history** of suicide attempt at baseline	RR and 95% CI in patients with history of suicide attempt at baseline
Prozac	0.91 (0.30, 2.72)	.92 (0.21, 4.14)
Paxil	1.36 (0.18, 10.35)	2.13 (0.66, 6.88)
Zoloft	2.42 (0.36, 16.06)	1.37 (0.18, 10.40)
Celexa	1.39 (0.30, 6.49)	1.16 (0.39, 3.44)
Effexor	5.67 (0.69, 46.68)	4.56 (0.52, 39.72)
Remeron	1.63 (0.07, 39.57)	No events
All SSRIs	1.26 (0.60, 2.64)	1.40 (0.73, 2.72)
All drugs	1.61 (0.83, 3.13)	1.60 (0.86, 2.98)

Stratifying the data by this variable showed no consistent finding to suggest that history of suicide attempt or ideation played a role in the risk for the primary outcome (outcome 3). The majority of trials had events occurring in both subsets of patients, those with a history of suicide attempt or ideation and those without. Graphs containing the details of the results of this analysis for all MDD trials are provided in Appendix XVIII.

5.7.4 Premature Discontinuation from the trial

The following graph shows the frequency of this variable in all trials by treatment group.



The rate of premature discontinuation was statistically significantly different between the drug and the placebo groups in one trial, namely trial # 1001 [Zoloft]. In trial # 141 [Serzone], the p-value was 0.06. Some of the other trials showed a trend towards higher frequency of discontinuation in either of the treatment groups, but none was statistically significant.

Stratifying the data by premature discontinuation showed that, for many of the trials, the preponderance of the primary outcome (outcome 3) events occurred in the subgroup of patients that discontinued, suggesting that patients exhibiting these events tend to discontinue from the trial. Details of the risk estimates of the primary outcome (outcome 3) stratified by premature discontinuation are provided in Appendix XIII.

The results in the subset of patients that did not discontinue can be considered as a "completers" analysis in which the risk estimates were calculated among the group of patients that basically completed the trial as planned. In this subgroup of "completers", many trials still revealed a signal, namely trials # 394 [Effexor]; 114 [Luvox]; 329, 377& 676 [Paxil]; and X065 [Prozac].

The following table summarizes the overall risk estimates of the primary outcome (outcome 3) in completers and non-completers by drug. Trials for all indications were used for each drug.

Table 9: Summary of the overall risk estimates of the primary outcome (outcome 3) in completers and non-completers by drug.

Drug	RR and 95% CI in completers	RR and 95% CI in non-completers
Prozac	1.17 (0.30, 4.61)	0.84 (0.29, 2.44)
Paxil	2.79 (0.47, 16.53)	1.86 (0.70, 4.95)
Zoloft	0.34 (0.01, 8.16)	1.35 (0.34, 5.40)
Celexa	0.94 (0.20, 4.50)	1.67 (0.52, 5.33)
Luvox	2.85 (0.12, 67.68)	4.20 (0.18, 97.89)
Effexor	3.12 (0.13, 75.39)	6.22 (0.81, 47.94)
Remeron	No events	1.73 (0.07, 40.32)
All SSRIs in MDD	1.08 (0.45, 2.60)	1.40 (0.76, 2.56)

5.8 Multivariate analysis

PROC LOGISTIC and PROC PHREG in SAS were used to model the data for trials with events in both groups with at least two events per group, namely trials # 94404 [Celexa], 377 [Paxil], and HCJE [Prozac].

The purpose of this step was to attempt to adjust for the confounding effect emerging from the imbalances in explanatory variables that might have resulted from partial randomization failure at baseline, or during the conduct of the study. However, none of those imbalances was found to meaningfully change the primary outcome (outcome 3) risk estimates for any of the drugs (the results of this work is not shown in this review). Therefore, crude estimates were used in the time-to-event analysis and the meta-analysis.

5.9 Time-to-Event analysis

Time-to-event analysis was conducted to address the potential for differential risk of the primary outcome (outcome 3) over time between the drug and the placebo groups.

5.9.1 Kaplan-Meier survival curves

The survival distribution function gives the probability of surviving past time T=t, where "t" is a specific time of interest. The survival function directly describes the survival experience of a trial cohort. The Kaplan-Meier product limit (K-M) method incorporates information from all the observations available, both censored and non-censored, to compute survival probabilities. In other words, rather than ignoring information on censored individuals, the K-M method utilizes this information up to the time the individual is actually censored.

PROC LIFETEST in SAS was used to compare K-M survival curves for drug and placebo groups. This analysis was done only for trials with events of the primary outcome (outcome 3) in both groups and with at least three events in one of the groups, namely trials number 94404 [Celexa], 377 & 329 [Paxil], and HCJE [Prozac]. These four trials had most of the events for the primary outcome (outcome 3) in all the MDD trials (39/66=59%) and in the SSRI MDD trials (39/57=68%). For illustration, the graphs depicting the survival curves for those trials are provided in Appendix XII.

The survival analysis revealed no particular clustering of events, i.e., they occurred over the course of these trials. None of the drug curves were significantly different from the placebo curves in any trial (i.e. log-rank test was not significant).

5.9.2 Hazard functions

The "hazard" is expressed as a rate and not as a probability, so it can range from zero to infinity. The hazard function allows examining the instantaneous hazard rates during the follow up period as it provides insight about the conditional failure (or event) rates (i.e. rate of event after time T=t among those who survived to that time).

The "sts graph" procedure in STATA was used to display graphically the smoothed hazard function estimates in the pooled MDD trials of four drugs that had events in both the drug and the placebo groups. Each drug was analyzed separately. This was specifically done for Celexa (two trials, 17 events, 422 patients), Prozac (three trials, 17 events, 355 patients), Paxil (three trials, 16 events, 662 patients), and Zoloft (two trials, 7 events, 373 patients). This analysis was also done for the pooled data from all SSRIs in MDD trials (10 trials, 57 events, 1812 patients).

To account for the fact that the data are gathered from more than one trial, the variable "trial" was adjusted for through stratified Cox regression model using "stcox" procedure in STATA with the "strata()" option. The basic idea of the stratified Cox model is that the baseline hazard function is allowed to vary across strata (in this case the stratum is the trial). In other words, the underlying hazard functions for trials can be different from each other, while the parameter estimates are the same across trials.

Adjusting for trial as a random effect by fitting a Cox model with shared frailty was done using the "shared()" option on the "stcox" procedure, but there was no meaningful difference between the two approaches.

The graphs depicting the hazard curves for the four drugs and for the pooled SSRIs described above are provided in Appendix XIV. It is worth noting that the confidence bands for drug and placebo curves overlapped for all drugs and were omitted from the graphs for simplification. Notwithstanding this limitation, the hazard was not constant over time and was not always proportional between the drug and the placebo groups. The pattern of hazard tends to change over time with a peak around 20-40 days for most drugs, except Prozac where the peak was around 10 days.

Note that there are large differences between the patterns of hazard in various placebo groups suggesting some heterogeneity in the background rates of suicidality among MDD pediatric patient populations recruited in various trials. Interestingly, the rate in some of the placebo groups, for example with Prozac, was higher than some of the drug groups, for example with Paxil.

When the data from all SSRIs in MDD trials were pooled, the resulting hazard curves showed consistent elevation of hazard in the drug group for most of the follow up period. Note, that the two curves crossed at around 65 days. However, the 95% CIs are very wide at this section of the curves reflecting a greater level of uncertainty because it relies only on only four events, one event in the drug group and three events in the placebo group.

The "hazard ratio" (HR) is a comparative measure of survival experience over the entire trial period, whereas the RR (which will be presented in the next section) is a comparative measure of event occurrence at the end of the trial. For example, a hazard ratio of two for "drug" means that at any given time during the study, the hazard of the event of interest for the drug group is twice that of placebo group.

For most drugs, the resulting overall HR did not differ meaningfully from the overall RR for each drug except for Zoloft where the former was higher than the latter (2.54 vs. 1.48, respectively). When the data from SSRIs in MDD trials were pooled the HR was 1.45 (0.85, 2.48). Compare this to the overall RR for SSRIs in MDD trials, which was 1.41 (0.84, 2.37).

Caution should be exercised in the interpretation of the HR because the basic assumption behind the calculation is that the hazards in the drug and the placebo groups are proportional over the entire period of the trial. This did not appear to be totally fulfilled for Celexa, Prozac, and the overall pooled analysis as depicted in the graphs referenced earlier in Appendix XIV.

5.10 Meta-analysis

Pooling of trials is often performed when investigating infrequently occurring adverse events observed in drug development programs as it provides a more robust point estimate of the risk associated with drug use. Single trials are almost invariably insufficiently powered for detecting signals for uncommon events. As such, this part of the review evaluates data pools to generate an overall estimate of various drug effects. To accomplish this pooling, a weighted average of treatment effects from individual trials was calculated by drug and by indication.

Two options were available for weighting the results of individual trials prior to generating an overall risk estimate, fixed-effect or random-effects models. In the fixed-effect approach, the premise is that the real effect that we are trying to estimate is fixed, and the observed variations between trials are by chance. In the random-effects approach, the premise is that the real effect varies around an average within a distribution reflected in the differences observed between trials.

To determine which approach was more appropriate, a test for heterogeneity was done. None of the results of the heterogeneity tests were significant, so the fixed-effect approach was conducted as the primary analysis, using the Mantel-Haenszel (M-H) method. The M-H method provides the weighted average of the treatment effects from the individual trials. It is preferred (more robust) when data are sparse, [9] both in terms of event rates being low and trials being small, where the inverse variance method may be poor.

However, it is possible that some of the residual heterogeneity between trials was missed due to lack of statistical power to detect its existence. Therefore, the results of the random-effects modeling are also shown for some of the overall estimates for comparison purposes.[10]

5.10.1 Meta-analysis procedures in STATA[11]

The meta-analysis procedures in STATA are not part of the "core" STATA package. They are user-written "add-ons" installed over the Internet though the *STATA Technical Bulletin*. To conduct the analysis undertaken in this review, I used the following procedures:

Metan: This procedure provides pooled RR, confidence limits, a test that the true pooled RR is one (the null hypothesis), and a test for heterogeneity between trials. The pooled RR can be obtained from a fixed-effect meta-analysis (using M-H weighting method) or from a random-effects meta-analysis (using the method of DerSimonian & Laird[12]).

The calculation of the weights used in the M-H method takes in consideration both the sample size and the number of events and is outlined as follows:

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[9] Sutton AJ and Abrams KR. Methods for meta-analysis in Medical Research. J Willy & Sons, NY, 2002, page 69.

[10] It is worth noting that in the presence of heterogeneity, the random-effects model weights are smaller and more similar to each other than the weights used in fixed-effect models. This means that the confidence intervals will be wider because the variance of the pooled effect is the inverse of the sum of the weights. It also means that the random-effects model gives relatively more weight to smaller trials than the fixed-effect model.

[11] Sterne et al. Meta-analysis in STATA. In: Egger M, Smith GD, Altman DG (editors). Systematic reviews in health care. Meta-analysis in context. London: BMJ Publishing Group, 2001: pp 347-369.

[12] The random-effects modeling was done using the method of DerSimonian & Laird, where the effect sizes of trials are assumed to have a normal distribution. When the heterogeneity is small, the weights reduce to those given by the inverse variance method (Deeks et al. Statistical Methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Smith GD, Altman DG (editors). Systematic reviews in health care. Meta-analysis in context. London: BMJ Publishing Group, 2001: pp 297).

	Event	No event	Group size
Drug	A	B	N1
Placebo	C	D	N2

The weight (W) assigned to the RR will be equal to:

W= (C * N1)/N

Where N = N1 + N2

The "metan" procedure was also used to produce a "Forest plot" in which the relative contribution of each trial to the meta-analysis (its weight) is represented by a box whose center represents the treatment effect estimated from that trial. The larger the area of the box is, the larger the contribution of the trial in the overall estimate. The confidence interval for the treatment effect from each study is also shown. The overall summary treatment effect is shown as a dotted vertical line on the graph in the middle of a diamond whose left and right extremes represent the corresponding confidence interval.

Metareg: This procedure extends a random-effects meta-analysis to estimate the extent to which one or more covariates, with values defined for each trial in the analysis, explain heterogeneity in the treatment effects between trials, if any. The regression model relates the treatment effect to the trial-level covariates, assuming a normal distribution for the residual errors with both a within-trial and an additive between-trials components of variance. The within-trial standard error was supplied by this reviewer and the between-trials component of variance was estimated by an iterative procedure using an estimate which is based on restricted maximum likelihood. The estimated between-trials variance is a measure of the residual heterogeneity having adjusted for the covariates.

The regression coefficients are the estimated increase in the log RR per unit change in the corresponding covariate. Trial-level covariates that were investigated were:
- Location of trial
- Setting of trial
- Presence of active control arm
- Sample size
- Total duration of trial
- Rate of discontinuation
- Number of centers
- Extensive screening process at baseline
- Exclusion of placebo respondents
- Exclusion of treatment resistant patients
- Exclusion of baseline suicide risk
- Exclusion of history of suicide attempt
- Exclusion of homicide risk

No covariate was found to be statistically significant, so no results are reported in this review.

5.10.2 Dealing with zero cells

A "zero cell" in a 2x2 table occurs when one group in a trial contains no events (see example below). Zero cells make it impossible to compute ratio measures of treatment effects or the standard error of those ratio measures.

For the purpose of this meta-analysis, trials with no events in any treatment group were dropped from the analysis. For the primary outcome (outcome 3), four trials did not have any events (namely trials # 75 [Wellbutrin, ADHD], 141 & 187 [Serzone, MDD], and 396 [Effexor, GAD]). Because of the distribution of these trials, it is not expected to get an inaccurate inference about the risk because of their exclusion. This is because trials 75, 141, & 187 represent all trials available for Wellbutrin and Serzone and trial 396 was not an MDD trial.

Ten trials had no events in one of the treatment groups (namely, trials HCCJ & HCJW [Prozac], 114 [Luvox], 676 & 704 [Paxil], 045 [Remeron], 1001 & 0498 [Zoloft], and 382 & 394 [Effexor]). To calculate the ratio measures in trials with zero events in one of the trial groups, the "metan" procedure automatically corrects for the zero cell problem by adding 0.5 to each of the four cells (so called "continuity correction")[13, 14] before proceeding with the analysis as will be illustrated below. It is worth noting that the 0.5 is an arbitrary value and that the risk estimates might differ based on the value used for imputation.

For illustration, the Paxil trial # 676 will be used as an example. This trial had three events under the primary outcome (outcome 3, "definitive suicidal behavior/ideation") in the drug group and none in the placebo group. The correction procedure was done as follows:

Data before correction:

	Event	No event
Drug	3	165
Placebo	0	156

Data after correction:

	Event	No event
Drug	3.5	165.5
Placebo	0.5	156.5

RR = (3.5/169)/(0.5/157) = 6.50

[13] Sutton AJ and Abrams KR. Methods for meta-analysis in Medical Research. J Willy & Sons, NY, 2002, page 70.

[14] Deeks et al. Statistical Methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Smith GD, Altman DG (editors). Systematic reviews in health care. Meta-analysis in context. London: BMJ Publishing Group, 2001: pp 288.

5.10.3 Findings of the meta-analysis

5.10.3.3 The primary outcome (outcome 3) by drug

Only 19 out of the 23 trials were evaluable for the primary outcome (outcome 3). No individual trial showed a statistically significant signal but eight trials had a RR of 2 or more. The pooled overall estimates varied by drug. The following table summarizes the overall RR estimates of the primary outcome (outcome 3) by drug. Note that Effexor was the only drug that did not include "1" in the 95% CI of its risk estimate.

Table 10: Summary of the overall risk estimates of the primary outcome (outcome 3) by drug across all indications and in MDD trials.

Drug	Relative Risk (95% CI), all trials, all indications	Relative Risk (95% CI), MDD trials
Prozac	0.92 (0.39, 2.19)	0.89 (0.36, 2.19)
Paxil	2.65 (1.00, 7.02)	2.15 (0.71, 6.52)
Zoloft	1.48 (0.42, 5.24)	2.16 (0.48, 9.62)
Celexa	1.37 (0.53, 3.50)	1.37 (0.53, 3.50)
Effexor	4.97 (1.09, 22.72)	8.84 (1.12, 69.51)
Remeron	1.58 (0.06, 38.37)	1.58 (0.06, 38.37)

In the following sections, the risk estimates are graphed for each trial within each drug development program. In addition, an overall drug risk estimate is provided for all indications, and for trials in MDD trials.

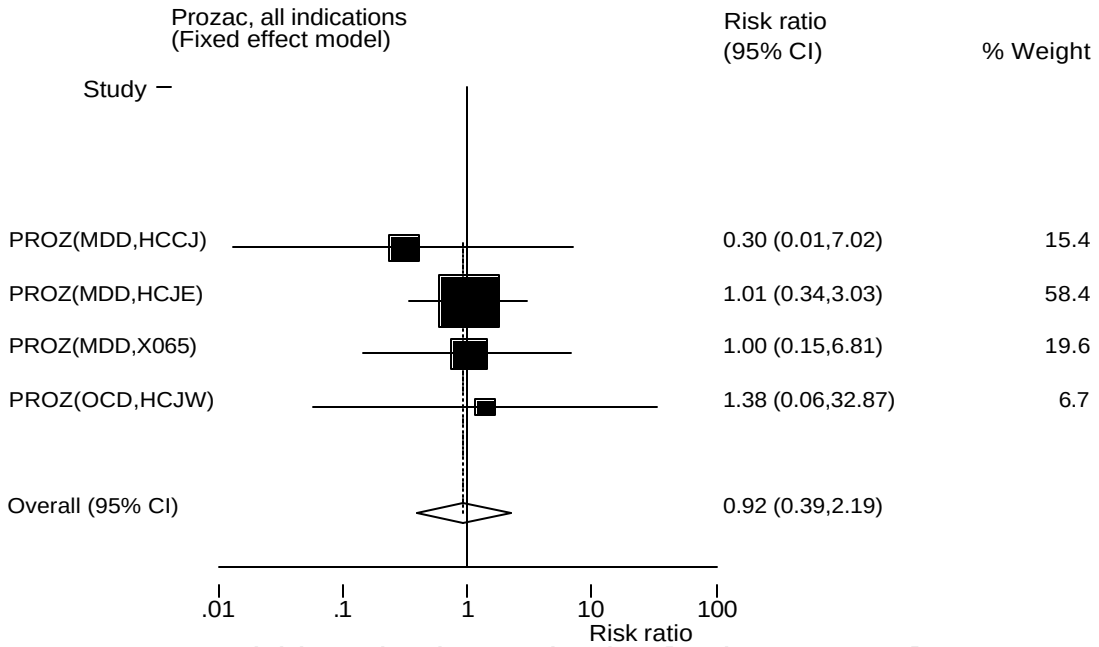
Those graphs show that there are variations between the risk estimates of various trials even within the same development program and the same indication. In an attempt to understand the observed discrepancies between the risk estimates of trials, the attributes of the trial designs were examined. The findings are summarized in a table for each drug that has more than one MDD trial. The examined attributes focused on inclusion/exclusion criteria that would affect the likelihood of recruiting high risk patients. Attributes that might have an impact on the observed discrepancies between risk estimates are in red color.

Prozac

Trial design attributes - MDD trials	Trial HCCJ	Trial X065	Trial HCJE
Location	North America	North America	North America
Setting	Outpatient	Outpatient	Outpatient
Excluded age 6-11 y	Yes	No	No
Excluded placebo responders (placebo lead-in)	Yes	Yes	Yes
Extensive screening process	No	Yes	Yes

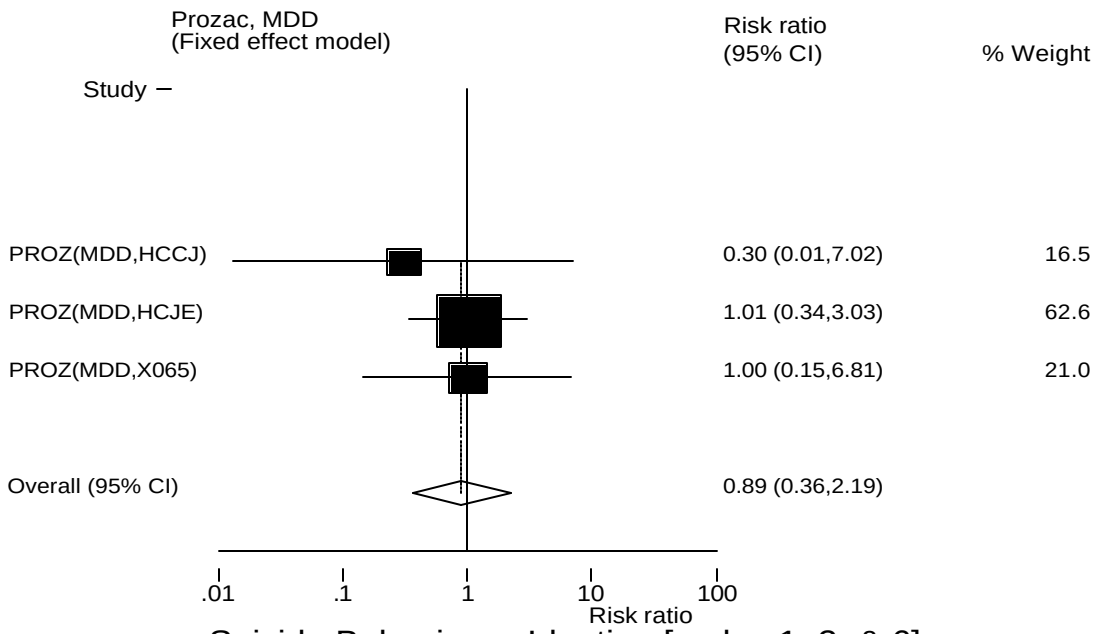
Trial design attributes - MDD trials	Trial HCCJ	Trial X065	Trial HCJE
Excluded treatment-resistant	No	No	Yes
Excluded baseline suicide risk	Yes	No	Yes
Excluded history of suicide attempt	No	No	No
Excluded homicide risk	No	No	No
Other attributes	Early termination		

Trial HCJE was the largest trial for Prozac (219 patients) and trial HCCJ was the smallest trial (40 patients; it was terminated early[15]). All trials excluded placebo responders. Both trials X065 and HCJE had an extensive screening process to assure ascertainment of patients' diagnosis. Trial HCJE excluded both treatment-resistant patients and patients with baseline suicide risk. Trial X065 is the only trial that did not exclude patients with evidence of suicide risk at baseline and had the highest discontinuation rate in a placebo group. Interestingly, this trial showed a signal in outcome 1 (suicidal behavior) as will be shown later.



Suicide Behavior or Ideation [codes 1, 2, & 6]

[15] The trial was terminated early because of difficulty in meeting the patient recruitment goals in a reasonable time.



Suicide Behavior or Ideation [codes 1, 2, & 6]

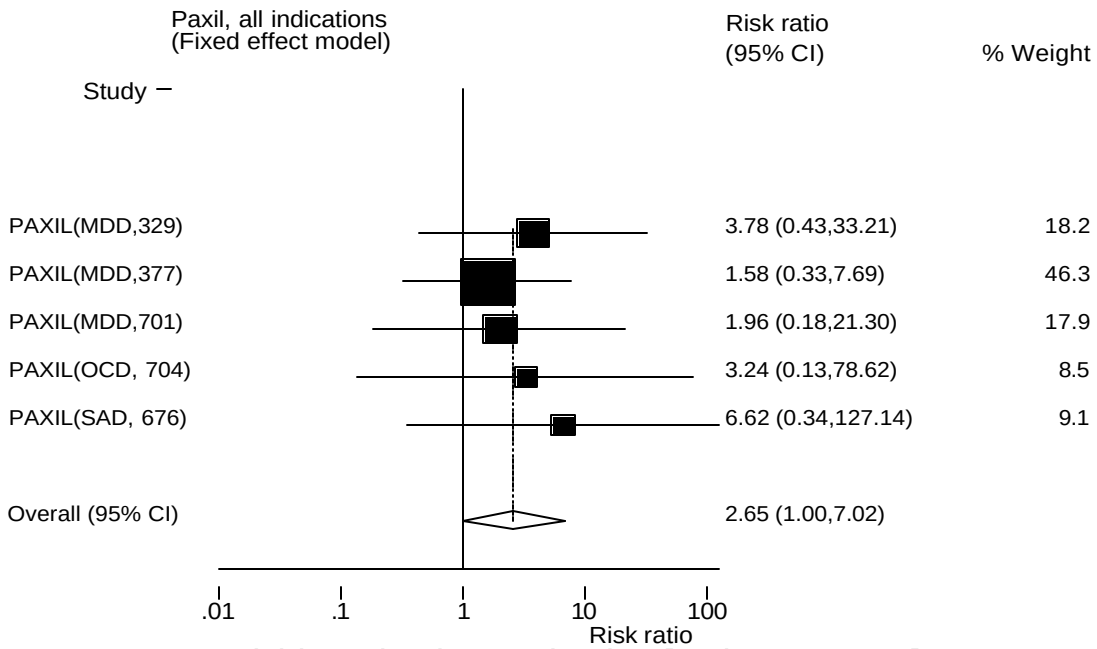
Paxil

Trial design attributes- MDD trials	Trial 329	Trial 377	Trial 701
Location	North America	Both	North America
Setting	Outpatient	Outpatient	Outpatient
Active control	Yes	No	No
Excluded age 6-11 y	Yes	Yes	No
Excluded placebo responders (placebo lead-in)	No	Yes	No
Extensive screening	Yes	No	No
Excluded treatment-resistant	No	No	Yes
Excluded baseline suicide risk	Yes	Yes	Yes
Excluded history of suicide attempt	No	No	No
Excluded homicide risk	No	No	Yes

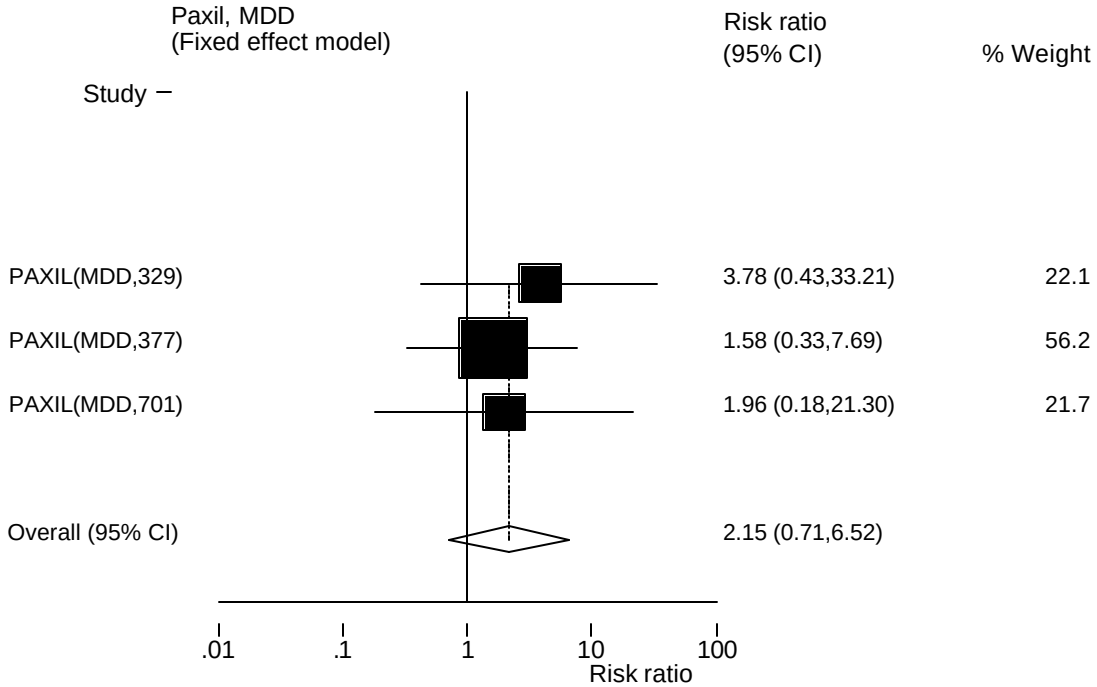
Interestingly, the trial with the highest risk estimate among Paxil MDD trials (329) was the only trial (in the Paxil development program and among all 23 pediatric trials under consideration) with an active control arm. Speculatively, this might have led to the inclusion of sicker patients as physicians knew that patients had two out of three chances of getting an active drug.

The largest trial was 377. This trial had the lowest risk estimate and it was the only trial that excluded placebo responders after a 2 weeks placebo lead-in period, which may have helped exclude some of the less depressed patients.

Note that the signal is suggested in both the MDD and the non-MDD trials.



Suicide Behavior or Ideation [codes 1, 2, & 6]



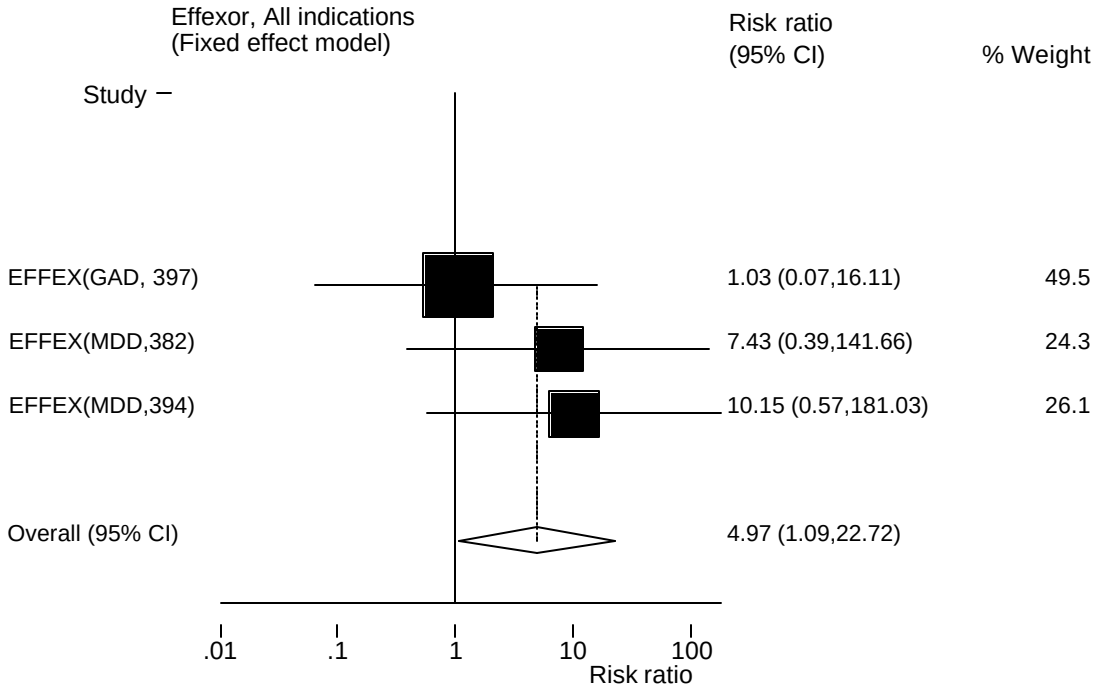
Suicide Behavior or Ideation [codes 1, 2, & 6]

Effexor

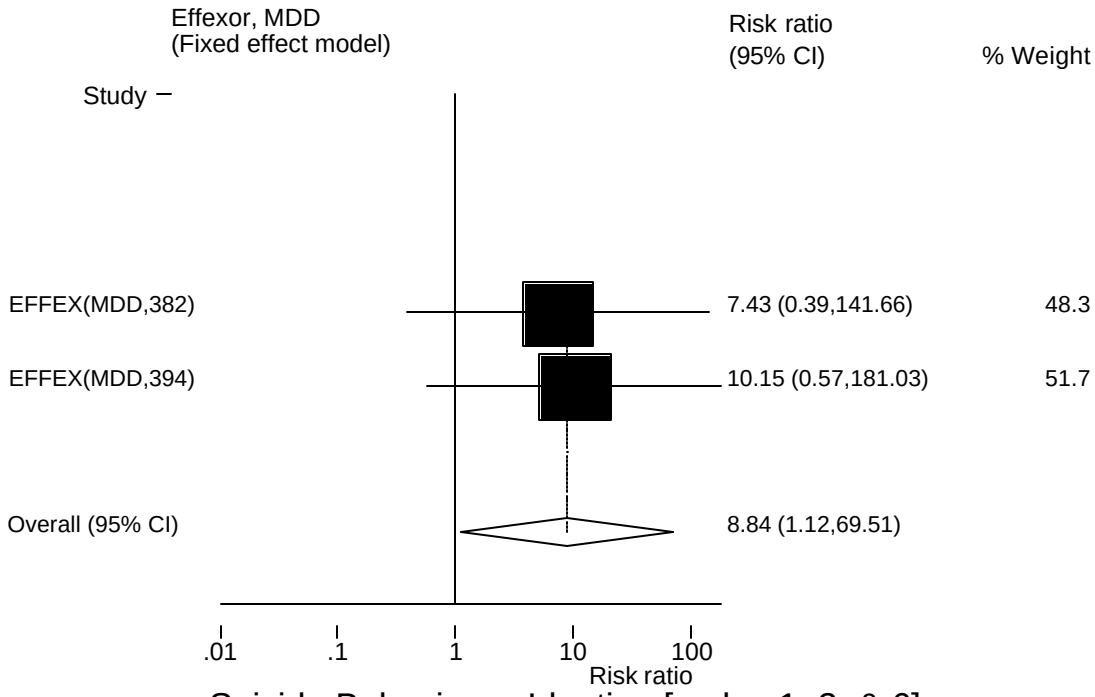
Trial design attributes-MDD trials	Trial 382	Trial 394
Location	North America	North America
Setting	Outpatient	Outpatient
Excluded age 6-11 y	No	No
Excluded placebo responders (placebo lead-in)	Yes	Yes
Extensive screening	No	No
Excluded treatment-resistant	No	No
Excluded baseline suicide risk	Yes	Yes
Excluded history of suicide attempt	No	No
Excluded homicide risk	No	No

Note that these two trials have the highest risk estimates among all trials. Interestingly, they did not exclude patients with treatment resistance, history of suicide attempt or homicide risk. They also did not have any extensive screening process. In addition, they have identical risk and apparently they are identical in their inclusion criteria.

Note that the signal is observed only in the MDD trials.



Suicide Behavior or Ideation [codes 1, 2, & 6]

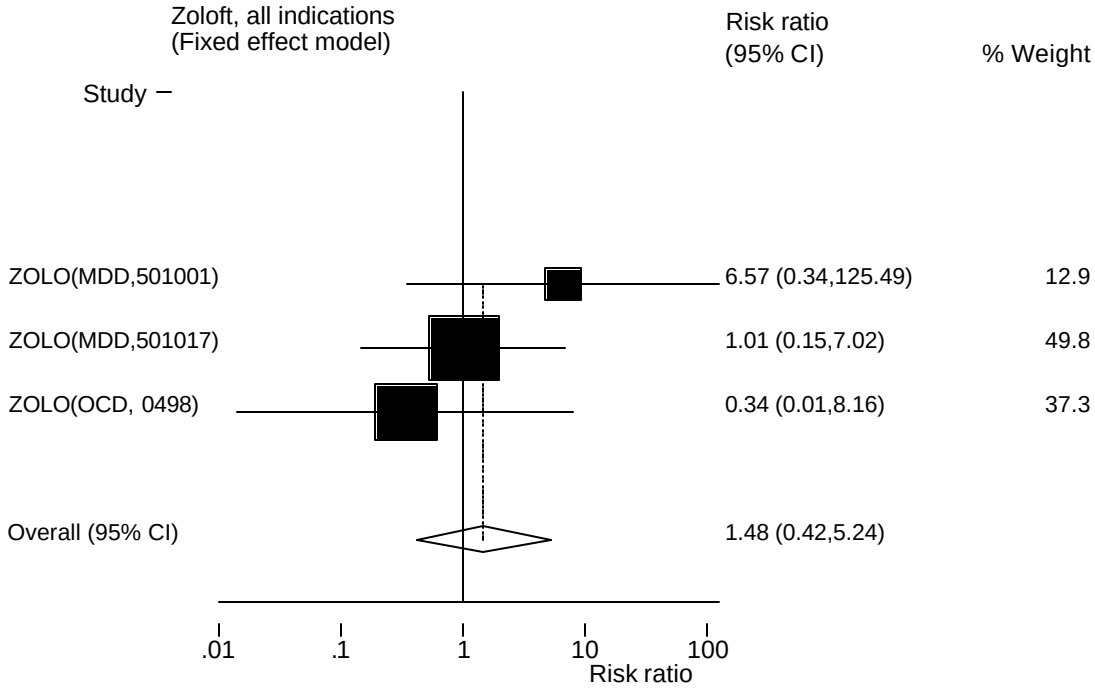


Suicide Behavior or Ideation [codes 1, 2, & 6]

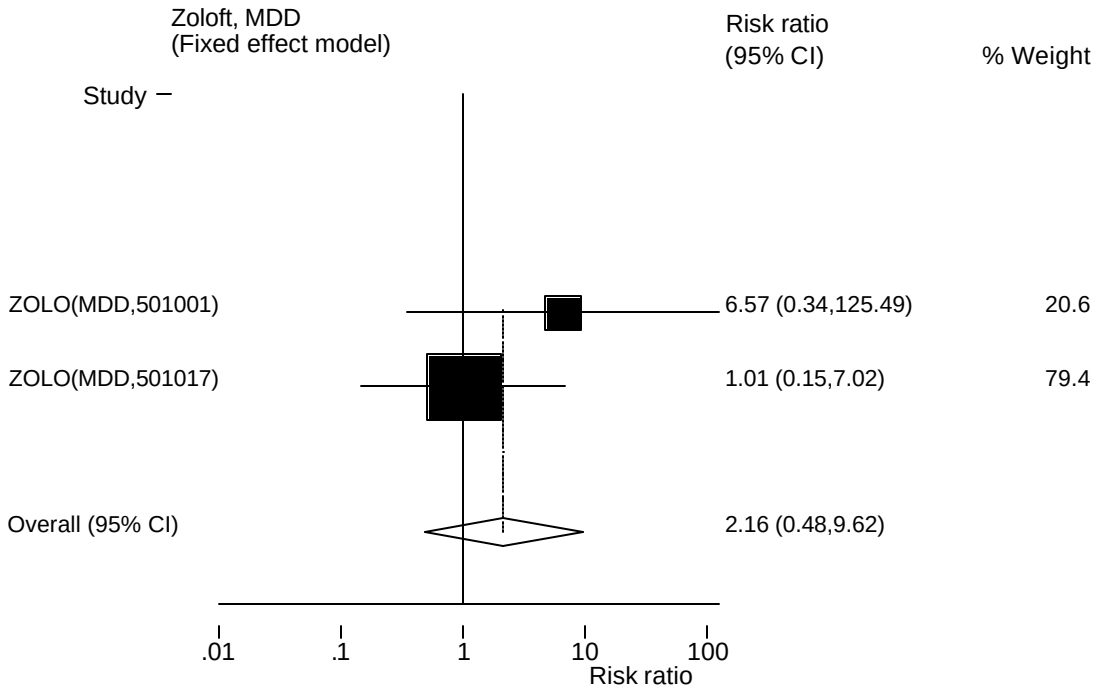
Zoloft

Trial design attributes-MDD trials	Trial 1001	Trial 1017
Location	Both	Both
Setting	Outpatient	Outpatient
Excluded age 6-11 y	No	No
Excluded placebo responders (placebo lead-in)	No	No
Extensive screening	No	No
Excluded treatment-resistant	No	Yes
Excluded baseline suicide risk	Yes	Yes
Excluded history of suicide attempt	Yes	Yes
Excluded homicide risk	Yes	No

Trial 1001 did not exclude treatment-resistant patients. Note in the following graph that the signal was more in that trial than in trial 1017.



Suicide Behavior or Ideation [codes 1, 2, & 6]

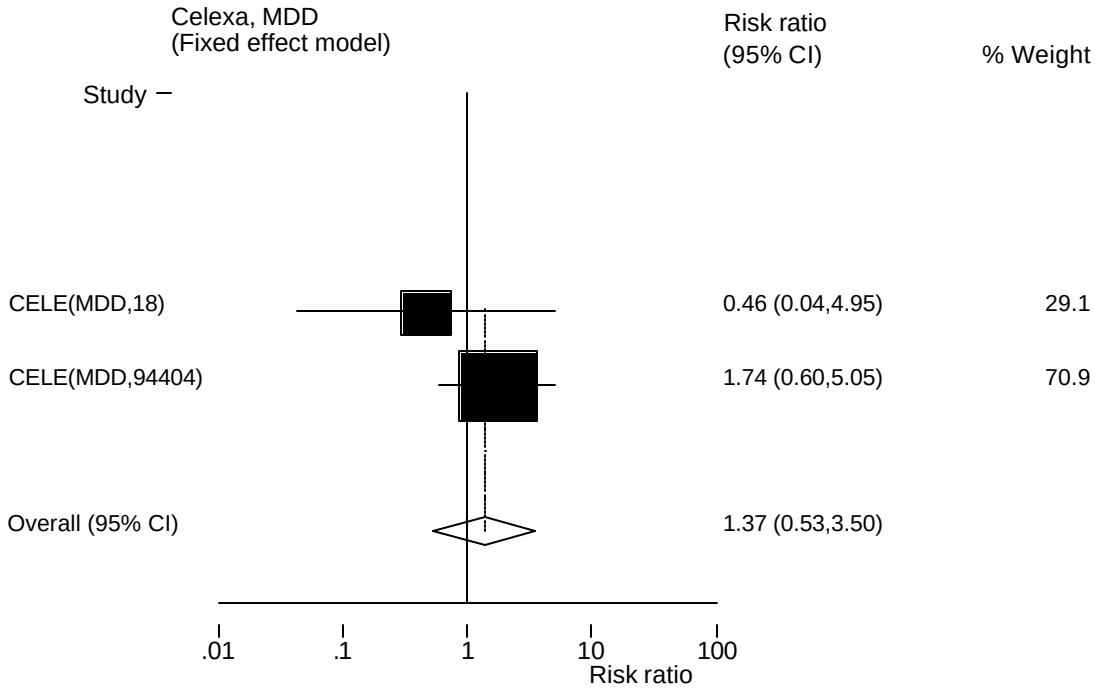


Suicide Behavior or Ideation [codes 1, 2, & 6]

Celexa

Trial design attributes-MDD trials	Trial CIT_18	Trial 94404
Location	North America	Non-North America
Setting	Outpatient	Both
Excluded age 6-11 y	No	Yes
Excluded placebo responders (placebo lead-in)	Yes	No
Extensive screening	No	No
Excluded Tx. resistant	Yes	No
Excluded baseline suicide risk	Yes	No
Excluded history of suicide attempt	Yes	No
Excluded homicide risk	No	No

These two Celexa trials varied in almost every aspect. The combination of the differences might have led to higher probability of having higher risk patients in trial 94404. Note in the following graph that the signal is observed in trial 94404 and not in CIT-18.



Suicide Behavior or Ideation [codes 1, 2, & 6]

5.10.3.4 Components of the primary outcome (outcome 3): outcome 1 (codes 1 and 2) and outcome 2 (code 6)

The following graphs show the RR and 95% CI for the components of the primary outcome (outcome 3). Note in the graphs that more trials appear in the "Forest plot" for suicidal ideation (outcome 2) than for suicidal behavior (outcome 1) because the latter has fewer events than the former.

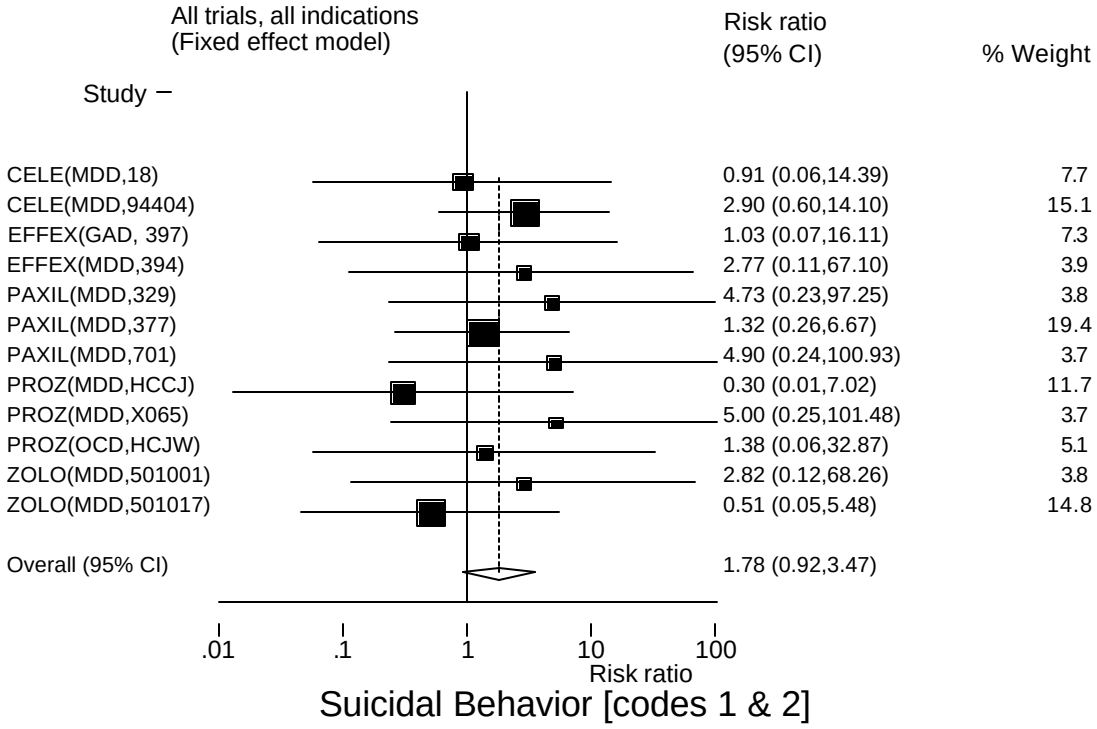
For outcome 1, signals are coming from most drugs including Prozac. However, such a signal is not coming consistently from the same trials for outcome 2. Specifically, this was true for trials # 18 & 94404 [Celexa], 701 [Paxil], and X065 [Prozac]. This led to dilution of the signal when the two outcomes were combined to make the primary outcome (outcome 3). This phenomenon might be a function of the ability to capture events. It is conceivable that suicidal ideation events might be more likely to be underreported than suicide attempt events. It is important to bear this observation in mind when interpreting the results of the primary outcome (outcome 3).

The following table summarizes the overall risk estimates for outcomes 1 & 2 by drug. It is worth noting that none of the drugs had a statistically significant overall RR for outcomes 1 or 2 individually.

Table 11: Summary of the overall risk estimates of outcomes 1 & 2 by drug in MDD trials.

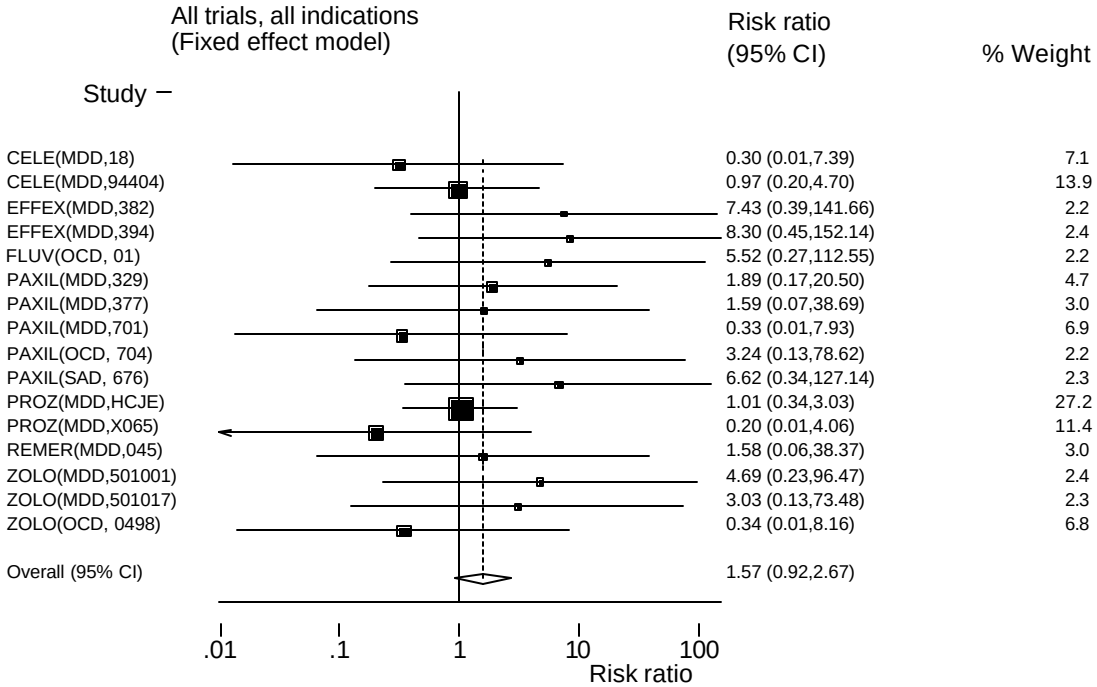
Drug	Relative Risk (95% CI), suicidal behavior (outcome 1)	Relative Risk (95% CI), suicidal ideation (outcome 2)
Prozac	1.44 (0.25, 8.20)	0.77 (0.29, 2.09)
Paxil	2.30 (0.67, 7.93)	1.09 (0.24, 5.01)
Zoloft	0.98 (0.17, 5.68)	3.88 (0.44, 34.54)
Celexa	2.23 (0.59, 8.46)	0.75 (0.19, 2.95)
Effexor	2.77 (0.11, 67.10)	7.89 (0.99, 62.59)
Remeron	No events	1.58 (0.07, 38.37)

Outcome 1: Suicidal behavior (codes 1 & 2)



Suicidal Behavior [codes 1 & 2]

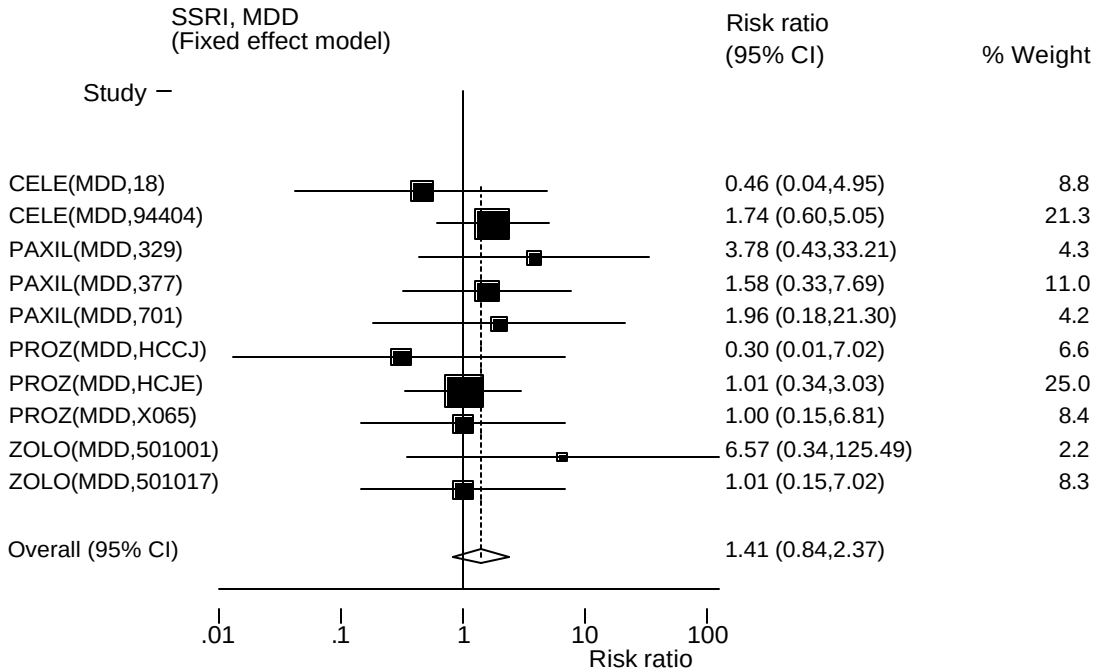
Outcome 2: Suicidal ideation (code 6)



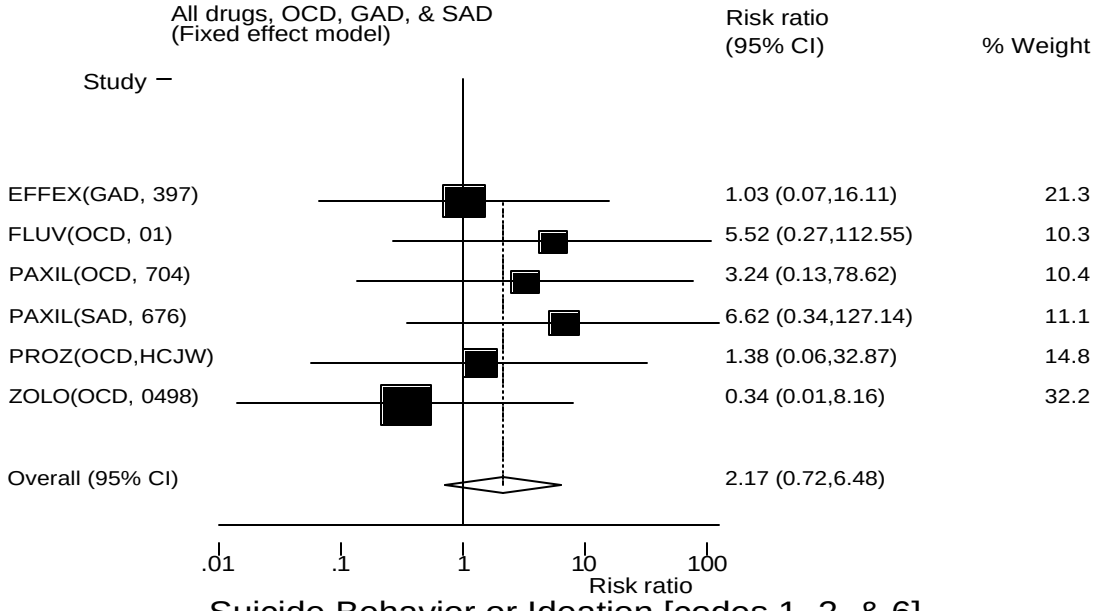
Suicidal Ideation [code 6]

5.10.3.5 The primary outcome (outcome 3), by indication

The next two graphs show the RRs of the primary outcome (outcome 3) among pooled MDD trials for the SSRI drugs and among all other indications. Note that the signal tends to be weaker in the former than the latter group of trials. However, the 95% CIs of both groups overlap.



Suicide Behavior or Ideation [codes 1, 2, & 6]



Suicide Behavior or Ideation [codes 1, 2, & 6]

5.10.3.6 Outcomes 1 to 7, all trials, all indications

The following table summarizes the overall risk estimates of all seven outcomes in addition to the sponsors' original classification, in all indications and in the SSRI MDD trials. Outcomes 1, 2, & 3 have been discussed above. The detailed graphs for the other outcomes are provided in Appendix XI.

Table 12: Summary of overall risk estimates of all seven outcomes and the sponsors' original events, in all indications and in the SSRI MDD trials

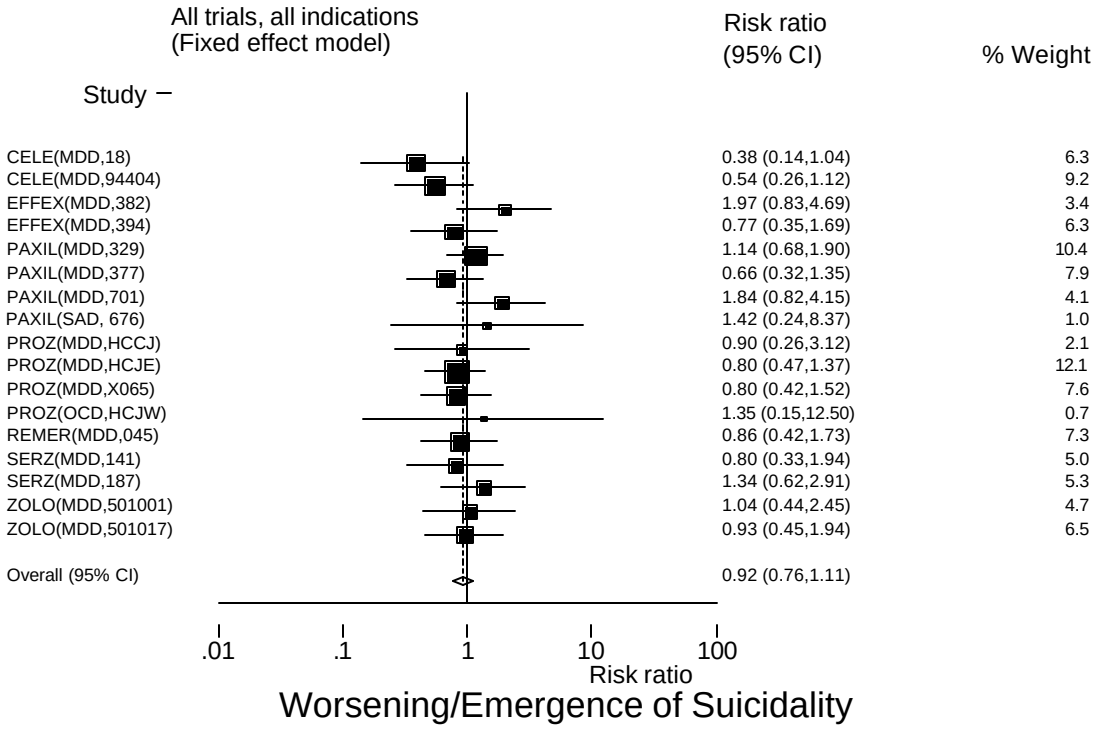
Outcomes	Overall RR (95% CI), all trials, all indications	Overall RR (95% CI), SSRI MDD trials
Outcome 1, Definitive suicidal behavior **n=33**	1.78 (0.92, 3.47)	1.83 (0.89, 3.77)
Outcome 2, Suicidal ideation **n=45**	1.57 (0.92, 2.67)	1.00 (0.52, 1.94)
The primary outcome (outcome 3), Definitive suicidal behavior /ideation **n=78**	1.78 (1.14, 2.77)	1.41 (0.84, 2.37)
Outcome 4, Possible suicidal behavior/ideation **n=109**	2.06 (1.39, 3.04)	1.78 (1.11, 2.86)
Outcome 5, Self-injurious behavior, non-suicidal **n=11**	1.61 (0.59, 4.40)	1.20 (0.35, 4.13)
Outcome 6, Worsening of suicidality score **n=434**	0.92 (0.76, 1.11)	0.85 (0.68, 1.06)
Outcome 7, Emergence of suicidality (a subset of outcome 6) **n=349**	0.93 (0.75, 1.15)	0.86 (0.66, 1.11)
Sponsors' classification, n=113	1.81 (1.24, 2.64)	1.62 (1.03, 2.54)

Outcome 5

For outcome 5, "self-injurious behavior, non-suicidal", no individual trial had a statistically significant finding. Nonetheless, some of the trials that showed a signal under the primary outcome (outcome 3) also showed a signal for this outcome, namely trials # 394 [Effexor], 329, and 676 [Paxil]. The results are provided in Appendix XI.

Outcome 6

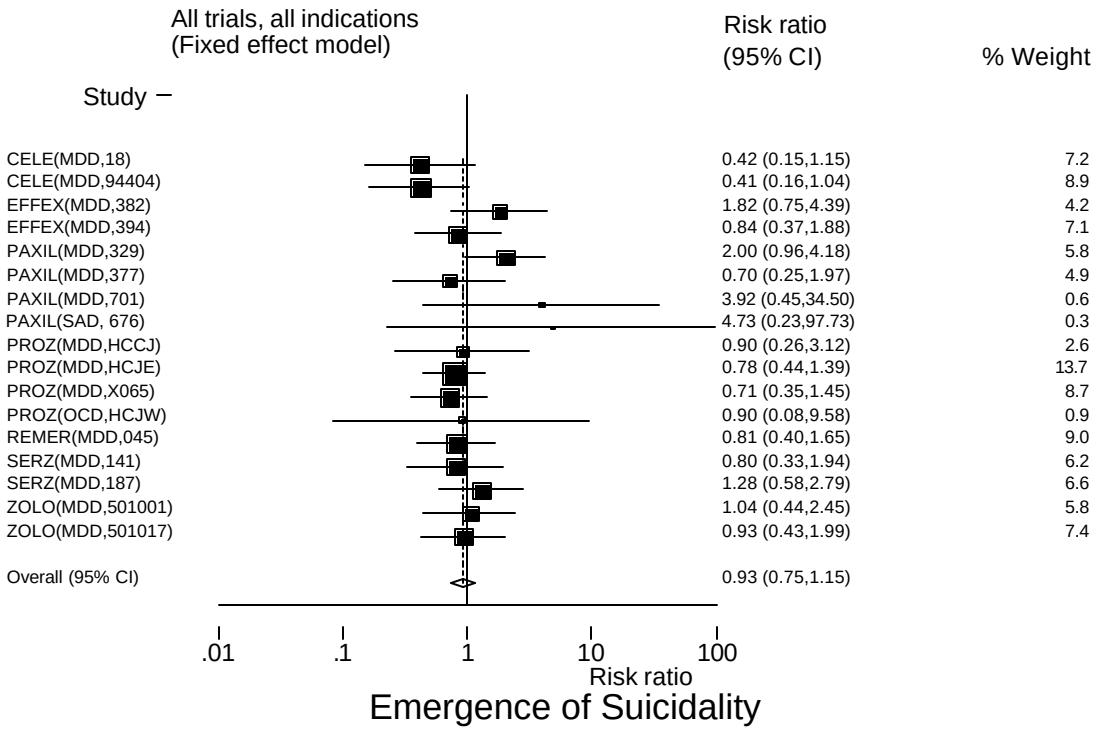
For outcome 6, "worsening/emergence of suicidality", very few trials had a finding suggestive of a signal, namely trials # 382 [Effexor], 701 & 676 [Paxil], and HCJW [Prozac]. Interestingly, all these trials, except trial HCJW, also showed a signal for the primary outcome (outcome 3) as was shown previously.



There was a concern that it was possible that some patients might have developed worsening of their suicidality score but did not return to the study site for their exit interview. In that scenario the patient would not have been identified by the algorithm used to define this outcome, leading to informative censoring. Consequently, the signal would be more pronounced in the subset of patients that completed the trial and weaker in the subset of patients that discontinued. However, this did not turn out to be true when the trials' RRs were compared between the group of patients that discontinued prematurely and those that completed the trial. The analysis in the latter group represents a "completers" analysis. The detailed results of the analysis are provided in Appendix XVI.

Outcome 7

For outcome 7, "emergence of suicidality", which is a subset of outcome 6, the results more or less mirrored those of outcome 6. Very few trials had a finding suggestive of a signal, namely trials # 382 [Effexor], 329, 701, and 676 [Paxil]. Interestingly, all these trials also showed a signal for the primary outcome (outcome 3) as was shown previously.



The suicidality items in various efficacy questionnaires constituted the basis for outcome 6 and outcome 7. Those suicidality items were collected regularly at study visits. The caveat with outcome 6 and outcome 7 is that the information gathered by the suicidality items might not have been collected at the time the suicidal behavior or ideation was manifesting itself. This might explain to some extent the lack of signal strength base on these outcomes.

The sponsors' original classification

The overall risk estimate for the sponsors' original classification is somewhat similar to that of the primary outcome (outcome 3). However, as for the individual trials, trials # 382 [Effexor], 377 & 701 [Paxil], HCJW [Prozac], & 045 [Remeron] showed more pronounced risk estimates, and trials 329 & 676 [Paxil] and HCCJ [Prozac] showed less pronounced risk estimates in the primary outcome (outcome 3) as compared to the sponsor's original classification.

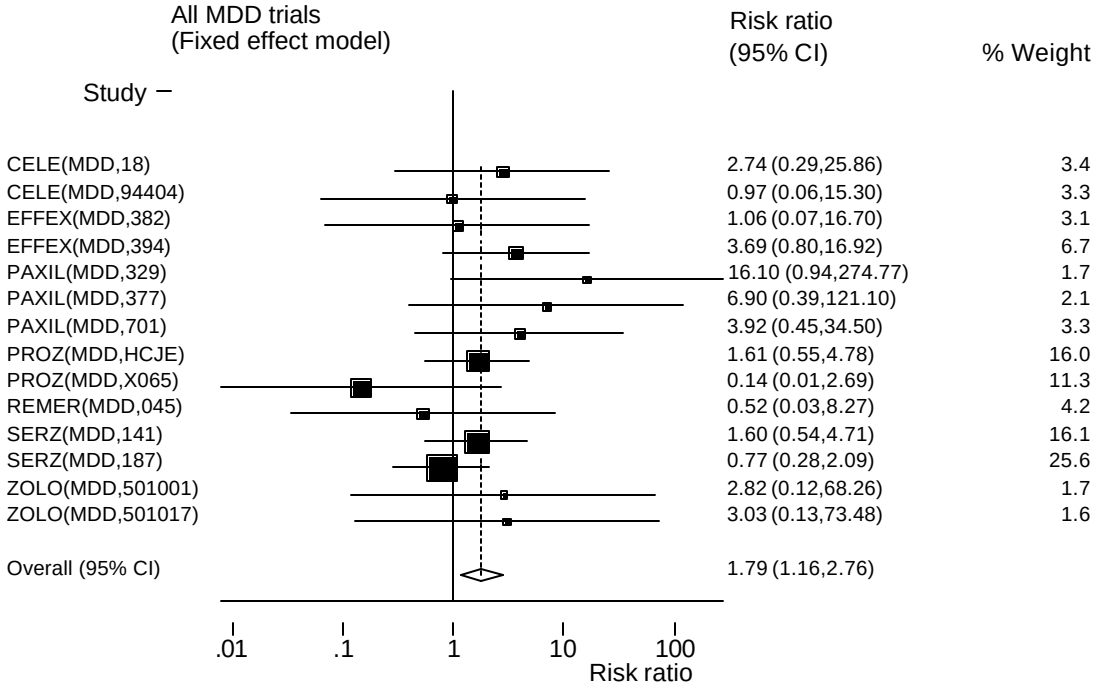
The random-effects approach for obtaining an overall risk estimate for the sponsors' original classification was slightly lower than that of the fixed-effect (1.57 and 1.81, respectively). The results are provided in Appendix XI.

5.10.3.7 Exploration of the potential for "activation syndrome"

At the joint meeting of the Psychopharmacological Drug Products Advisory Committee and Pediatric Subcommittee of the Infectious Diseases Advisory Committee held on February 2, 2004, the committee raised the concern that psychotropic drugs might induce an "activation syndrome" which might put a patient at risk for suicidal behavior or ideation.

To investigate this issue, the association between drug treatment and treatment emergent symptoms of hostility or agitation during the trial was examined. A total of 90 events with these symptoms were observed in all the MDD trials. A detailed listing of the frequency of these events by drug, trial and indication is included in Appendix XVII. The following graphs and table show the RRs of having these symptoms in MDD trials for all drugs and for SSRIs.

Although none of the individual trials had a statistically significant result, the overall RR for Paxil and the overall RRs for all drugs and for all SSRIs were statistically significant showing an increase in the risk of developing these symptoms in the drug group as compared to the placebo group.



Treatment emergent agitation or hostility

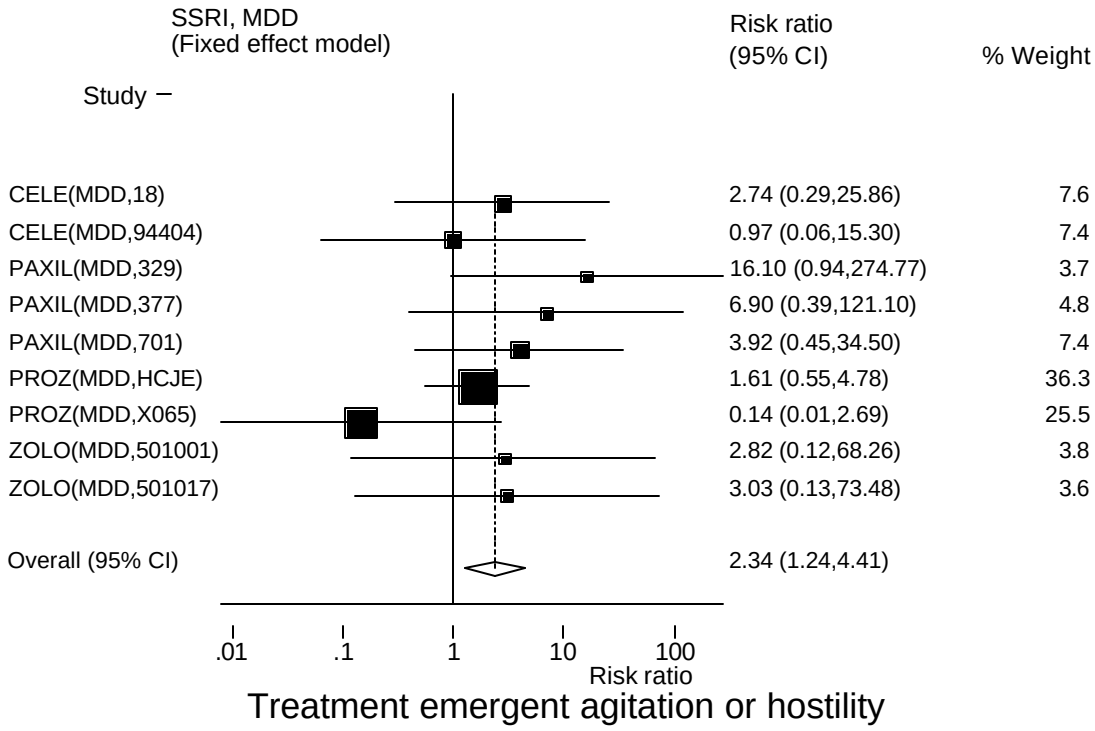


Table 13: Summary of the overall risk estimates of treatment-emergent agitation or hostility by drug in MDD trials.

Drug	Relative Risk (95% CI), MDD trials
Prozac	1.01 (0.40, 2.55)
Paxil	7.69 (1.80, 32.99)
Zoloft	2.92 (0.31, 27.83)
Celexa	1.87 (0.34, 10.13)
Effexor	2.86 (0.78, 10.44)
Remeron	0.52 (0.03, 8.27)
Serzone	1.09 (0.53, 2.25)

Unfortunately, examining the likelihood of having an event of the primary outcome (outcome 3) among patients with the symptoms of hostility or agitation was not evaluable because information on the timing of the latter events was not available in the data. Therefore, determining the time sequence was not possible.

5.10.4 Sensitivity Analysis

The sensitivity analysis focused on the meta-analysis results of the primary outcome (outcome 3). Two approaches to sensitivity analyses were undertaken and are discussed below.

5.10.4.8 Sensitivity of the results of the primary outcome (outcome 3) to meta-analysis method (results of random-effects models, overall and by indication)

First, the sensitivity of the results of the primary outcome (outcome 3) to the meta-analysis weighting method was examined by repeating the overall estimates using the random-effects model. No meaningful difference was observed in the risk estimates between the fixed-effect and the random-effects methods. Graphs showing the details of the risk estimates for this analysis are provided in Appendix XV. The following table summarized the risk estimates for the two methods, overall and by indication.

Table 14: Summary of risk estimates of the primary outcome (outcome 3) using the fixed-effect and the random-effects methods, overall and by indication

Outcomes	Overall RR (95% CI), fixed-effect model	Overall RR (95% CI), random-effects model
Outcome 3, overall	1.78 (1.14, 2.77)	1.59 (0.99, 2.56)
Outcome 3, SSRI MDD	1.41 (0.84, 2.37)	1.36 (0.79, 2.33)
Outcome 3, other indications	2.17 (0.72, 648)	1.99 (0.58, 6.85)

5.10.4.9 Sensitivity of the results of the primary outcome (outcome 3) to event ascertainment: results of outcome 4

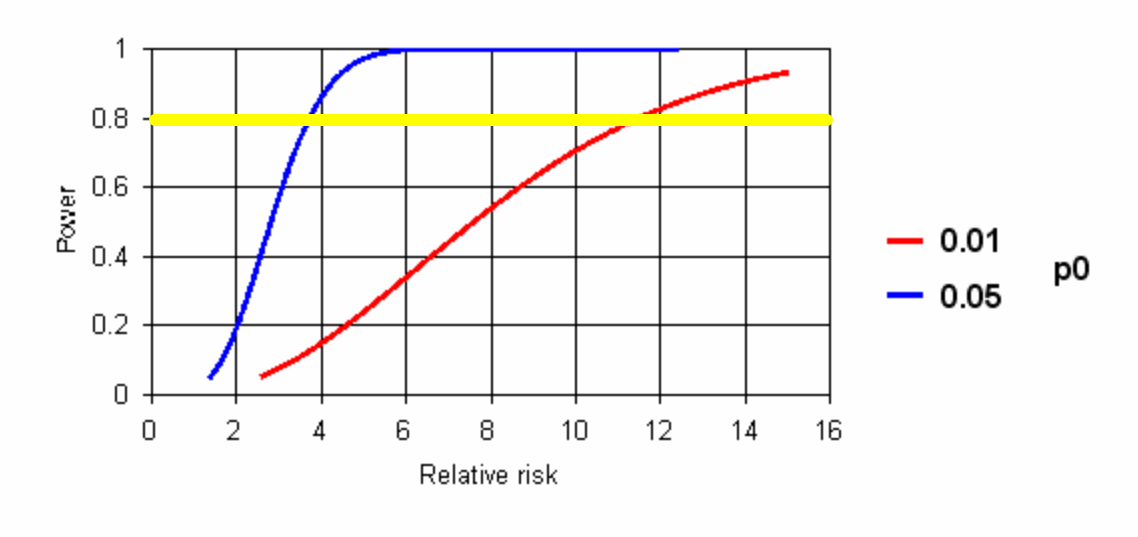
Second, the sensitivity of the results of the primary outcome (outcome 3) to event ascertainment was explored by comparing the overall analyses to that of outcome 4. Outcome 4 included all possible suicide-related events reported (i.e. with codes 3 and 10 added to outcome 3 codes 1, 2, and 6) and represents a "worst case scenario" of sorts. The graphs provided in Appendix XI show the results of this analysis. It is worth noting that the signal was not meaningfully altered for most drugs.

5.11 Statistical power for individual trials

To explore the statistical power of individual trials, the following graph was plotted to reflect the expected power in a given trial depending on the incidence of the outcome of interest in the placebo group. These calculations assume 100 patients per treatment group, which the majority of trials fulfilled.

Assuming an incidence of 1% of suicide behavior/ideation in the placebo group, trials with 100 patients in each arm had 80% power to detect a 12 fold increase or more in the

risk of suicidality. Assuming an incidence of 5% in the placebo group, trials with 100 patients in each arm had 80% power to detect about a 4 fold increase or more in the risk of suicidality.



p0 = incidence of events in the placebo group.

6 Limitations of the current investigation

- It is worth noting that what is reported in this review represents a post-hoc analysis with multiple outcomes involved. This is complicated by the lack of statistical significance for many of the sub-analyses, which increase the level of uncertainty. Therefore, caution is warranted in the interpretation of the findings.

- Given the size of the individual trials and the background rates of suicide behavior/ideation, the conducted trials were capable of detecting an increase in the risk of suicidality of 4-12 fold. Therefore, none of the individual trials showed statistically significant results. Clearly, these trials were designed for efficacy and were not powered for safety purposes.

- The current analyses used short term data (4-16 weeks). Therefore we could possibly miss suicidality effects that require a cumulative exposure or long latency period that exceeds the trial duration.

- Some of the covariates requested by the FDA to investigate their potential confounding effects on the risk estimates were missing from the submitted data. However, a reassuring finding is that in trials with complete data there were no significant imbalances detected between the drug and the placebo groups.

- Pooling data across drugs within a class assumes that the rate of suicidality is similar across that class of drugs, i.e. that there is a "class effect". In the current investigation, some of the drugs have smaller databases than others. Consequently, the smaller

opportunity to observe suicidality may have resulted in none or fewer cases being observed for that drug. There is also the potential role for the immeasurable and uncontrollable differences in the level of ascertainment of events and completeness of narratives between various trials and various sponsors. Thus, observed differences in the risk between drugs may have several possible explanations, including a true difference between drugs, inadequate power for studies of some of the drugs, or because of differences between trials in ascertainment and reporting of adverse events.

- Observed rates of suicidality might not reflect actual rates among patients in the general population because patients participating in randomized clinical trials might be a selected subgroup of patients due to what is known as "volunteer's bias". Therefore, it might not be easy to generalize the findings of these analyses.

- Most trials were conducted with a flexible dosing scheme, which made investigating the dose effect difficult. The only information available for each patient is the maximal modal dose with no specification of which dose was associated with the event and the timing of event as it relates to changes in dose.

- The patterns and causes of premature discontinuation across these trials may be an important finding, but they are difficult to explore. Ignoring these patterns assumes that there is no informative censoring; however, it needs to be acknowledged that this is an important assumption, given the fact that discontinuations were as high as 50% in some trials.

- Adolescents are known to take their medications erratically, and medication compliance may have influenced the occurrence of events of interest. However, the extent of noncompliance was assessed differently across drug development programs.

7 Reviewer's Conclusions

- The involved search of adverse events in various drug development programs and the blinded classification process identified many events not previously identified and also eliminated a number of events that were not appropriately classified, thus reducing misclassification and providing more accurate risk estimates.

- It should be noted that, among the events considered representative of suicidality in these 25 pediatric antidepressant trials, there were no completed suicides.

- No individual trial showed a statistically significant signal for suicidality. However, many had a RR of 2 or more and some of the overall estimates, across various trial groupings, were statistically significant.

- The strength of the suicidality signal, although it varies from drug to drug, is comparable to previous findings for most drugs.

- The sensitivity analyses did not yield a meaningful difference in the magnitude of the estimated risks.

- The differences in the risk estimates between trials within the same drug in the same indication might be partially explained by some of the trials' design attributes.

- Most of the events occurred in trials with the highest proportion of patients with a history of suicide attempt or ideation at baseline.

- Notwithstanding the missing data on covariates, no meaningful effect modification or confounding was detected for any trial.

- The time to event analysis showed that the hazard may not be constant over time, and may not always be proportional between the drug and the placebo groups.

- Drug treatment is associated with symptoms of hostility or agitation. However, it was not possible to explore a possible link between the occurrence of these symptoms and suicidality due to limitations in the available data

8 APPENDIX I: Requests for summary data regarding suicide-related events

DNDP data request dated 7/22/03

Data Request Regarding Pediatric Suicidality

We request the following data analyses to assess the risk of pediatric suicidality with your drug.

Please include data from any randomized controlled trial conducted in the pediatric age group (<=17 years old), regardless of the indication.

- Please submit a brief description of the study design of each trial included in the requested analyses.

Event Identification

The identification of the following events should be done **blinded to treatment** to avoid bias. All adverse events occurring within 30 days of the last dose of drug should be included in the search.

"Suicide-related events" should be identified using the following algorithm:

- Any events coded to preferred terms that include the text strings "suic" or "overdos"
  - Exclude "accidental overdose" cases[16]
- Regardless of the preferred term to which the verbatim term is mapped, all verbatim terms should be searched for the following text strings: "attempt", "cut", "gas", "hang", "hung", "jump", "mutilat-", "overdos-", "self damag-", "self harm", "self inflict", "self injur-", "shoot", "slash", "suic-"
  - Any terms identified by this search because the text string was a substring of an unrelated word should be excluded (for example, the text string "cut" might identify the word "acute")
- In addition to the algorithm above, narratives of all serious adverse events (SAEs) should be reviewed (in a blinded fashion) to identify any additional cases of suicidality or self- harm. In particular, SAEs related to mania and hostility should be examined closely for suicidality or self-harm.
- Any death found to be due to suicide or overdose should be included (if not already identified by the previous search methods)[17].

We are also interested in an analysis of suicide attempts. "Suicide attempts" are a subset of the "suicide-related events" identified above; they should be identified using a **blinded** hands-on review of the records of all patients identified by the above algorithm as having a "suicide-related event". For the purposes of this analysis, any case in which the patient

[16] See request regarding "accidental overdose" cases below
[17] See request regarding "accidental" deaths below

exhibited self-injurious behavior should be considered as a suicide attempt. Any case in which the patient's suicidal ideation did not lead to self-injurious behavior should be excluded from this subset.

Requested Analyses

Separate analyses should be performed for the group of "suicide-related" events and the group of "suicide attempts". Both the risk (# of events/# of patients) and the rate (# of events/person-time exposure[18]) should be presented by treatment group. All treatment groups should be presented, including active controls. If a study has a blinded extension phase, events identified while the patient is in that extension phase should be excluded.

In addition to presenting the overall risks and rates across all indications and within each indication, the following stratified analyses should be performed:

- Child (<12) vs. Adolescent (>= 12).
- On-therapy vs. On-therapy + 30 days.
- Within each indication, data from each trial should be presented separately.

A sample analysis table follows in Appendix 1.

Patient Table and Narratives

In addition to the above analyses, a table with patient characteristics (listed below) should be provided (with one line per patient). A narrative summary should also be included for each of the patients identified as having an event. The narrative summary should tell the story of what happened to the patient leading up to, during, and following the adverse event. It should elaborate on the information provided in the table.

Although we are not asking you to include cases of "accidental overdose" or "accidental" death in the analyses above, we request that you enter such cases in the patient table and provide narratives for these patients.

The following variables should be included in the patient table:

- Patient ID number
- Trial number
- Treatment group
- Dose at time of event (mg)
- Recent dose change (y/n) – if yes, elaborate on timing and amount of dose change in narrative
- Sex
- Age
- Diagnosis
- History of suicidal thoughts (y/n) - if yes, elaborate in narrative summary

[18] The person time exposure is the sum total of the days of exposure each patient in the treatment group has had to the drug.

- History of suicide attempt (y/n) - if yes, elaborate in narrative summary
- History of self harm (y/n) - if yes, elaborate in narrative summary
- 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)
- Event occurred after discontinuation (y/n)- if yes, elaborate on days since discontinuation in narrative summary
- Patient had an emergency department visit and was discharged (y/n)
- Patient was hospitalized (y/n)
- Patient died (y/n) – if yes, elaborate on cause of death in narrative summary
- Associated treatment emergent adverse events (y/n)- if yes, elaborate in narrative summary
- Concurrent psychosocial stressors (y/n)- if yes, elaborate in narrative summary
- Psychiatric comorbidities (y/n)- if yes, elaborate in narrative summary
- Concomitant medications (y/n)- if yes, elaborate in narrative summary
- Other pertinent information (e.g., family history of psychiatric disorders)- elaborate in narrative summary
- Included in Suicide Attempts subgroup - yes/no
- Included in On-therapy subgroup – yes/no

DATE: November 24 , 2003

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Updated request for information on instances of suicidality in controlled trials involving pediatric patients

TO: Sponsors of antidepressant drug products

First I want to let you know that I appreciate your taking the time to talk with me over the past few weeks about your approaches to applying the search strategies we outlined in our 7-22-03 letter on this matter. As I've indicated, the reason for these recent discussions with you is to try to make as transparent as possible each of your approaches to this task and to make sure we have the same type of case material for each program. In retrospect, our 7-22-03 letter might have been more specific on a number of points. Having now had some preliminary discussions with each of you, I have a much better feel for what was done and what your approaches have been for selecting cases for your analyses and for submission to FDA. As I've also explained to you, the purpose in trying to define very clearly what has been collected and submitted is to facilitate our efforts to put together a package of materials to be blindly reviewed and reclassified by an outside, independent group of experts in adolescent suicidality. This is important in order to be able to collect the fraction of cases from this much larger set of potential cases that can be considered by experts to actually represent suicidality. This is the first step in our attempt to independently analyze these data, and the cases selected will be those included in our hopefully more definitive analyses based on the patient level data sets that you are also preparing for us.

After having this initial round of discussions, it seems clear that there remains some lack of clarity on what we want, and so I thought it might be useful for me to spell out in precise detail what we need, and also suggest a precise format for how this material could be most usefully aggregated for our purposes. I realize that this effort may be at least partly redundant for most of you, however, I ask that you bear with me on this in order that we can get this accomplished in a timely way. The goal of this part of the program is to get the cases adjudicated in a standard manner by a group of recognized experts so that the end results of this work can stand up to scrutiny and so that we can fully evaluate this potential risk.

Toward this end, I am asking that each of you provide a report focusing on your approach to identifying potential instances of suicidality, and that you provide a detailed accounting of what was found, along with narrative information on certain of these cases. Many of you have already accomplished most of the components of what I am asking for, and thus, it will be mostly a matter of assembling these materials in our preferred format to facilitate our further review of these materials.

The report that I am requesting should include the following:

Section 1:

Studies Included in Search

This section should simple state and identify the placebo controlled studies in your program that are the focus of this search. Please also refer to **Appendix A** for a more detailed, yet still brief, description of each trial. You can simply utilize study descriptions already provided in previous submissions to us in creating Appendix A.

Section 2:

Methodology of Search

This section should describe in some detail your approach to applying the search strategies we outlined in our 7-22-03 letter.

In particular:
-Did you search preferred terms for the two text strings "suic" and "overdos"?
-Did you search verbatim terms for the following 15 text strings: attempt; cut; gas; hang; hung; jump; mutilat-; overdos-; self-damag-; self harm; self inflict; self injur-; shoot; slash; suic-

Please simply describe what you did regarding this aspect of the search (i.e., focus just on the search for potential events using the algorithm, and **not** your blinded evaluation of potential events). .

I will return to the narratives later.

Section 3:

In this section, I would like you to provide a very detailed accounting of the results of the search you have described in Section 2.

Subsection 1:

Total Count of Patients/Potential Events Identified by Search of Preferred/Verbatim Terms

The initial subsection should simply indicate the total number of patients/potential events identified by the combined preferred terms/verbatim terms searches. For example, it might simply state that these searches identified a total of 90 patients with 1 or more potential events. [Note: I will use the number 90 to illustrate the exercise I want you to go through in arriving at the patients for whom we need

narratives.] It should then refer to **Appendix B** that will include a table structured as follows, for these 90 patients:

Study #	Patient #	Treatment Assignment	Number of Potential Events for That Patient

This table in Appendix B should include **ALL** potential events identified, without any exclusions for any reason. Exclusions will be described in the following paragraphs.

Subsection 2:

Patients For Whom All Potential Events Occurred Before Randomization

This section should account for the patients identified in Appendix B for whom the event or events occurred before randomization. For example, this section might simply state that of the 90 patients identified in Appendix B, for 7 of these patients all of their events occurred prior to randomization, leaving 83 patients with potential events. These 7 patients with prerandomization events should be listed in a table in **Appendix C** in the following format:

Study Number	Patient Number	Treatment Assignment

Do not include in this listing any patients for whom 1 or more events occurred after randomization, even if 1 or more events also occurred before randomization, i.e., all events must have occurred before randomization.

There is no need to provide **ANY** additional information for these patients.

Subsection 3:

Patients For Whom All Potential Events Occurred More Than 30 Days Beyond the Last Dose of Randomized Treatment

This section should account for the patients identified among the remaining 83 patients with potential events for whom the event or events occurred more than 30 days beyond the last dose of randomized treatment. For example, this section might simply state that of the remaining 83 patients with potential events, for 5 of these patients, their event or events all occurred more than 30 days beyond the last dose of randomized treatment, leaving 78 with potential events. These 5 patients with post-30-day events should be listed in a table in **Appendix D** in the following format:

Study Number Patient Number Treatment Assignment

Do not include in this listing any patients for whom 1 or more events occurred either during the randomized double-blind phase or within 30 days of the last dose of randomized treatment, even if 1 or more events also occurred more than 30 days beyond the last dose of randomized treatment, i.e., all events must have occurred more than 30 days beyond the last dose of randomized treatment.

If there are any patients for whom any events occur both prerandomization and after the +30 post-last dose period (and none in between), include those patients here as well.

There is no need to provide **ANY** additional information for these patients.

Subsection 4:

Patients For Whom All the Potential Events Identified Represented a False Positive

This section should account for the patients identified among the remaining 78 patients with potential events for whom the event or events all could be characterized as "false positives" in the sense that a preferred or verbatim term was selected because one of the text strings occurred within that term and the term has no relevance to suicidality, e.g., "gas" in "gastrointestinal." For example, this section might simply state that of the remaining 78 patients with potential events, for 50 of these patients, their event or events all could be characterized as false positives in the above sense, leaving 28 patients with potential events. These 50 patients for whom all of their events are false positives should be listed in a table in **Appendix E** in the following format:

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

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

Do not include in this listing any patients who had other events that could not be characterized as false positives, e.g., a patient with 1 or more events that are false positives should not be included if he/she also has events that cannot be characterized in this way.

Importantly, **DO NOT** include in this list patients with events coded as either **accidental injury** or **accidental overdose**. These will be addressed separately.

There is no need to provide **ANY** additional information for patients in this table in Appendix E, unless our outside experts decide they need more information based on the nature of the false positive.

Subsection 5:

Patients With Events Requiring Additional Information

This section should account for the remaining 28 patients. Again, these are patients with 1 or more events identified by the text string searches for whom the event occurred during either the double-blind phase of the initial randomized phase or within 30 days of the last randomized dose. For the latter category, i.e., within 30 days of the last randomized dose, all such patients should be included here, regardless of what if any treatment they received during this 30 day phase. Such patients might have been given the active drug that was the focus of this particular development program, another active drug, placebo, or no drug. All such patients should be included here. [Note: We acknowledge the difficulty in analyzing data for such a heterogeneous group, however, we will address this issue during our analyses. For now, we want all such patients included, despite the advice in our 7-22-03 letter to exclude patients in "extension phases."]

Listings and Narrative information should be provided for these patients as follows:

Appendix F: Narratives for Accidental Injury or Accidental Overdose

For patients who have 1 or more events coded as either accidental injury or accidental overdose, and who have no other events that are suggestive of intentional self injury, suicidal ideation, or suicide attempt, a brief narrative should be provided in this section. For example, you might say that, of the remaining 28 patients, 11 had only events that were coded as either accidental injury or accidental overdose, leaving 17 patients with events suggestive of self-harm or suicidality. These would be patients with injuries for which there was absolutely no suggestion of intent of self-harm, or similarly with dosing of more than prescribed medication where there was every reason to believe that this was accidental. Nevertheless, we will want a very brief narrative for all such patients, including any information from the CRF that appears to have any relevance to further assessing that event. These need not be the more detailed narratives that will follow in Appendix G.

The collection of narratives should be preceded by a table in the following format:

Study Number Patient Number Treatment Assignment

Appendix G: Narratives for Patients with Events Suggestive of Intentional Self Injury, Suicidal Ideation, or Suicide Attempt

This appendix should include more complete narratives for the patients (17 for example) who have events that are suggestive of intentional self injury, suicidal ideation, or suicide attempt.

There should be no further exclusions from this group. In particular, do NOT exclude events because you feel they are not treatment-emergent. We may in fact agree with you, upon review, however, we want our expert reviewers to have an opportunity to review narratives for these cases as well.

The collection of narratives should be preceded by a table in the following format:

Study Number Patient Number Treatment Assignment

[Note: You have obviously already created narratives for all such patients and it is simply a matter of aggregating them in this manner.]

Section 4: Narratives for Serious Adverse Events (SAEs)

The other search strategy we asked you to employ was to blindly review your narratives for SAEs, and include any additional patients identified in this search in your analysis.

Please include in this section simply an indication of how many total patients there were having one or more SAEs that occurred either in the randomized double-blind phase of the controlled trials or within the +30 days beyond the last randomized dose period described earlier (i.e., this is a collection of ALL SAEs during these periods, not limited to the ones you have selected blindly as representing suicidality). This section should refer to **Appendix H** where narratives for all such patients having SAEs will be included, i.e., one narrative for each such patient, even if they had more than 1 SAE during the specified period of time.

Do NOT include patients for whom the SAEs occurred only outside of these specified time periods. However, the narratives for the patients with SAEs within the specified time periods should include any other SAEs that occurred outside the specified time

periods as well (but they should be identified in the narratives as either "prerandomization" or "post-30 days").

The collection of narratives should be preceded by a table in the following format:

Study Number	Patient Number	Treatment Assignment

There may be some overlap in patients for whom these narratives may have already been provided in Appendices F or G. There is no need to duplicate those narratives here. Rather, simply list those patients categorized as having 1 or more SAEs for whom the narrative is provided in an earlier appendix.

Note: I realize this is an additional burden beyond what you have already provided, however, having the information in this format will greatly facilitate our efforts to get this case material to our outside experts in an efficient manner. I expect to be calling each of you as follow-up to this request, and I will simultaneously be getting feedback both internally and from our outside experts on this proposed format, so that we can be efficient in making any changes that are needed. Hopefully, this proposed format is acceptable as it stands, or will need little modification, so that we can move forward with this effort. Again, I want to emphasize how important it is for us to get this information in this format and in a timely manner. My expectation is that most of the work in classifying patients in this way and writing narratives has already been done, and the major effort is in putting together this document in this preferred form. This is a key issue to try to get resolved as quickly as possible, and I appreciate your cooperation in helping us get this done.

As I indicated, I will be happy to further discuss this requested report with you and I expect to be calling to talk to your representatives either early this week, or early next week.

cc:
HFD-120/TLaughren

DOC: Updated Request 01.doc

DATE: December 9, 2003
FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120
SUBJECT: Updated request for information on instances of suicidality in controlled trials involving pediatric patients
TO: Sponsors of antidepressant drug products

This is a follow-up request to the request dated 11-24-03.

One of the sponsors identified a flaw in the 11-24-03 document. The problem occurs in Subsection 5 under Section 3, i.e., in Appendix F. The 11-24-03 document suggests that we want included in this appendix only those patients identified by the search algorithms and coded under the preferred terms of either "accidental injury" or "accidental overdose" and for whom there are no events suggestive of intentional self injury, suicidal ideation, or suicide attempt. In fact, we intended that this appendix would include any such patients coded under the preferred terms of either "accidental injury" or "accidental overdose," regardless of whether or not they had been picked up by the algorithms. Of course, any patients coded under the preferred term "accidental overdose" would have been selected by the algorithm. However, it is possible that some patients coded under the preferred term "accidental injury" would not have been selected by the algorithms. We would also like brief narratives for all such patients included in this appendix. In the text of this section, they should be referred to as additional patients coded as "accidental injury," since they will not be represented in the overall count of patients/events identified by the algorithms.

If your have already completed your response to the 11-24-03 request, narratives for any additional patients meeting this criterion should be submitted as an amendment to your response. If your response is not yet completed, these narratives can be included in an integrated response to both requests.

cc:
HFD-120/TLaughren

DOC: Updated Request 02.doc

9 APPENDIX II: Requests for patient level data regarding suicide-related events

An example of DNDP data request letters that was sent to various sponsors 10/3/03

NDAs 20-822, 21-046, 21-323, & 21-365

Forest Laboratories, Inc.
Attention: Andrew Friedman, R.Ph.
Manager, Regulatory Affairs
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, NJ 07311

Dear Mr. Friedman:

Please refer to your new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Celexa (citalopram hydrobromide) 10 mg, 20 mg and 40 mg Tablets (20-822), Celexa (citalopram hydrobromide) 10 mg/5 ml Oral Solution (21-046), Lexapro (escitalopram oxalate) 5 mg, 10 mg, and 15 mg Tablets, and Lexapro (escitalopram oxalate) 5 mg/5 ml Oral Solution.

Reference is also made to an Agency letter dated July 22, 2003, requesting data regarding pediatric suicidality.

In order to better understand what covariates might be modifying the relationship between pediatric exposure to psychotropic drugs and suicide-related events, we request that you submit the following information from your development program:

- a brief summary describing the design of each randomized controlled trial (RCT) that was included in your response to our data request of July 2003; this summary should include, but is not limited to, the following characteristics:
  - the title of the trial
  - the trial number
  - diagnosis(es) studied,
  - the calendar year the study initiated,
  - the type of control used (i.e., placebo, active, or both),
  - the duration of the trial,
  - whether there was a run-in period, and if so, what did it consist of
  - whether family history of the disorder being studied (e.g., MDD, OCD, etc.) was an exclusion criterion for study entry

- a description of the primary scale used to rate severity of depression,

· datasets derived from these randomized controlled trials containing the variables[19] described in detail below.

Please use only generic drug names and include a glossary with any abbreviations used.

PATIENT FILE: this file should contain the following variables for each patient participating in a randomized controlled trial, leading to one row per patient.

Variable name	Length	Type	Description	Coding notes
TRIAL	NS	Character	Trial ID	No missing values are allowed in this variable.
CTPID	NS	Character	Patient ID within each trial.	No missing values are allowed in this variable
UNIQUEID	NS	Character	A unique ID for every patient	It should incorporate both the trial ID and the patient ID within each trial. No missing values are allowed in this variable.
DIAG	NS	Character	Condition for which patient was being treated	Should be one of the diagnoses listed for the corresponding trial in the "Controlled Trial File". No missing values are allowed in this variable.
DIAGCAT	3	Numeric	Diagnosis category	1= major depressive disorder 2= obsessive compulsive disorder 3= social anxiety disorder 4= other anxiety disorder
AGE	3	Numeric	Age of patient in years	. = Missing.
AGECAT	3	Numeric	Categories of age	1= AGE < 12

[19] Please submit the datasets as SAS transport files created with an x-port engine (.xpt).

Variable name	Length	Type	Description	Coding notes
				2= AGE >= 12 . = Missing
GENDER	3	Numeric	Patient gender	1= Female 2= Male . = Missing
RACE	3	Numeric	Race	1= White Caucasian 2= African-American 3= Hispanic 4= Asian 5= Other . = Missing
BMI	3	Numeric	Body mass index	Calculated as weight in kg/(height in meters)^2 . = Missing
SET	3	Numeric	Setting at randomization	1= Inpatient 2= Outpatient . = Missing
LOC	3	Numeric	Location of trial center	1= North America 2= Non-north America . = Missing
HXSUIATT	3	Numeric	The subject had a history of suicide attempt prior to entering the RCT	0=No 1=Yes . = Missing
HXSUIID	3	Numeric	The subject had a history of suicidal ideation prior to entering the RCT	0=No 1=Yes . = Missing
HXPSHOSP	3	Numeric	The subject had a history of psychiatric hospitalization prior to entering the RCT	0=No 1=Yes . = Missing
HXSUBAB	3	Numeric	The subject had a history of substance abuse prior to entering the RCT	0=No 1=Yes . = Missing
HXHOST	3	Numeric	The subject had a history of hostility or aggressive behavior prior to entering the RCT	0=No 1=Yes . = Missing
HXIRRAG	3	Numeric	The subject had a history of irritability or agitation prior to entering the RCT	0=No 1=Yes . = Missing
RANTX	NS	Character	Name of post-randomization treatment assignment	”Your drug name”, “Placebo”, or the name of the active control drug

Variable name	Length	Type	Description	Coding notes
				No missing values are allowed in this variable.
RANTXCAT	3	Numeric	Category of the drug	1=SSRI 2=non-SSRI 3=placebo
DOSE	3	Numeric	Dose of the post-randomization investigational treatment; If a flexible dose scheme was used, then report the modal dose. If there were multiple modal doses, select the maximal modal dose	0=Placebo . = Missing
DFRAN	10	Date	Date of first dose of randomized treatment	Use date format: MM /DD/YYYY, e.g. 3/4/2000 . = Missing
DLRAN	10	Date	Date of last dose of randomized treatment	Use date format: MM /DD/YYYY e.g. 6/14/2000 . = Missing
EXPOSURE	3	Numeric	Number of days of exposure to randomized treatment	Should represent the difference between "DFRAN" and "DLRAN". [DLRAN-DFRAN]+1 . = Missing
HXNONCOM	3	Numeric	There is some evidence in the subject's medical record or case report form that the subject had a history of erratic compliance with the study medication during the RCT	0=No 1=Yes
RCTYEARS	12	Numeric	Exposure in years	=Exposure/365.25 . = Missing
SEVSCALE[20]	3	Numeric	Primary scale used to rate baseline severity of	1=HAM-D 2=CDRS-R

[20] HAM-D – Hamilton Depression Scale; CDRS =Children's Depression Rating Scale-Revised ; K-SADS-L = 9 item depression subscale of the Schedule for Affective Disorders and Schizophrenia for School Age Children- Lifetime version ; Kutcher = Kutcher Adolescent Depression Rating Scale

Variable name	Length	Type	Description	Coding notes
			depression	3=K-SADS-L 4=Kutcher 5=Other 6= NA (if not measured)
BASESEV	3	Numeric	Baseline severity score	. = Missing
HAMD17	3	Numeric	Score on HAM-D 17 if performed (or adapted from HAM-D 21)	. = Missing
SCALESUI	3	Numeric	The score of the suicide item for the primary scale used to rate baseline severity of depression	. = Missing
DURATION [Add DURACAT variable if duration of illness was recorded as a categorical variable]	3	Numeric	Duration of illness prior to randomization in months	. = Missing
SUIEVENT	3	Numeric	A suicide-related event as defined in July 2003 submission occurred during the RCT	0= No 1=Yes
SUIATT	3	Numeric	A suicide attempt as defined in July 2003 submission occurred during the RCT [Suicide attempt is a subset of suicide-related event]	0=No 1=Yes
EVENTDC	3	Numeric	The first suicide-related event occurred following discontinuation	0=No 1=Yes
DAYEVENT	3	Numeric	The number of days to the first suicide-related event counting from the day of the first dose. Counting from the first day of drug should occur even if the event occurred after the patient discontinued the drug.	. = Missing or patient did not have an event
TEAEAG	3	Numeric	A treatment-emergent adverse event coded to	0=No 1=Yes

Variable name	Length	Type	Description	Coding notes
			the preferred term agitation occurred during the RCT	
TEAEHOST	3	Numeric	A treatment-emergent adverse event coded to the preferred term hostility occurred during the RCT	0=No 1=Yes
SOURCE	4	Character	First 4 letters of your drug name	

NS=not specified.

We appreciate your participation in this project so we can continue our evaluation of suicide-related events associated with psychotropic drug use in children. Additionally, and as you are aware, we intend to take this issue to the Psychopharmacological Drugs Advisory Committee (PDAC) in February 2004 (specific date to be announced). It would be very beneficial to have these data available to present to the PDAC. Therefore, we are requesting that you respond within one month from the date of this letter.

If you have any questions, call Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

10 APPENDIX III: Requests for patient level data regarding suicidality items on depression rating scales

DNDP request send 3/17/04

In order to perform additional analyses investigating the relationship between pediatric exposure to psychotropic drugs and suicide-related events, we would appreciate your submitting the following variables in a file along with previously submitted patient identifiers "TRIAL","CTPID", and "UNIQUEID" as outlined in the next table:

Variable name	Type	Description	Coding notes
TRIAL	Character	Trial ID	No missing values are allowed in this variable
CTPID	Character	Patient ID within each trial	No missing values are allowed in this variable
UNIQUEID	Character	A unique ID for every patient. Please make sure to use the **same** unique ID that was used in your previous submissions for this project	It should incorporate both the trial ID and the patient ID within each trial. No missing values are allowed in this variable
DISCONT	Numeric	The patient discontinued before the end of the controlled portion of the trial	0=No 1=Yes No missing values are allowed in this variable
THRESHSC[21]	Numeric	Scale used to rate suicidality	1=HAM-D 2=CDRS-R 3=K-SADS 4=Kutcher 5=Other 6= NA (if not measured) No missing values are allowed in this variable
SUITHRESH	Numeric	The patient reached the threshold for "emergence of suicidality" at anytime during the controlled portion of the trial based on the	0=No 1=Yes . = Missing

[21] HAM-D – Hamilton Depression Scale; CDRS =Children's Depression Rating Scale-Revised ; Depression subscale of the Schedule for Affective Disorders and Schizophrenia for School Age Children; Kutcher = Kutcher Adolescent Depression Rating Scale

		definition provided **below this table**	
THRETIME	Numeric	Number of days to the first occurrence of reaching the threshold described under "SUITHRESH". The time should count from the date of the first dose of randomized therapy For the remainder of the patients (those who did not reach the threshold), the variable should contain number of days until censored (either by discontinuation or by end of trial)	No missing values are allowed in this variable
VISITTH	Numeric	Contains the visit number when the patient developed the first occurrence of reaching the threshold described under "SUITHRESH"	99=not applicable (use for those patients who did not reach the threshold) No missing values are allowed in this variable for patients who developed the event described under "SUITHRESH"
SUIWORSE	Numeric	The patient reached the threshold for "worsening of suicidality" at any time during the controlled portion of the trial based on an increase of **two points or more** on the suicidality item regardless of subsequent change	0=No 1=Yes . = Missing
WORSTIME	Numeric	Number of days to the first occurrence of reaching the threshold described under "SUIWORSE". The time should count from the date of the first dose of randomized therapy For the remainder of the patients (those who did not	No missing values are allowed in this variable

		reach the threshold), the variable should contain number of days until censored (either by discontinuation or by end of trial)	
VISITW	Numeric	Contains the visit number when the patient developed the first occurrence of reaching the threshold described under "SUIWORSE"	99=not applicable (use for those patients who did not reach the threshold) No missing values are allowed in this variable for patients who developed the event described under "SUIWORSE"
HXINSOM	Numeric	The patient had a history of insomnia prior to entering the RCT as defined by: CDRS-R item 4 >=4, HAMD items 4, 5, or 6=2, MADRS item 4 >=4, or relevant K-SADS item	0=No 1=Yes 2= History of insomnia prior to entering the RCT was an exclusion criterion . = Missing
HXIRRAGB	Numeric	The subject had a history of irritability or agitation prior to entering the RCT as defined by: CDRS-R item 8 >=3, HAMD item 9 >=3, or relevant K-SADS item	0=No 1=Yes . = Missing
HXSUIATB	Numeric	The subject had a history of suicide attempt prior to entering the RCT as defined by: CDRS-R item 13 =7, HAMD item 3=4, or relevant K-SADS screen interview "suicidal acts" item	0=No 1=Yes 2= History of suicide attempt prior to entering the RCT was an exclusion criterion . = Missing
HXSUIIDB	Numeric	The subject had a history of suicidal ideation prior to entering the RCT as defined by: CDRS-R item 13 >=3 and < 7, HAMD item 3=3, MADRS item 10 >=3, or relevant K-SADS screen interview "suicidal ideation"	0=No 1=Yes 2= history of suicidal ideation prior to entering the RCT was an exclusion criterion . = Missing

		item	

Definition of patient reaching the threshold of "emergence of suicidality" under the variable named "SUITHRESH" depends on the scale used to rate suicidality:

HAM-D
The patient is assigned a value of "1" if there is a change in rating of "suicide" item (item number 3) from 0 at baseline to 1 or from 1 at baseline to 2 or more, at any time during the controlled phase of the trial. The variable should reflect the first time such a change occurs regardless of subsequent changes.

CDRS-R
The patient is assigned a value of "1" if there is a change in rating of "suicidal ideation" item (item number 13) from 1 or 2 at baseline to 3 or more at any time during the controlled phase of the trial. The variable should reflect the first time such a change occurs regardless of subsequent changes.

MADRS
The patient is assigned a value of "1" if there is a change in rating of "suicidal thoughts" item (item number 10) from 0 or 1 at baseline to 2 or more at any time during the controlled phase of the trial. The variable should reflect the first time such a change occurs regardless of subsequent changes.

Clarifications for the DNDP request sent on 4/1/04

In order to respond to all the feedback that we have received from sponsors, we have the following clarifications/modifications to our previous data request dated March 17, 2004.

1- There seem to have been some confusion about what is meant by the term "coding dictionaries". DNDP intends for the sponsor to provide a list of all the investigator verbatim terms from the trials included in the data request, along with the preferred term to which the verbatim term was mapped. Preferably, these terms would be submitted as a SAS transport file (.xpt); however, if they are already in PDF, that format is acceptable.

2- For clarification, the DNDP data request is intended to cover all subjects in controlled trials submitted in response to our data request letter dated 10/03/03 and not just the subjects identified as having potential events.

3- If more than one scale with a suicide item is used in a particular study (e.g., the CDRS-R and MADRS), only the primary scale should be used for all variables.

4- Some studies had more than one pre-treatment assessment, for example at – 2 weeks, -1 week, and at randomization. For consistency, the value of the variable recorded at the randomization visit should be considered the baseline.

5- For the variables "SUITHRESH" and "SUIWORSE", the value of these variables should be assigned as missing if the patient is missing either the baseline score or all post-baseline scores.

6- In defining "SUITHRESH", some sponsors suggested that we consider the value as "missing" if the patient has a baseline score >1 for HAM-D, >2 for CDRS-R, and >1 for MADRS. Their argument is that it is impossible for these patients to be included in the numerator and thus should not be included in the denominator for any analyses. DNDP recognizes this issue, but for the sake of simplifying the data request we will not modify our request. Although including those patients in the denominator might slightly affect the absolute estimate for incidence, it is not expected to affect the ratio between the estimated incidence in the drug and the placebo groups because this type of patient would occur at random in both groups. In addition, many studies excluded those patients at baseline. Furthermore, those patients can still get worse during the study and flagging them as missing will unnecessarily complicate analyzing the data.

7- For the definition of the variable "SUITHRESH" using the HAM-D, the FDA intended the patient to be assigned a value of "1" if there is a change in rating of item 3 from 0 at baseline to 1 **or more**, or from 1 at baseline to 2 or more, at any time during the controlled phase of the trial.

8- For the variable "SUIWORSE", DNDP recognizes that a change of two points on HAM-D item 3 is different than a change of two points on CDRS-R item 13. Initially DNDP did not ask sponsors to address differences in the scaling across the various rating scales to simplify the data request and because the main focus of the comparison is within trials between the drug and the placebo groups. However, DNDP has re-evaluated this issue and requests the following change in the definition of patients with a value of "1" in the variable "SUIWORSE" as follows:

   a. Patient reached the threshold for "worsening of suicidality" at any time during the controlled portion of the trial based on an increase of **one point or more** on the HAM-D item 3 or **two points or more** on the suicidality item 13 in CDRS-R or on the suicidality item 10 in MADRS, regardless of subsequent change. DNDP is aware that this definition will not capture some patients like those who moved from a score of 6 to 7 on CDRS or a score 5 to 6 on MADRS. However, it is extremely unlikely that those patients are in the data because they would have been excluded at baseline in most studies.
   b. DNDP would like to further clarify that the definition of this variable is intended to capture only patients that exhibit the listed changes in their suicidality items in relation to their respective **baseline values**.

9- In some studies the suicidality assessment was done only at baseline and at endpoint when the patient completed the study. As a result, all values requested for the variables "SUITHRESH", "THRETIME", "SUIWORSE", and

"WORSTIME" will be based on values collected at endpoint. In this situation the variables "THRETIME", and "WORSTIME" should be set as missing.

10- For variables "THRETIME" and "WORSTIME", the definition implies that if the occurrence of the respective event is on day number 4 (with 1st dose on day 1 as usual), the value of the variable should be 4.

11- Some studies had more than one pre-treatment assessment. For consistency, the value of the history variables, "HXINSOM", "HXIRRAGB", "HXSUIATB", and "HXSUIIDB", should be assigned to "1" if the history was positive at baseline, which is defined as the visit of randomization (as stated above).

12- For variable "HXINSOM", the meaning of value=2 was meant to reflect the same meaning for the other history variables. Specifically, for this variable it would be "history of insomnia prior to entering the RCT was an exclusion criterion".

13- DNDP has reconsidered the value of the visit number variables "VISITH" and "VISITW". Please delete these variables from the data request.

P.S.

On 4/15/04, DNDP asked sponsors were to rename the variable "SUITHRESH" to "SUITHRES" to conform to formatting requirements.

Individual Responses

To Lilly

Regarding the comment number "7" in you response, you stated "We are aware of at least one method, the Mantel-Haenszel incidence difference (or risk difference), in which trial is the unit of analysis but trials with no suicidality in both arms can be included." Please provide the references and the SAS code for the cited method.

To GSK

Please provide the corresponding anchors for all of the scores of the KSADS-L items number 84, 86, 88, and 90 that you intend to use.

To Pfizer

Your inquiry states "Should R-0498 be excluded from this request since it did not contain a depression scale which measured suicide (only HAM-D measured at day 1 of washout and baseline used as a diagnostic measure for depression)?" The FDA requests that you use the HAM-D, whenever possible, to get information about the history variables ("HXINSOM", "HXIRRAGB", "HXSUIATB", and "HXSUIIDB") in the listed study.

To Forest

Please provide the corresponding anchors for all of the scores of the KSADS items that you intend to use for the following variables: “SUITHRESH”, “HXINSOM”, “HXIRRAGB”, “HXSUIATB”, and “HXSUIIDB”. In your list of variables you omitted the variable “SUIWORSE”. Please provide the source for this variable from the version of KSADS that you will use.

11 APPENDIX IV: Depression rating scales.

11.1 *Children's Depression Rating Scale-Revised (CDRS-R*)

The CDRS-R assesses 17 symptom areas including those that serve as the criteria in the DSM-IV for the diagnosis of depressive disorders. The first 14 items of the scale are rated on the basis of the child's verbal responses to interview questions. The remaining 3 symptom areas (Depressed Facial Affect, Listless Speech and Hypoactivity) of the CDRS-R are rated by the clinician on the basis of the child's non-verbal behavior for signs of depression. Each symptom is then graded on a 5 or 7 point scale.

Question Number	Question	Number of Responses	Response Range
Rated by patient, parent, and/or other caretaker:			
1	Impaired Schoolwork	7	1-7
2	Difficulty Having Fun	7	1-7
3	Social Withdrawal	7	1-7
4	Sleep Disturbance	5	1-5
5	Appetite Disturbance	5	1-5
6	Excessive Fatigue	7	1-7
7	Physical Complaints	7	1-7
8	Irritability	7	1-7
9	Excessive Guilt	7	1-7
10	Low Self-Esteem	7	1-7
11	Depressed Feelings	7	1-7
12	Morbid Ideation	7	1-7
13	Suicidal Ideation	7	1-7
14	Excessive Weeping	7	1-7
Rated by investigator:			
15	Depressed Facial Affect	7	1-7
16	Listless Speech	5	1-5
17	Hypoactivity	7	1-7

For items 1-14, the highest rating from child, parent or other caretaker, is taken as the item score that best describes the child. The total score is the sum of item scores. The CDRS-R score range is 17-113. A score of 40 or higher is consistent with a diagnosis of major depressive disorder.

11.2 Schedule for Affective Disorders and Schizophrenia for School Aged Children, Present Episode Version (K - SADS-P)

The depression module of the KSADS-P rating scale is a validated schedule in assessing present depression in children and adolescent patients. It is a semi-structured diagnostic interview that is designed to obtain severity ratings of depression symptomatology during the past 7 days, in children and adolescents. It has 9 ordinally scaled items, 4 of which

consist of 2-3 sub-items. Each of the items or sub-items is rated from 0 to 4, 6, or 7 (depending on the item), with higher numbers corresponding to greater severity. Items and score ranges are below:

1. a) depressed mood (1-7)
   b) irritability (1-7)
   c) quality of dysphoria (1-4)
2. excessive or inappropriate guilt (1-6)
3. loss of interest, anhedonia and boredom (1-6)
4. fatigue, lack of energy, and tiredness (1-6)
5. difficulty concentrating, slowed thinking (1-6)
6. a) psychomotor agitation (1-6)
   b) psychomotor retardation (1-6)
7. a) insomnia (1-6)
   b) hypersomnia (1-6)
8. a) anorexia (1-6)
   b) increased appetite (1-6)
9. suicidal ideation (1-7)

The highest sub-item score is used as the item score. The total score is the sum of item scores. The KSADS-P Depression Module score range is 9-56.

11.3 Hamilton Psychiatric Rating Scale for Depression (HAM-D)

The Hamilton Psychiatric Rating Scale for Depression (HAM-D) was the protocol-defined primary efficacy instrument used in some studies. Although several variations of the scale exist, the version requested consists of 17 questions with multiple choice responses, each of which is numerically scored on a scale of 0 to 2 or 0 to 4.

Question No.	Question	Number of Responses	Response Range
1	Depressed Mood	5	0-4
2	Feelings of Guilt	5	0-4
3	Suicide	5	0-4
4	Insomnia Early	3	0-2
5	Insomnia Middle	3	0-2
6	Insomnia Late	3	0-2
7	Work and Activities	5	0-4
8	Retardation	5	0-4
9	Agitation	5	0-4
10	Anxiety Psychic	5	0-4
11	Anxiety Somatic	5	0-4
12	Somatic Symptoms Gastrointestinal	3	0-2
13	Somatic Symptoms General	3	0-2
14	Genital Symptoms	3	0-2
15	Hypochondriasis	5	0-4
16	Loss of Weight	3	0-2

Question No.	Question	Number of Responses	Response Range
17	Insight	3	0-2

11.4 Montgomery and Asberg Depression Rating Scale (MADRS)

The rating scale consists of 10 items with multiple choice responses, each of which is numerically scored on a scale of 0 to 6.

Question Number	Question	Number of Responses	Response Range
1	Apparent Sadness	7	0-6
2	Reported Sadness	7	0-6
3	Inner Tension	7	0-6
4	Reduced Sleep	7	0-6
5	Reduced Appetite	7	0-6
6	Concentration Difficulties	7	0-6
7	Lassitude	7	0-6
8	Inability to Feel	7	0-6
9	Pessimistic Thoughts	7	0-6
10	Suicidal Thoughts	7	0-6

12 APPENDIX V: Description of pediatric clinical trials under consideration

12.1 Description of all controlled clinical trials in nine drug development programs.

Drug	Trial number	Indication	Variables						
			Title	Year initiated	Control used	Duration	Placebo run in period	Family history as an exclusion criterion	Scale of depression
Selective serotonin re-uptake inhibitors (SSRI) group									
Prozac	HCCJ	MDD	Fluoxetine versus Placebo in Adolescent Depressed Patients	1984	Placebo	6 weeks	One week, single blind	No	HAM-D
	X065	MDD	Fluoxetine versus Placebo in the Acute Treatment of Major Depressive Disorder in Children and Adolescents	1991	Placebo	8 weeks	Two weeks	If history of Bipolar I disorder in >=1 first-degree relatives	CDRS-R
	HCJE	MDD	Fluoxetine versus Placebo in Childhood/Adolescent Depression	1998	Placebo	19 weeks++	One week	If history of Bipolar I disorder in >=1 first-degree relatives	CDRS-R
	HCJW	OCD	Fluoxetine vs. Placebo in the Treatment of Children and Adolescents with Obsessive Compulsive Disorder	1999	Placebo	13 weeks	One week	If history of Bipolar I disorder in >=1 first-degree relatives	CDRS-R
Zoloft	90CE21-0498	OCD	Double-Blind Comparison of Sertraline and Placebo in Children and Adolescents With Obsessive Compulsive Disorder	1994	Placebo	12 weeks	One week, single blind	No	HAM-D
	A0501001	MDD	A Multicenter 10-Week Randomized Double-blind Placebo-controlled Flexible Dose Outpatient Study of Sertraline in Children and Adolescents With Major Depressive Disorder	2001	Placebo	10 weeks	Two weeks	No	CDRS
	A0501017	MDD	A Multicenter 10-Week Randomized Double-blind Placebo-controlled Flexible Dose Outpatient Study of Sertraline in Children	2001	Placebo	10 weeks	Two weeks	No	CDRS

Drug	Trial number	Indication	Variables						
			Title	Year initiated	Control used	Duration	Placebo run in period	Family history as an exclusion criterion	Scale of depression
			and Adolescents With Major Depressive Disorder						
Paxil	329	MDD	A Multicenter, Double-blind, Placebo Controlled Study of Paroxetine and Imipramine in Adolescents with Unipolar Major Depression.	1994	Placebo and Imipramine	8 weeks+	No	No	HAM-D/ (K-SADS-L at screen.)
	377	MDD	A Double-blind, Multicenter Placebo Controlled Study of Paroxetine in Adolescents with Unipolar Major Depression	1995	Placebo	12 weeks	Two week, single blind	No	MADRS/ (K-SADS-L at screen.)
	701	MDD	A Randomized, Multicenter, 8-Week, Double-blind, Placebo-Controlled Flexible-Dose Study to Evaluate the Efficacy and Safety of Paroxetine in Children and Adolescents with Major Depressive Disorder	2000	Placebo	8 weeks	No	No	CDRS-R/ (K-SADS-PL at screen.)
	704	OCD	A Randomized, Multicenter, 10-Week, Double-Blind, Placebo-Controlled, Flexible-Dose Study to Evaluate the Efficacy and Safety of Paroxetine in Children and Adolescents with Obsessive-Compulsive Disorder (OCD)	2000	Placebo	10 weeks	No	No	NA
	453*	OCD	A 32 Week, Two Phase, Multicenter Study to Investigate the Safety and Effectiveness of Paroxetine (10-60 mg/day) in the Treatment of Children and Adolescent Outpatients with Obsessive Compulsive Disorder	1997	Placebo	16 weeks	No	No	HAM-D
	676	SAD	A 16 Week Double-Blind, Placebo Controlled Study to Investigate the Efficacy and Tolerability of Paroxetine in the Treatment of Children and Adolescents with Social Anxiety Disorder/Social Phobia (29060/676)	1999	Placebo	16 weeks	No	No	CDRS-R
Luvox	RH_114_02_01	OCD	Fluvoxamine in the Treatment of OCD: A Multicenter double-blind placebo-controlled study in outpatient children and adolescents	1991	Placebo	10 weeks	Yes	No	CDRS-R
Celexa	CIT-MD-18	MDD	A randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of citalopram in children and adolescents with depression (MDD).	2000	Placebo	8 weeks	1 week, single blind	No	CDRS-R
	94404	MDD	A double-blind study comparing citalopram tablets (Lu 10-171, 10-40 mg per day) and placebo in the treatment of major depression in Adolescents (MDD).	1996	Placebo	12 weeks	No	No	K-SADS-P
Atypical antidepressants group									
Wellbutrin#	75	ADHD	A double-blind comparison of efficacy and	1983	Placebo	4 weeks,	1 week,	No	NA

Drug	Trial number	Indication	Variables						
			Title	Year initiated	Control used	Duration	Placebo run in period	Family history as an exclusion criterion	Scale of depression
			safety of bupropion versus placebo in children with attention deficit disorder and/or conduct disorder			1wk single blind post-tx	single blind		
Effexor@	382	MDD	Double-Blind, Placebo-Controlled Study Of Venlafaxine Er In Children And Adolescents With Major Depression	1997	Placebo	8 weeks	2 weeks, single blind	No	CDRS-R/ K-SADS-PL at screen.)
	394	MDD	Double-Blind, Placebo-Controlled Study Of Venlafaxine Er In Children And Adolescents With Major Depressive Disorder	2000	Placebo	8 weeks	1 week, single blind	No	CDRS-R/ K-SADS-PL at screen.)
	396	GAD	Double-Blind, Placebo-Controlled Study Of Venlafaxine Er In Children And Adolescents With Generalized Anxiety Disorder	2000	Placebo	8 weeks	1 week, single blind	No	CDRS-R
	397	GAD	Double-Blind, Placebo-Controlled Study Of Venlafaxine Er In Children And Adolescents With Generalized Anxiety Disorder	2000	Placebo	8 weeks	1 week, single blind	No	CDRS-R
Serzone	CN104-141	MDD	A Multicenter, Double-Blind, Placebo-Controlled Trial of Nefazodone in Depressed Adolescents	1998	Placebo	8 weeks	2-4 Wks baseline phase	No	CDRS-R
	CN104-187	MDD	A Multicenter, Double-Blind, Placebo-Controlled Trial of Two Dose Ranges of Nefazodone in the Treatment of Children and Adolescents With a Major Depressive Episode	2000	Placebo	8 weeks	2-4 Wks baseline phase	No	CDRS-R
Remeron	003-045	MDD	A multi-center, randomized, double-blind, placebo-controlled, efficacy and safety study of Remeron in outpatient children and adolescents with major depressive disorder.	1999	Placebo	8 weeks	No	No	CDRS-R/ (K-SADS-PL & HAM-D at screen.)

++ Includes sub-acute phase (weeks 10-19), during which poorly responding patients could receive a higher dose of double-blind study medication

+ Study 329 also included a continuation phase in which responders at Week 8 had the option to continue to receive blinded study medication for an additional six months→ from data on exposure the maximum is 79 days.

Drug	Trial number	Indication	Variables						
			Title	Year initiated	Control used	Duration	Placebo run in period	Family history as an exclusion criterion	Scale of depression

* Study 453 included two phases, an open-label phase (Phase I) in which patients received open-label paroxetine for 16 weeks, and a 16 week double-blind, placebo-controlled phase (Phase II) in which responders were eligible to participate. This study was excluded from the analysis because the design is different from the others

Trial 41(ADHD) was excluded from further analysis because it is not a controlled trial.

@ Administered as Effexor XR in all trials; dosage based upon weight of subject, and tapered over $\leq$2 weeks following double-blind treatment. Based on the sponsor submission the data of the 2 weeks are not included when calculating the exposure.

KEY: HAM-D (Hamilton Rating Scale for Depression), MADRS (Montgomery and Asberg Depression Rating Scale), K-SADS-L (Schedule for Affective Disorders and Schizophrenia for School Age Children - Lifetime Version), K-SADS-PL (Kiddie-SADS–Present and Lifetime Version), CDRS-R (Children's Depression Rating Scale-Revised), NA (not applicable).

12.2 Sources of history and erratic compliance variables in all submissions

Drug	Trial	Indication	Variables							
			History of suicide attempt	History of suicidal ideation	History of psychiatric hospitaliz.	History of substance abuse	History of hostility or aggressive behavior	History of irritability or agitation	History of Insomnia	Erratic compliance
Selective serotonin re-uptake inhibitors (SSRI) group										
Prozac	HCCJ	MDD	HAMD	HAMD	M	Exclusion	M	HAMD	HAMD	M
	X065	MDD	CDRS	CDRS	M	Exclusion	M	CDRS	CDRS	NS
	HCJE	MDD	CDRS	CDRS	M	Baseline survey	M	CDRS	CDRS	NS
	HCJW	OCD	CDRS	CDRS	M	M	M	CDRS	CDRS	NS
Zoloft	90CE21-0498	OCD	HAMD	HAMD	M	NS	NS	HAMD	HAMD	NS
	A0501001	MDD	CDRS	CDRS	M	NS	NS	CDRS	CDRS	NS
	A0501017	MDD	CDRS	CDRS	M	NS	NS	CDRS	CDRS	NS
Paxil	329	MDD	HAMD	HAMD	NS	KSADS-L	KSADS-L	HAMD	HAMD	NS
	377	MDD	KSADS-L	MADRS	M	KSADS-L	KSADS-L	KSADS-L	KSADS-L	NS
	701	MDD	CDRS	CDRS	M	KSADS-PL	M	CDRS	CDRS	NS
	704	OCD	NS	NS	M	KSADS-PL	M	NS	NS	NS
	453	OCD	HAMD	HAMD	M	KSADS-L	M	HAMD	HAMD	NS
	676	SAD	CDRS	CDRS	M	Exclusion	M	CDRS	CDRS	NS
Luvox	RH_114_02_01	OCD	CDRS	CDRS	M	NS	M	CDRS	CDRS	NS
Celexa	CIT-MD-18	MDD	CDRS	CDRS	M	M	M	CDRS	CDRS	Post hoc, medicat. record has "forgotten", "forget", "miss"
	94404	MDD	KSADS	KSADS	NS	M	M	KSADS	KSADS	
Atypical antidepressants group										
Wellbutrin	75	ADHD	BPRSC	BPRSC	M	M	M	BPRSC	BPRSC	M
Effexor	382	MDD	CDRS	CDRS	M	M	M	CDRS	CDRS	Post hoc, missing any dose
	394	MDD	CDRS	CDRS	M	M	M	CDRS	CDRS	
	396	GAD	NS	NS	M	M	M	NS	NS	
	397	GAD	NS	NS	M	M	M	NS	NS	
Serzone	CN104-141	MDD	CDRS	CDRS	M	NS	M	CDRS	CDRS	NS
	CN104-187	MDD	CDRS	CDRS	M	NS	M	CDRS	CDRS	NS
Remeron	003-045	MDD	CDRS	CDRS	CPD	K-SADS-L	CPD	CDRS, CPD		Protocol specific, doses missed >= 4

Key: CPD= Children's Personal Data Inventory, BPRSC=Brief Psychiatric Rating Scale for Children, NS= not specified, M=missing

12.3 Percent records missing for variables in all submissions by drug and trial.

Variable name	Description	Prozac				Zoloft			Paxil					
		HCCJ	X065	HCJE	HCJW	90CE21-0498	A0501001	A0501017	329	377	704	701	453	676
BASESEV	Baseline severity score	0	0	0	0	0	0	0	0	0	100	0	0	0.3
BMI	Body mass index	0	18	0.5	2	0.5	2	5	1	1	0.5	0	100	1
DFRAN	Date of first dose	100	100	100	100	0	0	0	0	0	0	0	0	0
DLRAN	Date of last dose	100	100	100	100	0	0	0	0	0	0	0	0	0
DOSE	Maximal modal dose	0	0	0	0	0	0	0	0	0	0	0	0	0
DURACAT	Duration of illness in categories	100	100	100	100	100	100	100	100	100	100	100	100	100
DURATION (months)	Duration of illness prior to randomizat.	100	100	0	100	16	37	56	2	1	0.5	2	0	100
DISCONT	Patient discontinued	0	0	0	0	0	0	0	0	0	0	0	0	0
EXPOSURE	Exposure in days	0	0	0	0	0	0	0	0	0	0	0	0	0
HAMD17	Score on HAM-D 17	0	100	100	100	0	100	100	0	100	100	100	0	100
HXHOST	Hx-hostility or aggressive behavior	100	100	100	100	0	0	0	1	3	100	100	100	100
HXINSOM	Hx-insomnia	20	0	0	0	6	0	0	0	0	100	0	0	1
HXIRRAGB	Hx- irritability or agitation	0	0	0	0	6	0	0	0	0	100	0	0	1
HXNONCOM	Erratic compliance	100	12	0.5	0	0	0	0	3	0	15	2	0.5	3
HXPSHOSP	Hx- psychiatric hospitalization	100	100	100	100	100	98	98	6	100	99	98	99	100
HXSUBAB	Hx- substance abuse	0	0	0	100	0	0	0	2	0	0	0	100	0
HXSUIATB	Hx-suicide attempt	0	0	0	0	6	0	0	0	1	100	0	0	1
HXSUIIDB	Hx-suicidal ideation	0	0	0	0	6	0	0	0	0	100	0	0	1
SCALESUI	Suicide item score at baseline	0	0	0	0	100	0	0	0	0.4	100	0	0	1
SUITHRES	Suicidality emerged	0	1	2	3	100	1	1	3	1	100	2	6	19
SUIWORSE	Worsening of suicidality score	0	1	2	3	100	1	1	3	1	100	2	6	19
THRESHSC	Scale used to score suicidality	0	0	0	0	0	0	0	0	0	0	0	0	0
THRETIME	Time to emergence	0	0	0	0	100	1	1	3	1	100	2	6	100
WORSTIME	Time to worsening	0	0	0	0	100	1	1	3	1	100	2	6	100

Other variables were complete in all trials (TRIAL, CTPID, UNIQUEID, DIAG, DIAGCAT, AGE, AGECAT, GENDER, RACE, SET, LOC, RANTX, RANTXCAT, SEVSCALE, SUIEVENT, SUIATT, TEAEAG, TEAEHOST, and SOURCE).

Variables in red met the criteria of being excluded from the confounding analysis (10% or more missing records).

Percent records missing for variables in all submissions, continued…

Variable name	Description	Luvox	Celexa		Wellbutrin	Effexor				Serzone		Remeron
		114	CIT-MD-18	94404	75	382	394	396	397	CN104-141	CN104-187	003-045
BASESEV	Baseline severity score	0	0	3	100	2	0	0	0	0	0	0
BMI	Body mass index	0	0	7	2	1	0	0.6	0	3	0	1
DFRAN	Date of first dose	0	2	2	1	0	0	0	0	100	100	0.4
DLRAN	Date of last dose	0	2	5	1	0	0	0	0	100	100	0.4
DOSE	Maximal modal dose	0	2	5	1	0	0	0	0	0	1	0.4
DURACAT	Duration of illness in categories	100	100	100	100	100	100	100	100	100	100	0
DURATION (months)	Duration of illness prior to randomizat .	0	0	21	100	0	0	0	1	0	0	100
DISCONT	Patient discontinued	0	0	0	0	0	0	0	0	2	2	0
EXPOSURE	Exposure in days	0	2	6	1	0	0	0	0	0	0	0.4
HAMD17	Score on HAM-D 17	100	100	100	100	2	0.5	100	100	0	100	0
HXHOST	Hx-hostility or aggressive behavior	100	100	100	100	100	100	99	98	100	100	0
HXINSOM	Hx-insomnia	0	0	4	0	2	0	1	1	2	2	0
HXIRRAGB	Hx- irritability or agitation	0	0	4	0	2	0	1	1	2	2	0
HXNONCOM	Erratic compliance	0	2	5	100	0	0	0	0	0	0	0
HXPSHOSP	Hx- psychiatric hospitalization	100	100	4	100	99	99	99	99	98	99	0
HXSUBAB	Hx- substance abuse	0	100	100	100	99	100	100	99	0	0	0.4
HXSUIATB	Hx-suicide attempt	0	0	4	0	2	0	1	1	2	2	0
HXSUIIDB	Hx-suicidal ideation	0	0	4	0	2	0	1	1	2	2	0
SCALESUI	Suicide item score at baseline	0	0	4	100	2	0	0	0	0	0	0
SUITHRES	Suicidality emerged	100	2	8	2	3	2	100	100	2	2	2
SUIWORSE	Worsening of suicidality score	100	2	8	2	3	2	100	100	2	2	2
THRESHSC	Scale used to score suicidality	0	0	0	0	0	0	0	0	2	2	0
THRETIME	Time to emergence	100	2	8	1	0	0	0	0	2	2	0
WORSTIME	Time to worsening	100	2	8	1	0	0	0	0	2	2	0

Other variables were complete in all trials (TRIAL, CTPID, UNIQUEID, DIAG, DIAGCAT, AGE, AGECAT, GENDER, RACE, SET, LOC, RANTX, RANTXCAT, SEVSCALE, SUIEVENT, SUIATT, TEAEAG, TEAEHOST, and SOURCE).

Variables in red met the criteria of being excluded from the confounding analysis (10% or more missing records).

13 APPENDIX VI: Potential imbalances in baseline demographics and other variable

13.1 Potential imbalances between intervention and placebo in baseline demographics and other variables in all submissions by drug and trial.

Variable name	Description	Prozac				Zoloft			Paxil					
		HCCJ	X065	HCJE	HCJW	90CE21-0498	A0501001	A0501017	329	377	704	701	453	676
Age	Age in years	0.13	NS	NS	NS	NS	NS	NS	NS	0.1	NS	NS	NS	NS
BASESEV	Baseline severity score	NS	NS	NS	NS	NS	NS	NS	NS	NS	NT	0.14	NS	NS
BMI	Body mass index	NS	NT	NS	NS	NS	NS	NS	NS	NS	NS	NS	NT	NS
DURACAT	Duration of illness in categories	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
DURATION (months)	Duration of illness prior to randomizat .	NT	NT	NS	NT	NT	NT	NT	NS	NS	NS	NS	NS	NT
DISCONT	Patient discontinued	NS	NS	NS	NS	NS	0.005	NS	0.06	NS	NS	0.11	NS	0.10
EXPOSURE	Exposure in days	0.11	0.03	0.01	0.11	NS	0.02	NS	0.09	NS	0.11	NS	0.09	NS
HAMD17	Score on HAM-D 17	NS	NT	NT	NT	NS	NT	NT	NS	NT	NT	NT	NS	NT
GENDER	Gender	NS	NS	NS	NS	NS	NS	0.02	NS	NS	NT	NS	NS	0.01
HXHOST	Hx-hostility or aggressive behavior	NT	NT	NT	NT	NS	NS	NS	NS	NS	NT	NT	NT	NT
HXINSOM	Hx-insomnia	NT	NS	NS	NS	NS	NS	0.03	NS	NS	NT	NS	NS	0.08
HXIRRAGB	Hx- irritability or agitation	NS	0.08	NS	NS	NS	NS	NS	NS	NS	NT	NS	NS	NS
HXNONCOM	Erratic compliance	NT	NT	NS	NS	NS	NS	NS	0.13	NS	NT	NS	NS	NS
HXPSHOSP	Hx- psychiatric hospitalization	NT	NT	NT	NT	NT	NT	NT	NS	NT	NT	NT	NT	NT
HXSUBAB	Hx- substance abuse	NS	NS	0.12	NT	NS	NS	NS	NS	NS	NS	NS	NT	NS
HXSUIATB	Hx-suicide attempt	NT	NS	NT	NT	NT	NT	NT	NS	NS	NT	NT	NT	NT
HXSUIIDB	Hx-suicidal ideation	NS	NS	NS	NS	NT	0.14	NS	NS	NS	NT	NS	NT	NT
LOC	Location of trial center	NT	NT	NT	NT	NT	NS	NS	NT	NS	NT	NT	NT	NS
SCALESUI	Suicide item score at baseline	NS	NS	0.13	NS	NT	NS	NS	0.06	NS	NT	0.07	NS	NS
RACE	Race	NS	NS	0.03	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
SET	Setting at randomization	NT	NT	NT	NT	NT	NS	NS	NT	NT	NT	NT	NT	NT
TEAEAG	Agitation occurred during the RCT	NT	NS	0.06	NS	NT	NS	NS	NS	0.1	NS	NS	NS	NS
TEAEHOST	Hostility occurred during the RCT	NT	NS	NS	NS	NT	NT	NT	0.02	NS	0.008	NS	0.01	NS

NT =not tested because information is missing in this variable, there were zero events of interest, or all patients had the same value.
NS=not significant at p-value of <=0.1. Some of the binary variables have no events in one of the comparison groups.
P-values are derived from Mantel-Haenszel chi-square (or Fisher exact for tables with 25% or more of the cells have expected counts less than 5), t-test (or Wilcoxon Rank Sum test for small groups), or ANOVA (study 329) as appropriate. For a variable to be a confounder it should be associated with the outcome of interest in addition to being imbalanced between the drug and the placebo group.

Potential imbalances, continued…

Variable name	Description	Luvox	Celexa		Wellbutrin	Effexor				Serzone		Remeron
		114	CIT-MD-18	94404	75	382	394	396	397	CN104-141	CN104-187	003-045
Age	Age in years	NS	NS	0.07	NS	NS	NS	NS	NS	NS	NS	NS
BASESEV	Baseline severity score	NS	NS	NS	NT	NS	NS	NS	NS	NS	0.007	NS
BMI	Body mass index	NS	NS	NS	0.03	NS	NS	NS	NS	NS	NS	NS
DURACAT	Duration of illness in categories	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NS
DURATION (months)	Duration of illness prior to randomizat.	NS	NS	NT	NT	NS	NS	NS	NS	NS	0.11	NT
DISCONT	Patient discontinued	NS	NS	NS	NS	NS	0.12	NS	NS	0.06	NS	NS
EXPOSURE	Exposure in days	NS	NS	NS	NS	NS	NS	NS	NS	0.06	NS	NS
HAMD17	Score on HAM-D 17	NT	NT	NT	NT	NS	NS	NT	NT	NS	NT	NS
GENDER	Gender	NS	NS	NS	NS	NS	NS	0.01	NS	0.1	NS	NS
HXHOST	Hx-hostility or aggressive behavior	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NS
HXINSOM	Hx-insomnia	NS	NS	NS	NS	NS	NS	NT	NT	NS	NS	NS
HXIRRAGB	Hx- irritability or agitation	NS	NS	NS	NS	NS	NS	0.04	0.09	NS	NS	NS
HXNONCOM	Erratic compliance	NS	NS	NS	NT	NS	NS	NS	NS	NS	NS	NS
HXPSHOSP	Hx- psychiatric hospitalization	NT	NT	0.13	NT	NT	NT	NT	NT	NT	NT	0.05
HXSUBAB	Hx- substance abuse	NS	NT	NT	NT	NT	NT	NT	NT	NS	0.03	NS
HXSUIATB	Hx-suicide attempt	NT	NT	NS	NT	NT	NT	NT	NT	NT	NT	NT
HXSUIIDB	Hx-suicidal ideation	NS	NS	NS	NS	NS	NS	0.04	0.09	NS	NS	NS
LOC	Location of trial center	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
SCALESUI	Suicide item score at baseline	NS	NS	NS	NS	NS	NS	0.14	NS	NS	0.11	NS
RACE	Race	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
SET	Setting at randomization	NT	NT	NS	NT	NT	NT	NT	NT	NT	NT	NT
TEAEAG	Agitation occurred during the RCT	0.08	NS	NS	NS	NT	NS	NS	NS	NS	NS	NS
TEAEHOST	Hostility occurred during the RCT	NS	NT	NT	NT	NS	0.07	NT	0.12	NS	NT	NS

NT =not tested because information is missing in this variable, there were zero events of interest, or all patients had the same value.
NS=not significant at p-value of <=0.1. Some of the binary variables have no events in one of the comparison groups.
P-values are derived from Mantel-Haenszel chi-square (or Fisher exact for tables with 25% or more of the cells have expected counts less than 5), t-test (or Wilcoxon Rank Sum test for small groups), or ANOVA (study 329) as appropriate. For a variable to be a confounder it should be associated with the outcome of interest in addition to being imbalanced between the drug and the placebo group.

13.2 Potential associations (P<=0.1) between various outcomes and explanatory variables within each trial.

Drug	Trial	Outcomes		
		Definitive suicide behavior or ideation (outcome 3)	Emergence of suicidality (outcome 7)	Worsening of suicidality (outcome 6)
Selective serotonin re-uptake inhibitors (SSRI) group				
Prozac	HCCJ	ND	NV	NV
	X065	ND	NV	NV
	HCJE	Hxsubab? (0.05)	NV	Duration (0.09)
	HCJW	ND	Hxnoncom (0.07)	Exposure (0.1) Hxirragb (0.11)
Zoloft	90CE21-0498	ND	NE	NE
	A0501001	ND	Exposure (0.1)	Exposure (0.09)
	A0501017	ND	Duration (0.06)	Duration (0.06)
Paxil	329	ND	Exposure (0.06) HAMD-17 (0.03) Duration (0.05) Discont (0.07) Hxhost (0.08)	Exposure (0.07) HAMD-17 (0.05) Duration (0.002) Gender (0.08) Discont (0.11) Hxhost (0.12)
	377	Exposure ? (0.01), scalesui ? (0.04), discont ? (0.008), Hxsuiatb ? (0.03)	Hxhost (0.08)	HxHost (0.12) Loc (0.02)
	701	ND	Exposure (0.06) Discont (0.13)	NV
	704	ND	NE	NE
	453	NE	Duration (0.08)	Duration (0.08)
	676	ND	Exposure (0.14) Discont (0.09)	Exposure (0.09) BMI (0.04)
Luvox	RH_114_02_01	ND	NE	NE
Celexa	CIT-MD-18	ND	NV	BMI (0.05)
	94404	Baseserv ? (0.02), exposure ? (0.0001), scalesui	Exposure (0.05) Discont (0.09) Hxpshosp (0.14)	Exposure (0.0003) Discont (0.0004)

Drug	Trial	Outcomes		
		Definitive suicide behavior or ideation (outcome 3)	Emergence of suicidality (outcome 7)	Worsening of suicidality (outcome 6)
		? (0.008), discont ? (0.11), Hxnoncom ? (0.06), Hxpshosp ? (0.0002), Hxsuiidb? (0.05), set inpat ? (0.006)		
Atypical antidepressants group				
Wellbutrin	75	NE	NE	NE
Effexor	382	ND	Age (0.008) Hxirragb (0.03)	Age (0.1) Hxirragb (0.13)
	394	ND	Hxirragb (0.005)	Hxirragb (0.05)
	396	NE	NE	NE
	397	ND	NE	NE
Serzone	CN104-141	NE	NV	NV
	CN104-187	NE	Exposure (0.008)	Exposure (0.007)
Remeron	003-045	ND	Exposure (0.11) Age (0.08) BMI (0.1) Discont (0.08)	Exposure (0.1) Age (0.09) BMI (0.12) Discont (0.03)

NE =no events. NV=no variables associated with the outcome. ND=not done because of small number of events
For meaning of variables names, see previous table

14 APPENDIX VII: Listings of patients with events

14.1 Listing of all patients with suicide-related AEs in all submissions according to Columbia University classification during the double-blind (phase 1).

Development program	Trial	Unique ID	Age	Gender	Treatment	Dose	Indication
BUPR	75	75_18	6	Male	PLACEBO	0	ADHD
CITA	94404	94404009	17	Female	CITALOPRAM	20	MDD
CITA	94404	94404071	16	Female	PLACEBO	0	MDD
CITA	94404	94404148	17	Female	CITALOPRAM	20	MDD
CITA	94404	94404412	18	Female	PLACEBO	0	MDD
CITA	94404	94404426	14	Female	CITALOPRAM	20	MDD
CITA	94404	94404573	14	Female	CITALOPRAM	20	MDD
CITA	94404	94404575	14	Female	CITALOPRAM	20	MDD
CITA	94404	94404605	13	Male	PLACEBO	0	MDD
CITA	94404	94404607	17	Male	PLACEBO	0	MDD
CITA	94404	94404664	15	Male	CITALOPRAM	20	MDD
CITA	94404	94404691	17	Female	PLACEBO	0	MDD
CITA	94404	94404693	16	Female	PLACEBO	0	MDD
CITA	94404	94404713	16	Male	CITALOPRAM	30	MDD
CITA	94404	94404715	17	Female	CITALOPRAM	10	MDD
CITA	94404	94404729	16	Male	CITALOPRAM	10	MDD
CITA	94404	94404761	13	Male	CITALOPRAM	30	MDD
CITA	94404	94404776	17	Female	CITALOPRAM	10	MDD
CITA	94404	94404787	13	Female	PLACEBO	0	MDD
CITA	94404	94404841	17	Female	CITALOPRAM	30	MDD
CITA	94404	94404864	16	Male	CITALOPRAM	20	MDD
CITA	94404	94404867	17	Female	CITALOPRAM	30	MDD
CITA	94404	94404871	17	Female	PLACEBO	0	MDD
CITA	94404	94404874	17	Female	CITALOPRAM	20	MDD
CITA	94404	94404884	16	Female	CITALOPRAM	20	MDD
CITA	CIT_MD_18	CIT_MD_1813519	12	Female	PLACEBO	0	MDD
CITA	CIT_MD_18	CIT_MD_1818137	10	Male	PLACEBO	0	MDD
CITA	CIT_MD_18	CIT_MD_1822193	9	Male	CITALOPRAM	20	MDD

FLUO	HCCJ	HCCJ6401	17	Female	FLUOXETINE	20	MDD
FLUO	HCCJ	HCCJ6408	13	Male	PLACEBO	0	MDD
FLUO	HCJE	HCJE0133	12	Female	FLUOXETINE	20	MDD
FLUO	HCJE	HCJE0302	17	Female	FLUOXETINE	20	MDD
FLUO	HCJE	HCJE0806	15	Male	PLACEBO	0	MDD
FLUO	HCJE	HCJE1217	16	Male	FLUOXETINE	20	MDD
FLUO	HCJE	HCJE1605	11	Male	FLUOXETINE	20	MDD
FLUO	HCJE	HCJE1652	9	Male	FLUOXETINE	20	MDD
FLUO	HCJE	HCJE1901	11	Female	PLACEBO	0	MDD
FLUO	HCJE	HCJE2203	10	Male	PLACEBO	0	MDD
FLUO	HCJE	HCJE2207	8	Male	PLACEBO	0	MDD
FLUO	HCJE	HCJE2210	16	Male	PLACEBO	0	MDD
FLUO	HCJE	HCJE2212	17	Male	PLACEBO	0	MDD
FLUO	HCJE	HCJE2214	13	Male	FLUOXETINE	20	MDD
FLUO	HCJE	HCJE2216	15	Female	FLUOXETINE	20	MDD
FLUO	HCJE	HCJE2220	10	Female	FLUOXETINE	20	MDD
FLUO	HCJW	HCJW0609	16	Female	PLACEBO	0	OCD
FLUO	HCJW	HCJW1300	13	Female	FLUOXETINE	10	OCD
FLUO	HCJW	HCJW1811	7	Female	FLUOXETINE	20	OCD
FLUO	X065	X0652051	17	Female	FLUOXETINE	20	MDD
FLUO	X065	X0652052	17	Male	PLACEBO	0	MDD
FLUO	X065	X0652087	14	Female	PLACEBO	0	MDD
FLUO	X065	X0652163	18	Female	FLUOXETINE	20	MDD
FLUV	RH_114_02_01	RH_114_02_0165265	15	Female	FLUV	200	OCD
FLUV	RH_114_02_01	RH_114_02_0165815	16	Male	FLUV	200	OCD
NEFA	CN104-141	104141-3-1065	12	Male	NEFAZODONE	600	MDD
NEFA	CN104-141	104141-5-1279	16	Female	NEFAZODONE	300	MDD
PARO	329	329.001.00123	16	Female	PLACEBO	0	MDD
PARO	329	329.002.00245	14	Female	PAROXETINE	20	MDD
PARO	329	329.003.00089	14	Female	PAROXETINE	20	MDD
PARO	329	329.003.00250	15	Female	PAROXETINE	20	MDD
PARO	329	329.003.00313	18	Male	PAROXETINE	20	MDD
PARO	329	329.004.00015	16	Female	PAROXETINE	20	MDD
PARO	329	329.005.00113	15	Female	IMIPRAMINE	20	MDD
PARO	329	329.005.00295	13	Female	IMIPRAMINE	20	MDD

PARO	329	329.005.00333	16	Female	PAROXETINE	20	MDD
PARO	329	329.006.00038	15	Female	PAROXETINE	20	MDD
PARO	329	329.006.00039	15	Female	PAROXETINE	20	MDD
PARO	329	329.012.00223	13	Female	IMIPRAMINE	20	MDD
PARO	377	377.005.00231	14	Female	PLACEBO	0	MDD
PARO	377	377.009.00225	17	Female	PAROXETINE	20	MDD
PARO	377	377.010.00068	14	Female	PLACEBO	0	MDD
PARO	377	377.011.00061	17	Female	PAROXETINE	40	MDD
PARO	377	377.023.00172	15	Male	PAROXETINE	40	MDD
PARO	377	377.024.00158	14	Female	PAROXETINE	30	MDD
PARO	377	377.029.00024	16	Female	PLACEBO	0	MDD
PARO	377	377.030.00181	17	Female	PAROXETINE	40	MDD
PARO	377	377.040.00298	17	Female	PAROXETINE	20	MDD
PARO	377	377.042.00310	15	Female	PAROXETINE	20	MDD
PARO	377	377.042.00554	16	Female	PAROXETINE	30	MDD
PARO	377	377.053.00508	14	Female	PAROXETINE	20	MDD
PARO	676	676.011.24283	14	Male	PAROXETINE	30	SAD
PARO	676	676.014.24376	13	Female	PAROXETINE	10	SAD
PARO	676	676.100.24705	16	Female	PAROXETINE	10	SAD
PARO	676	676.100.24708	14	Male	PAROXETINE	40	SAD
PARO	676	676.101.24629	13	Female	PAROXETINE	40	SAD
PARO	676	676.209.24966	16	Male	PAROXETINE	10	SAD
PARO	701	701.154.25768	13	Male	PLACEBO	0	MDD
PARO	701	701.163.25718	16	Female	PAROXETINE	50	MDD
PARO	701	701.183.27617	13	Female	PLACEBO	0	MDD
PARO	701	701.185.25965	10	Female	PAROXETINE	30	MDD
PARO	701	701.192.25869	13	Female	PAROXETINE	20	MDD
PARO	704	704.016.27018	6	Female	PAROXETINE	20	OCD
PARO	704	704.033.25513	15	Male	PAROXETINE	30	OCD
REME	003-045	003-0450404	15	Male	Remeron	15	MDD
REME	003-045	003-0450801	9	Male	Remeron	45	MDD
REME	003-045	003-0451603	12	Female	PLACEBO	0	MDD
SERT	90CE21-0498	90CE21-0498-90N0242-19	12	Female	PLACEBO	0	OCD
SERT	A0501001	A0501001-29533-2006	12	Male	SERTRALINE	50	MDD

SERT	A0501001	A0501001-29534-1089	10	Female	SERTRALINE	100	MDD
SERT	A0501001	A0501001-30506-1076	9	Female	SERTRALINE	50	MDD
SERT	A0501001	A0501001-6193-1022	10	Male	SERTRALINE	50	MDD
SERT	A0501017	A0501017-29384-4022	16	Female	SERTRALINE	150	MDD
SERT	A0501017	A0501017-30627-3095	6	Male	SERTRALINE	100	MDD
SERT	A0501017	A0501017-31940-4329	17	Female	PLACEBO	0	MDD
SERT	A0501017	A0501017-31942-4321	15	Female	PLACEBO	0	MDD
VENL	382	38204023	11	Female	Venlafaxine ER	37.5	MDD
VENL	382	38205008	12	Male	Venlafaxine ER	75	MDD
VENL	382	38205019	8	Female	Venlafaxine ER	37.5	MDD
VENL	382	38207023	14	Female	PLACEBO	0	MDD
VENL	382	38209020	13	Female	Venlafaxine ER	37.5	MDD
VENL	382	38211012	10	Female	Venlafaxine ER	75	MDD
VENL	394	39400041	7	Male	Venlafaxine ER	75	MDD
VENL	394	39400126	14	Male	Venlafaxine ER	37.5	MDD
VENL	394	39400405	14	Female	Venlafaxine ER	150	MDD
VENL	394	39400447	14	Male	Venlafaxine ER	75	MDD
VENL	394	39400769	13	Male	Venlafaxine ER	225	MDD
VENL	394	39401087	16	Male	Venlafaxine ER	150	MDD
VENL	394	39401366	17	Female	Venlafaxine ER	225	MDD
VENL	394	39401561	12	Female	Venlafaxine ER	75	MDD
VENL	397	39700012	17	Female	PLACEBO	0	GAD
VENL	397	39700361	10	Male	Venlafaxine ER	75	GAD

14.2 Listing of 20 patients with more than one event

The second column represents the final status for every patient that was used in the analysis. If more than one event occurred in the same phase, the most severe one was chosen.

Drug	Trial	Random	Unique ID	Event used	Phase	Event2	Phase	Event3	Phase	Event4	Phase
CITA	94404	127	94404148	3	1	3	1	.	.	.	.
CITA	94404	784	94404573	3	1	3	1	.	.	.	.
CITA	94404	1249	94404693	6	1	6	5	.	.	.	.

Drug	Trial	Random	Unique ID	Event used	Phase	Event2	Phase	Event3	Phase	Event4	Phase
CITA	94404	1922	94404874	1	1	1	1	.	.	.	.
CITA	94404	3670	94404071	3	1	10	1	.	.	.	.
CITA	94404	3830	94404884	1	1	6	1	1	1	.	.
CITA	CIT_MD_18	1674	CIT_MD_1818137	1	1	10	5	.	.	.	.
FLUO	HCJE	2593	HCJE0804	1	4	3	4	6	4	.	.
FLUO	HCJE	3220	HCJE0806	6	1	5	1	.	.	.	.
FLUO	HCJE	3563	HCJE2203	6	1	6	6	3	6	3	6
FLUV	RH_114_02_01	1831	RH_114_02_0165815	6	1	3	5	.	.	.	.
FLUV	RH_114_02_01	3465	RH_114_02_0165265	6	1	5	1	.	.	.	.
PARO	329	2849	329.003.00313	2	1	3	1	.	.	.	.
PARO	329	3570	329.003.00250	3	1	1	5	.	.	.	.
PARO	329	3598	329.004.00015	5	1	6	5	.	.	.	.
SERT	A0501001	150	A0501001-30506-1076	3	1	5	1	.	.	.	.
SERT	A0501017	243	A0501017-31942-4321	1	1	2	1	.	.	.	.
VENL	382	1388	38207008	6	5	3	5	.	.	.	.
VENL	382	1980	38211012	3	1	3	1	.	.	.	.
VENL	397	4537	39700361	2	1	3	1	.	.	.	.

14.3 Listing of 20 patients with events occurring in post-double-blind (phases 2-6) period by drug, trial, and treatment group

Drug	Trial	Treatment	Phase	Event code	Unique ID
CITA	94404	CITALOPRAM	5	1	94404007
CITA	94404	CITALOPRAM	5	1	94404121
CITA	94404	PLACEBO	3	6	94404152
FLUO	HCJE	FLUOXETINE	4	6	HCJE0419
FLUO	HCJE	FLUOXETINE	6	5	HCJE0901
FLUO	HCJE	FLUOXETINE	6	6	HCJE1510
FLUO	HCJE	PLACEBO	4	1	HCJE0804
FLUV	RH_114_02_01	FLUVOXAMINE	4	6	RH_114_02_0165855

Drug	Trial	Treatment	Phase	Event code	Unique ID
FLUV	RH_114_02_01	PLACEBO	5	5	RH_114_02_0166069
NEFA	CN104-187	NEFAZODONE	3	1	104187-18-322
NEFA	CN104-187	NEFAZODONE	6	6	104187-18-231
NEFA	CN104-187	PLACEBO	4	6	104187-17-405
PARO	329	PAROXETINE	3	6	329.002.00106
PARO	377	PAROXETINE	3	3	377.042.00315
PARO	377	PAROXETINE	3	6	377.049.00479
PARO	377	PLACEBO	2	1	377.041.00294
PARO	701	PAROXETINE	3	1	701.180.25639
PARO	701	PAROXETINE	3	2	701.185.25963
PARO	701	PAROXETINE	3	6	701.183.27620
VENL	382	PLACEBO	5	6	38207008

15 APPENDIX VIII: Categorical and continuous variables by drug, indication, and trial

15.1 Averages of continuous variables by drug, indication, and trial

Program	Indicat.	Trial #	Tx Category	Subj.	Age mean	BMI mean	Duration mean	Dose mean	Baseline severity mean	HAMD17 mean	Suicide score mean
BUPR	ADHD	75	Atypical	72	8.57	17.17	.	164.44	.	.	.
			Placebo	37	8.49	18.54	.	0.00	.	.	.
CITA	MDD	94404	SSRI	124	15.77	22.30	1.40	24.46	32.50	.	2.83
			Placebo	120	16.11	21.61	1.07	0.00	32.25	.	2.68
		CIT_MD_18	SSRI	93	11.95	23.12	20.57	24.72	58.47	.	1.67
			Placebo	85	12.07	23.57	18.64	0.00	57.84	.	1.82
FLUO	MDD	HCCJ	SSRI	21	15.95	22.53	.	27.14	24.62	21.76	1.81
			Placebo	19	15.16	23.25	.	0.00	24.63	22.05	1.79
		HCJE	SSRI	109	12.70	22.99	14.10	20.73	57.12	.	1.82
			Placebo	110	12.69	23.54	14.30	0.00	55.36	.	1.61
		X065	SSRI	48	12.67	25.10	.	20.00	58.85	.	2.44
			Placebo	48	13.00	20.80	.	0.00	57.52	.	2.54
	OCD	HCJW	SSRI	71	11.42	20.32	.	30.56	26.17	.	1.11
			Placebo	32	11.41	19.59	.	0.00	26.00	.	1.16
FLUV	OCD	RH_114_02_01	SSRI	57	13.42	21.01	44.96	161.84	27.07	.	1.12
			Placebo	63	12.72	20.00	40.35	0.00	27.56	.	1.25
NEFA	MDD	CN104-141	Atypical	95	14.71	24.94	24.88	359.47	60.24	16.80	1.97
			Placebo	95	14.63	23.90	28.55	0.00	61.40	16.72	2.02
		CN104-187	Atypical	184	11.89	24.26	27.39	263.19	60.55	.	1.91
			Placebo	94	12.39	24.21	32.55	0.00	57.82	.	1.69
PARO	Anxiety	676	SSRI	165	13.01	22.06	.	30.73	29.61	.	1.20
			Placebo	156	13.26	22.65	.	0.00	30.94	.	1.24
	MDD	329	Active control	95	14.88	23.61	28.58	20.21	18.44	18.44	0.85
			SSRI	93	14.80	23.97	26.57	20.86	19.42	19.42	0.82
			Placebo	88	15.09	24.10	24.77	0.00	19.47	19.47	1.13
		377	SSRI	180	15.50	21.45	16.59	24.50	25.97	.	1.77

Program	Indicat.	Trial #	Tx Category	Subj.	Age mean	BMI mean	Duration mean	Dose mean	Baseline severity mean	HAMD17 mean	Suicide score mean
PARO	MDD	377	Placebo	95	15.83	21.54	19.05	0.00	25.85	.	1.66
		701	SSRI	104	11.92	24.19	29.10	23.56	60.69	.	1.74
			Placebo	102	12.15	22.91	30.30	0.00	62.58	.	2.05
	OCD	453	SSRI	96	11.83	.	31.18	34.17	2.35	2.35	0.08
			Placebo	98	11.63	.	29.65	0.00	2.31	2.31	0.09
		704	SSRI	99	11.06	20.11	49.33	27.37	.	.	.
			Placebo	107	11.56	20.87	52.54	0.00	.	.	.
REME	MDD	003-045	Atypical	170	12.08	22.35	.	35.47	57.98	19.33	1.70
			Placebo	89	12.37	22.17	.	0.00	58.62	19.43	1.66
SERT	MDD	A0501001	SSRI	97	12.01	22.92	16.63	100.52	63.98	.	1.91
			Placebo	91	11.99	21.86	14.82	0.00	63.41	.	1.80
		A0501017	SSRI	92	11.91	20.42	19.78	122.28	64.41	.	1.89
			Placebo	93	11.98	20.47	21.23	0.00	65.52	.	1.87
	OCD	90CE21-0498	SSRI	92	12.08	19.96	14.92	165.76	9.18	4.28	.
			Placebo	95	12.16	20.18	12.47	0.00	9.07	3.92	.
VENL	Anxiety	396	Atypical	80	11.38	21.70	41.76	119.53	34.36	.	1.21
			Placebo	84	11.11	22.81	40.02	0.00	33.52	.	1.10
		397	Atypical	77	11.65	21.97	40.27	114.94	31.74	.	1.05
			Placebo	79	11.29	21.51	41.29	0.00	32.13	.	1.09
	MDD	382	Atypical	80	12.16	22.70	22.30	118.59	54.89	17.91	1.65
			Placebo	85	12.21	22.43	20.02	0.00	53.57	17.10	1.75
		394	Atypical	102	12.23	23.28	28.88	124.63	57.20	16.10	1.68
			Placebo	94	12.12	23.63	30.49	0.00	57.43	16.09	1.61

15.2 Distribution of categorical variables by drug

Development program BUPR

Indication	TRIAL	Treatment category	GENDER Female #	GENDER Female %	GENDER Male #	GENDER Male %	RACE White Caucasian #	RACE White Caucasian %	RACE African American #	RACE African American %	RACE Other #	RACE Other %	Setting Outpatient #	Setting Outpatient %	Location North America #	Location North America %
ADHD	75	Atypical	7	10	65	90	55	76	15	21	2	3	72	100	72	100
		Placebo	4	11	33	89	27	73	10	27	0	0	37	100	37	100

Development program CITA

Indication	TRIAL	Treatment category	GENDER Female #	GENDER Female %	GENDER Male #	GENDER Male %	RACE White Caucasian #	RACE White Caucasian %	RACE African American #	RACE African American %	RACE Hispanic #	RACE Hispanic %	RACE Asian #	RACE Asian %	RACE Other #	RACE Other %	Setting Inpatient #	Setting Inpatient %	Setting Outpatient #	Setting Outpatient %	Location North America #	Location North America %	Location Non-North America #	Location Non-North America %
MDD	94404	SSRI	92	74	32	26	119	96	0	0	0	0	3	2	2	2	19	15	105	85	0	0	124	100
		Placebo	88	73	32	27	118	98	0	0	0	0	1	1	1	1	13	11	107	89	0	0	120	100
	CIT_MD_18	SSRI	48	52	45	48	74	80	10	11	6	6	0	0	3	3	0	0	93	100	93	100	0	0
		Placebo	46	54	39	46	62	73	11	13	6	7	0	0	6	7	0	0	85	100	85	100	0	0

Development program FLUO

Indication	TRIAL	Treatment category	GENDER Female #	GENDER Female %	GENDER Male #	GENDER Male %	RACE White Caucasian #	RACE White Caucasian %	RACE African American #	RACE African American %	RACE Hispanic #	RACE Hispanic %	RACE Asian #	RACE Asian %	RACE Other #	RACE Other %	Setting Outpatient #	Setting Outpatient %	Location North America #	Location North America %	Location Non-North America #	Location Non-North America %
MDD	HCCJ	SSRI	12	57	9	43	21	100	0	0	0	0	0	0	0	0	21	100	0	0	21	100
		Placebo	10	53	9	47	19	100	0	0	0	0	0	0	0	0	19	100	0	0	19	100
	HCJE	SSRI	54	50	55	50	96	88	6	6	3	3	1	1	3	3	109	100	109	100	0	0
		Placebo	54	49	56	51	84	76	8	7	10	9	0	0	8	7	110	100	110	100	0	0
	X065	SSRI	22	46	26	54	35	73	4	8	8	17	0	0	1	2	48	100	48	100	0	0
		Placebo	22	46	26	54	41	85	4	8	2	4	0	0	1	2	48	100	48	100	0	0
OCD	HCJW	SSRI	37	52	34	48	62	87	2	3	4	6	0	0	3	4	71	100	71	100	0	0
		Placebo	17	53	15	47	27	84	0	0	3	9	1	3	1	3	32	100	32	100	0	0

Development program FLUV

Indication	TRIAL	Treatment category	GENDER Female #	GENDER Female %	GENDER Male #	GENDER Male %	RACE White Caucasian #	RACE White Caucasian %	RACE African American #	RACE African American %	RACE Other #	RACE Other %	Setting Outpatient #	Setting Outpatient %	Location North America #	Location North America %
OCD	RH_114_02-_01	SSRI	28	49	29	51	55	96	2	4	0	0	57	100	57	100
		Placebo	28	44	35	56	60	95	1	2	2	3	63	100	63	100

Development program NEFA

Indication	TRIAL	Treatment category	GENDER Female #	GENDER Female %	GENDER Male #	GENDER Male %	RACE White Caucasian #	RACE White Caucasian %	RACE African American #	RACE African American %	RACE Hispanic #	RACE Hispanic %	RACE Asian #	RACE Asian %	RACE Other #	RACE Other %	Setting Outpatient #	Setting Outpatient %	Location North America #	Location North America %
MDD	CN104-141	Atypical	51	54	44	46	68	72	12	13	12	13	0	0	3	3	95	100	95	100
		Placebo	62	65	33	35	79	83	6	6	6	6	1	1	3	3	95	100	95	100
	CN104-187	Atypical	90	49	94	51	130	71	22	12	19	10	1	1	12	7	184	100	184	100
		Placebo	47	50	47	50	74	79	6	6	8	9	2	2	4	4	94	100	94	100

Development program PARO

Indication	TRIAL	Treatment category	GENDER Female #	GENDER Female %	GENDER Male #	GENDER Male %	RACE White Caucasian #	RACE White Caucasian %	RACE African American #	RACE African American %	RACE Hispanic #	RACE Hispanic %	RACE Asian #	RACE Asian %	RACE Other #	RACE Other %	Setting Outpatient #	Setting Outpatient %	Location North America #	Location North America %	Location Non-North America #	Location Non-North America %
MDD	329	SSRI	58	62	35	38	77	83	5	5	5	5	1	1	5	5	93	100	93	100	0	0
		Placebo	58	66	30	34	71	81	6	7	7	8	2	2	2	2	88	100	88	100	0	0
		Active control	56	59	39	41	83	87	3	3	5	5	2	2	2	2	95	100	95	100	0	0
	377	SSRI	121	67	59	33	125	69	2	1	19	11	4	2	30	17	180	100	10	6	170	94
		Placebo	62	65	33	35	63	66	4	4	11	12	0	0	17	18	95	100	4	4	91	96
	701	SSRI	50	48	54	52	79	76	13	13	8	8	1	1	3	3	104	100	104	100	0	0
		Placebo	47	46	55	54	84	82	11	11	7	7	0	0	0	0	102	100	102	100	0	0
OCD	453	SSRI	48	50	48	50	88	92	1	1	3	3	1	1	3	3	96	100	96	100	0	0
		Placebo	40	41	58	59	89	91	2	2	2	2	3	3	2	2	98	100	98	100	0	0
	704	SSRI	46	46	53	54	86	87	8	8	2	2	0	0	3	3	99	100	99	100	0	0
		Placebo	41	38	66	62	95	89	6	6	3	3	0	0	3	3	107	100	107	100	0	0
Anxiety	676	SSRI	94	57	71	43	141	85	4	2	7	4	5	3	8	5	165	100	109	66	56	34
		Placebo	67	43	89	57	131	84	6	4	3	2	4	3	12	8	156	100	101	65	55	35

Development program REME

Indication	TRIAL	Treatment category	GENDER Female #	GENDER Female %	GENDER Male #	GENDER Male %	RACE White Caucasian #	RACE White Caucasian %	RACE African American #	RACE African American %	RACE Hispanic #	RACE Hispanic %	RACE Asian #	RACE Asian %	RACE Other #	RACE Other %	Setting, Outpatient #	Setting, Outpatient %	Location, North America #	Location, North America %
MDD	003-045	Atypical	85	50	85	50	137	81	23	14	6	4	2	1	2	1	170	100	170	100
		Placebo	50	56	39	44	72	81	9	10	5	6	1	1	2	2	89	100	89	100

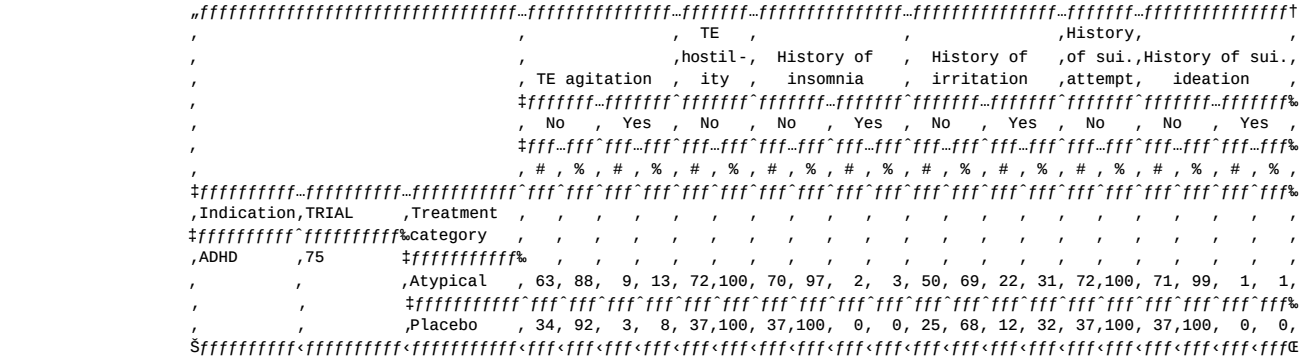
Development program SERT

Indication	TRIAL	Treatment category	GENDER Female #	GENDER Female %	GENDER Male #	GENDER Male %	RACE White Caucasian #	RACE White Caucasian %	RACE African American #	RACE African American %	RACE Hispanic #	RACE Hispanic %	RACE Asian #	RACE Asian %	RACE Other #	RACE Other %	Setting, Outpatient #	Setting, Outpatient %	Location North America #	Location North America %	Location Non-North America #	Location Non-North America %
MDD	A0501001	SSRI	53	55	44	45	76	78	6	6	4	4	7	7	4	4	97	100	91	94	6	6
		Placebo	42	46	49	54	72	79	8	9	5	5	4	4	2	2	91	100	88	97	3	3
	A0501017	SSRI	55	60	37	40	59	64	1	1	11	12	19	21	2	2	92	100	65	71	27	29
		Placebo	40	43	53	57	57	61	1	1	14	15	18	19	3	3	93	100	65	70	28	30
OCD	90CE21-0498	SSRI	40	43	52	57	78	85	3	3	3	3	1	1	7	8	92	100	92	100	0	0
		Placebo	48	51	47	49	79	83	8	8	6	6	0	0	2	2	95	100	95	100	0	0

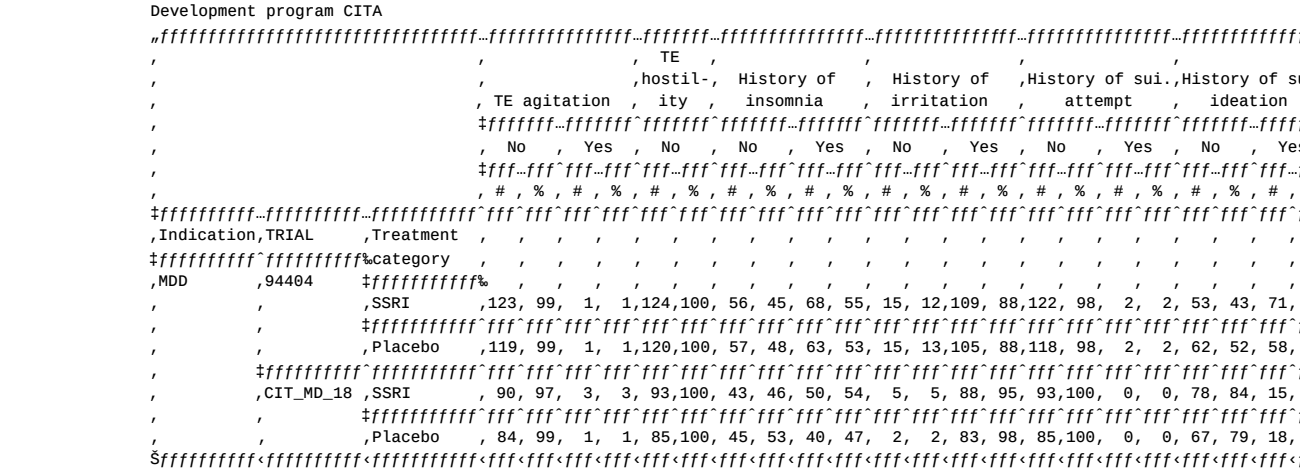
Development program VENL

Indication	TRIAL	Treatment category	GENDER Female #	GENDER Female %	GENDER Male #	GENDER Male %	RACE White Caucasian #	RACE White Caucasian %	RACE African American #	RACE African American %	RACE Hispanic #	RACE Hispanic %	RACE Asian #	RACE Asian %	RACE Other #	RACE Other %	Setting, Outpatient #	Setting, Outpatient %	Location, North America #	Location, North America %
MDD	382	Atypical	36	45	44	55	70	88	6	8	3	4	0	0	1	1	80	100	80	100
		Placebo	47	55	38	45	75	88	7	8	3	4	0	0	0	0	85	100	85	100
	394	Atypical	44	43	58	57	64	63	15	15	13	13	3	3	7	7	102	100	102	100
		Placebo	39	41	55	59	71	76	10	11	11	12	1	1	1	1	94	100	94	100
Anxiety	396	Atypical	28	35	52	65	58	73	7	9	13	16	1	1	1	1	80	100	80	100
		Placebo	46	55	38	45	60	71	7	8	14	17	0	0	3	4	84	100	84	100
	397	Atypical	30	39	47	61	60	78	10	13	5	6	1	1	1	1	77	100	77	100
		Placebo	32	41	47	59	65	82	9	11	3	4	1	1	1	1	79	100	79	100

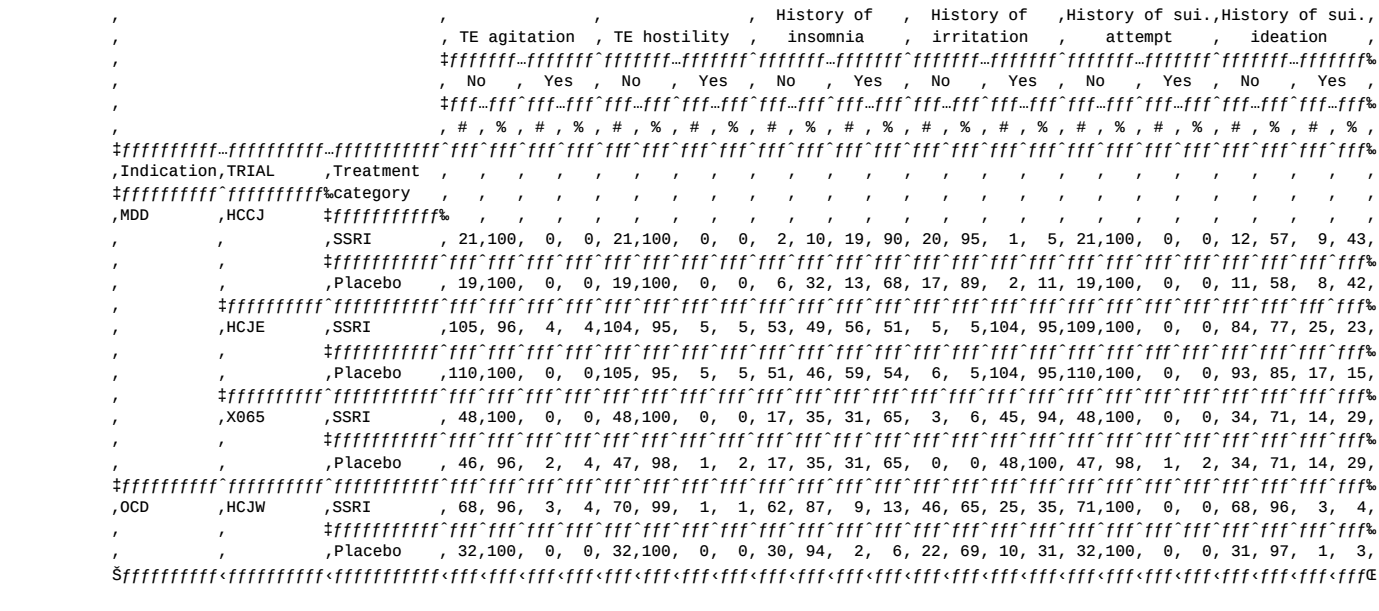
Development program BUPR



Development program CITA



Development program FLUO



Development program FLUV

Indication	TRIAL	Treatment category	TE agitation				TE hostility				History of insomnia				History of irritation				History of sui. attempt		History of sui. ideation			
			No		Yes		No		Yes		No		Yes		No		Yes		No		No		Yes	
			#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%
OCD	RH_114_02-_01	SSRI	50	88	7	12	56	98	1	2	50	88	7	12	29	51	28	49	57	100	54	95	3	5
		Placebo	61	97	2	3	62	98	1	2	59	94	4	6	28	44	35	56	63	100	57	90	6	10

Development program NEFA

Indication	TRIAL	Treatment category	TE agitation				TE hostility				History of insomnia				History of irritation				History of sui. attempt		History of sui. ideation			
			No		Yes		No		Yes		No		Yes		No		Yes		No		No		Yes	
			#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%
MDD	CN104-141	Atypical	88	93	7	7	94	99	1	1	35	37	60	63	6	6	89	94	95	100	67	71	28	29
		Placebo	92	97	3	3	93	98	2	2	39	41	56	59	5	5	90	95	95	100	67	71	28	29
	CN104-187	Atypical	175	95	9	5	184	100	0	0	72	39	112	61	11	6	173	94	184	100	132	72	52	28
		Placebo	88	94	6	6	94	100	0	0	29	31	65	69	2	2	92	98	94	100	73	78	21	22

Development program PARO

Indication	TRIAL	Treatment category	TE agitation				TE hostility				History of insomnia				History of irritation				History of sui. attempt				History of sui. ideation			
			No		Yes		No		Yes		No		Yes		No		Yes		No		Yes		No		Yes	
			#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%
MDD	329	SSRI	91	98	2	2	86	92	7	8	9	10	84	90	2	2	91	98	89	96	4	4	22	24	71	76
		Placebo	88	100	0	0	88	100	0	0	12	14	76	86	2	2	86	98	82	93	6	7	15	17	73	83
		Active control	93	98	2	2	92	97	3	3	16	17	79	83	5	5	90	95	87	92	8	8	23	24	72	76
	377	SSRI	175	97	5	3	179	99	1	1	47	26	133	74	8	4	172	96	153	85	27	15	50	28	130	72
		Placebo	95	100	0	0	95	100	0	0	28	29	67	71	5	5	90	95	76	80	19	20	28	29	67	71
	701	SSRI	101	97	3	3	103	99	1	1	36	35	68	65	5	5	99	95	104	100	0	0	82	79	22	21
		Placebo	101	99	1	1	102	100	0	0	33	32	69	68	6	6	96	94	102	100	0	0	77	75	25	25
OCD	453	SSRI	94	98	2	2	90	94	6	6	89	93	7	7	95	99	1	1	96	100	0	0	96	100	0	0
		Placebo	96	98	2	2	98	100	0	0	92	94	6	6	95	97	3	3	98	100	0	0	98	100	0	0
	704	SSRI	94	95	5	5	90	91	9	9	99	100	0	0	99	100	0	0	99	100	0	0	99	100	0	0
		Placebo	105	98	2	2	106	99	1	1	107	100	0	0	107	100	0	0	107	100	0	0	107	100	0	0
Anxiety	676	SSRI	162	98	3	2	160	97	5	3	155	94	10	6	117	71	48	29	165	100	0	0	154	93	11	7
		Placebo	153	98	3	2	154	99	2	1	138	88	18	12	106	68	50	32	156	100	0	0	143	92	13	8

Development program REME

Indication	TRIAL	Treatment category	TE agitation				TE hostility		History of insomnia				History of irritation				History of sui. attempt		History of sui. ideation			
			No		Yes		No		No		Yes		No		Yes		2		No		Yes	
			#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%
MDD	003-045	Atypical	169	99	1	1	170	100	64	38	106	62	8	5	162	95	170	100	135	79	35	21
		Placebo	88	99	1	1	89	100	38	43	51	57	5	6	84	94	89	100	73	82	16	18

Development program SERT

Indication	TRIAL	Treatment category	TE agitation				TE hostility		History of insomnia				History of irritation				History of sui. attempt				History of sui. ideation			
			No		Yes		No		No		Yes		No		Yes		No		2		No		Yes	
			#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%
MDD	A0501001	SSRI	96	99	1	1	97	100	34	35	63	65	1	1	96	99	0	0	97	100	69	71	28	29
		Placebo	91	100	0	0	91	100	40	44	51	56	2	2	89	98	0	0	91	100	73	80	18	20
	A0501017	SSRI	91	99	1	1	92	100	31	34	61	66	4	4	88	96	0	0	92	100	67	73	25	27
		Placebo	93	100	0	0	93	100	46	49	47	51	7	8	86	92	0	0	93	100	68	73	25	27
OCD	90CE21-0498	SSRI	92	100	0	0	92	100	81	88	11	12	92	100	0	0	92	100	0	0	92	100	0	0
		Placebo	95	100	0	0	95	100	85	89	10	11	95	100	0	0	95	100	0	0	95	100	0	0

Development program VENL

Indication	TRIAL	Treatment category	TE agitation				TE hostility				History of insomnia				History of irritation				History of sui. attempt		History of sui. ideation			
			No		Yes		No		Yes		No		Yes		No		Yes		No		No		Yes	
			#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%
MDD	382	Atypical	80	100	0	0	79	99	1	1	74	93	6	8	67	84	13	16	80	100	67	84	13	16
		Placebo	85	100	0	0	84	99	1	1	80	94	5	6	66	78	19	22	85	100	66	78	19	22
	394	Atypical	99	97	3	3	95	93	7	7	96	94	6	6	80	78	22	22	102	100	80	78	22	22
		Placebo	93	99	1	1	93	99	1	1	91	97	3	3	73	78	21	22	94	100	73	78	21	22
Anxiety	396	Atypical	77	96	3	4	80	100	0	0	80	100	0	0	72	90	8	10	80	100	72	90	8	10
		Placebo	83	99	1	1	84	100	0	0	84	100	0	0	82	98	2	2	84	100	82	98	2	2
	397	Atypical	74	96	3	4	74	96	3	4	77	100	0	0	77	100	0	0	77	100	77	100	0	0
		Placebo	78	99	1	1	79	100	0	0	79	100	0	0	76	96	3	4	79	100	76	96	3	4

16 APPENDIX IX: Exposure-time, discontinuation, and all outcomes by drug, indication, and trial

16.1 Percentages and rates of ORIGINAL suicidal events provided by sponsor in the initial datasets. Also, mean and 95% CI of exposure-time in days.

Program	Indicat.	Trial #	Tx Category	Subj.	Tx days Mean	Tx days stderr	LL 95%CI	UL 95%CI	Person Yrs	Sui. Rel.	%	Rate 1000 y	Atte mpt	%	Rate 1000 y
BUPR	ADHD	75	Atypical	72	26.8	0.7	25.5	28.0	5.3	0	0.00	0.0	0	0.00	0.00
			ZPlacebo	37	27.7	0.9	26.0	29.4	2.8	0	0.00	0.0	0	0.00	0.00
CITA	MDD	94404	SSRI	124	68.6	2.4	63.8	73.4	23.3	16	12.90	687.0	16	12.90	687.0
			ZPlacebo	120	67.5	2.6	62.5	72.6	22.2	9	7.50	405.1	9	7.50	405.1
		CIT_MD_18	SSRI	93	52.5	1.4	49.8	55.2	13.4	1	1.08	74.9	1	1.08	74.88
			ZPlacebo	85	51.4	1.4	48.6	54.1	12.0	2	2.35	167.3	1	1.18	83.64
FLUO	MDD	HCCJ	SSRI	21	36.6	2.4	31.8	41.4	2.1	1	4.76	475.0	1	4.76	475.0
			ZPlacebo	19	40.6	1.6	37.5	43.7	2.1	1	5.26	473.7	1	5.26	473.7
		HCJE	SSRI	109	59.0	1.0	57.0	61.0	17.6	4	3.67	227.0	1	0.92	56.76
			ZPlacebo	110	53.5	1.7	50.3	56.8	16.1	4	3.64	247.9	2	1.82	124.0
		X065	SSRI	48	51.0	1.7	47.7	54.4	6.7	2	4.17	298.2	2	4.17	298.2
			ZPlacebo	48	44.3	2.4	39.6	49.1	5.8	2	4.17	343.3	0	0.00	0.00
	OCD	HCJW	SSRI	71	77.8	3.1	71.8	83.8	15.1	2	2.82	132.3	2	2.82	132.3
			ZPlacebo	32	68.3	5.4	57.7	78.8	6.0	1	3.13	167.2	1	3.13	167.2
FLUV	OCD	RH_114_02_01	SSRI	57	60.1	2.5	55.1	65.0	9.4	1	1.75	106.7	0	0.00	0.00
			ZPlacebo	63	57.7	2.4	52.9	62.5	9.9	0	0.00	0.0	0	0.00	0.00
NEFA	MDD	CN104-141	Atypical	95	52.3	1.5	49.4	55.3	13.6	2	2.11	146.9	2	2.11	146.9
			ZPlacebo	95	47.9	1.8	44.5	51.4	12.5	0	0.00	0.0	0	0.00	0.00
		CN104-187	Atypical	184	50.5	1.2	48.2	52.8	25.4	1	0.54	39.3	1	0.54	39.32
			ZPlacebo	94	50.3	1.6	47.2	53.4	12.9	1	1.06	77.2	1	1.06	77.24
PARO	Anxiety	676	SSRI	165	111.8	3.0	105.9	117.7	50.5	4	2.42	79.2	1	0.61	19.80
			ZPlacebo	156	108.9	3.4	102.2	115.5	46.5	0	0.00	0.0	0	0.00	0.00
	MDD	329	Active control	95	48.8	1.9	45.0	52.6	12.7	3	3.16	236.3	1	1.05	78.77
			SSRI	93	49.2	1.9	45.5	53.0	12.5	8	8.60	638.5	5	5.38	399.1
			ZPlacebo	88	54.3	2.0	50.5	58.2	13.1	1	1.14	76.4	0	0.00	0.00
		377	SSRI	180	81.6	2.2	77.2	86.0	40.2	9	5.00	223.8	8	4.44	199.0

Percentages and rates of ORIGINAL suicidal events provided by sponsor in the initial datasets, continued…

Program	Indicat.	Trial #	Tx Category	Subj.	Tx days Mean	Tx days stderr	LL 95%CI	UL 95%CI	Person Yrs	Sui. Rel.	%	Rate 1000 y	Atte mpt	%	Rate 1000 y
PARO	MDD	377	Placebo	95	82.4	3.2	76.2	88.7	21.4	4	4.21	186.5	4	4.21	186.5
		701	SSRI	104	55.4	2.3	50.9	59.9	15.8	3	2.88	190.3	2	1.92	126.9
			Placebo	102	59.4	2.0	55.6	63.2	16.6	2	1.96	120.5	1	0.98	60.26
	OCD	453	SSRI	96	83.2	5.1	73.1	93.3	21.9	0	0.00	0.0	0	0.00	0.00
			Placebo	98	70.4	5.3	60.1	80.8	18.9	0	0.00	0.0	0	0.00	0.00
		704	SSRI	99	68.9	2.8	63.5	74.4	18.7	1	1.01	53.5	0	0.00	0.00
			Placebo	107	75.2	2.7	69.8	80.6	22.0	0	0.00	0.0	0	0.00	0.00
REME	MDD	003-045	Atypical	170	51.7	1.1	49.6	53.8	24.0	1	0.59	41.6	0	0.00	0.00
			Placebo	89	52.2	1.4	49.4	55.0	12.7	1	1.12	78.6	1	1.12	78.63
SERT	MDD	A0501001	SSRI	97	58.6	2.2	54.4	62.9	15.5	4	4.12	257.9	1	1.03	64.47
			Placebo	91	65.2	1.6	62.1	68.3	16.2	0	0.00	0.0	0	0.00	0.00
		A0501017	SSRI	92	66.0	1.4	63.3	68.6	16.5	2	2.17	121.4	2	2.17	121.4
			Placebo	93	64.0	1.7	60.5	67.4	16.3	2	2.15	123.0	2	2.15	123.0
	OCD	90CE21-0498	SSRI	92	74.8	2.3	70.3	79.3	18.9	0	0.00	0.0	0	0.00	0.00
			Placebo	95	75.9	2.3	71.3	80.5	19.7	1	1.05	50.7	0	0.00	0.00
VENL	Anxiety	396	Atypical	80	52.1	1.5	49.0	55.1	11.3	0	0.00	0.0	0	0.00	0.00
			Placebo	84	50.7	1.6	47.6	53.9	11.6	0	0.00	0.0	0	0.00	0.00
		397	Atypical	77	48.3	2.0	44.3	52.3	10.1	1	1.30	98.6	1	1.30	98.64
			Placebo	79	46.5	2.0	42.6	50.4	9.9	1	1.27	100.6	1	1.27	100.6
	MDD	382	Atypical	80	45.4	2.0	41.6	49.2	10.9	5	6.25	458.3	1	1.25	91.67
			Placebo	85	44.6	2.1	40.5	48.7	11.6	3	3.53	257.6	3	3.53	257.6
		394	Atypical	102	50.4	1.5	47.6	53.3	14.3	7	6.86	490.2	3	2.94	210.1
			Placebo	94	53.0	1.4	50.2	55.9	13.6	0	0.00	0.0	0	0.00	0.00

16.2 Percentages & rates of suicide behavior (outcome 1), suicide ideation (outcome 2), or both (outcome 3, the primary outcome)

Program	Indicat.	Trial #	Tx Category	Person Subj.	Person Yrs	Outc ome1	%	Rate 1000 y	Outco me2	%	Rate 1000 y	Outc ome3	%	Rate 1000 y
BUPR	ADHD	75	Atypical	72	5.3	0	0.00	0.0	0	0.00	0.0	0	0.00	0.00
			ZPlacebo	37	2.8	0	0.00	0.0	0	0.00	0.0	0	0.00	0.00
CITA	MDD	94404	SSRI	124	23.3	6	4.84	257.6	3	2.42	128.8	9	7.26	386.5
			ZPlacebo	120	22.2	2	1.67	90.0	3	2.50	135.0	5	4.17	225.0
		CIT_MD_18	SSRI	93	13.4	1	1.08	74.9	0	0.00	0.0	1	1.08	74.88
			ZPlacebo	85	12.0	1	1.18	83.6	1	1.18	83.6	2	2.35	167.3
FLUO	MDD	HCCJ	SSRI	21	2.1	0	0.00	0.0	0	0.00	0.0	0	0.00	0.00
			ZPlacebo	19	2.1	1	5.26	473.7	0	0.00	0.0	1	5.26	473.7
		HCJE	SSRI	109	17.6	0	0.00	0.0	6	5.50	340.5	6	5.50	340.5
			ZPlacebo	110	16.1	0	0.00	0.0	6	5.45	371.9	6	5.45	371.9
		X065	SSRI	48	6.7	2	4.17	298.2	0	0.00	0.0	2	4.17	298.2
			ZPlacebo	48	5.8	0	0.00	0.0	2	4.17	343.3	2	4.17	343.3
	OCD	HCJW	SSRI	71	15.1	1	1.41	66.1	0	0.00	0.0	1	1.41	66.14
			ZPlacebo	32	6.0	0	0.00	0.0	0	0.00	0.0	0	0.00	0.00
FLUV	OCD	RH_114_02_01	SSRI	57	9.4	0	0.00	0.0	2	3.51	213.3	2	3.51	213.3
			ZPlacebo	63	9.9	0	0.00	0.0	0	0.00	0.0	0	0.00	0.00
NEFA	MDD	CN104-141	Atypical	95	13.6	0	0.00	0.0	0	0.00	0.0	0	0.00	0.00
			ZPlacebo	95	12.5	0	0.00	0.0	0	0.00	0.0	0	0.00	0.00
		CN104-187	Atypical	184	25.4	0	0.00	0.0	0	0.00	0.0	0	0.00	0.00
			ZPlacebo	94	12.9	0	0.00	0.0	0	0.00	0.0	0	0.00	0.00
PARO	Anxiety	676	SSRI	165	50.5	0	0.00	0.0	3	1.82	59.4	3	1.82	59.40
			ZPlacebo	156	46.5	0	0.00	0.0	0	0.00	0.0	0	0.00	0.00
	MDD	329	Active control	95	12.7	1	1.05	78.8	1	1.05	78.8	2	2.11	157.5
			SSRI	93	12.5	2	2.15	159.6	2	2.15	159.6	4	4.30	319.3
			ZPlacebo	88	13.1	0	0.00	0.0	1	1.14	76.4	1	1.14	76.41
		377	SSRI	180	40.2	5	2.78	124.4	1	0.56	24.9	6	3.33	149.2
			ZPlacebo	95	21.4	2	2.11	93.3	0	0.00	0.0	2	2.11	93.27

Percentages & rates of suicide behavior (outcome 1), suicide ideation (outcome 2), or both (outcome 3), continued…

Program	Indicat.	Trial #	Tx Category	Person Subj.	Person Yrs	Outc ome1	%	Rate 1000 y	Outco me2	%	Rate 1000 y	Outc ome3	%	Rate 1000 y
PARO	MDD	701	SSRI	104	15.8	2	1.92	126.9	0	0.00	0.0	2	1.92	126.9
			Placebo	102	16.6	0	0.00	0.0	1	0.98	60.3	1	0.98	60.26
	OCD	453	SSRI	96	21.9	0	0.00	0.0	0	0.00	0.0	0	0.00	0.00
			Placebo	98	18.9	0	0.00	0.0	0	0.00	0.0	0	0.00	0.00
		704	SSRI	99	18.7	0	0.00	0.0	1	1.01	53.5	1	1.01	53.51
			Placebo	107	22.0	0	0.00	0.0	0	0.00	0.0	0	0.00	0.00
REME	MDD	003-045	Atypical	170	24.0	0	0.00	0.0	1	0.59	41.6	1	0.59	41.58
			Placebo	89	12.7	0	0.00	0.0	0	0.00	0.0	0	0.00	0.00
SERT	MDD	A0501001	SSRI	97	15.5	1	1.03	64.5	2	2.06	128.9	3	3.09	193.4
			Placebo	91	16.2	0	0.00	0.0	0	0.00	0.0	0	0.00	0.00
		A0501017	SSRI	92	16.5	1	1.09	60.7	1	1.09	60.7	2	2.17	121.4
			Placebo	93	16.3	2	2.15	123.0	0	0.00	0.0	2	2.15	123.0
	OCD	90CE21-0498	SSRI	92	18.9	0	0.00	0.0	0	0.00	0.0	0	0.00	0.00
			Placebo	95	19.7	0	0.00	0.0	1	1.05	50.7	1	1.05	50.74
VENL	Anxiety	396	Atypical	80	11.3	0	0.00	0.0	0	0.00	0.0	0	0.00	0.00
			Placebo	84	11.6	0	0.00	0.0	0	0.00	0.0	0	0.00	0.00
		397	Atypical	77	10.1	1	1.30	98.6	0	0.00	0.0	1	1.30	98.64
			Placebo	79	9.9	1	1.27	100.6	0	0.00	0.0	1	1.27	100.6
	MDD	382	Atypical	80	10.9	0	0.00	0.0	3	3.75	275.0	3	3.75	275.0
			Placebo	85	11.6	0	0.00	0.0	0	0.00	0.0	0	0.00	0.00
		394	Atypical	102	14.3	1	0.98	70.0	4	3.92	280.1	5	4.90	350.1
			Placebo	94	13.6	0	0.00	0.0	0	0.00	0.0	0	0.00	0.00

16.3 Percentages & rates of possible suicidal behavior or ideation (outcome 4) and self injury (outcome 5)

Program	Indicat.	Trial #	Tx Category	Person Subj.	Yrs	Outc ome4	%	Rate 1000 y	Outc ome5	%	Rate 1000 y
BUPR	ADHD	75	Atypical	72	5.3	0	0.00	0.0	0	0.00	0.00
			ZPlacebo	37	2.8	1	2.70	356.3	0	0.00	0.00
CITA	MDD	94404	SSRI	124	23.3	14	11.29	601.2	2	1.61	85.88
			ZPlacebo	120	22.2	6	5.00	270.0	2	1.67	90.01
		CIT_MD_18	SSRI	93	13.4	1	1.08	74.9	0	0.00	0.00
			ZPlacebo	85	12.0	2	2.35	167.3	0	0.00	0.00
FLUO	MDD	HCCJ	SSRI	21	2.1	1	4.76	475.0	0	0.00	0.00
			ZPlacebo	19	2.1	1	5.26	473.7	0	0.00	0.00
		HCJE	SSRI	109	17.6	8	7.34	454.1	0	0.00	0.00
			ZPlacebo	110	16.1	6	5.45	371.9	0	0.00	0.00
		X065	SSRI	48	6.7	2	4.17	298.2	0	0.00	0.00
			ZPlacebo	48	5.8	2	4.17	343.3	0	0.00	0.00
	OCD	HCJW	SSRI	71	15.1	2	2.82	132.3	0	0.00	0.00
			ZPlacebo	32	6.0	1	3.13	167.2	0	0.00	0.00
FLUV	OCD	RH_114_02_01	SSRI	57	9.4	2	3.51	213.3	0	0.00	0.00
			ZPlacebo	63	9.9	0	0.00	0.0	0	0.00	0.00
NEFA	MDD	CN104-141	Atypical	95	13.6	1	1.05	73.5	1	1.05	73.46
			ZPlacebo	95	12.5	0	0.00	0.0	0	0.00	0.00
		CN104-187	Atypical	184	25.4	0	0.00	0.0	0	0.00	0.00
			ZPlacebo	94	12.9	0	0.00	0.0	0	0.00	0.00
PARO	Anxiety	676	SSRI	165	50.5	5	3.03	99.0	1	0.61	19.80
			ZPlacebo	156	46.5	0	0.00	0.0	0	0.00	0.00
	MDD	329	Active control	95	12.7	3	3.16	236.3	0	0.00	0.00
			SSRI	93	12.5	7	7.53	558.7	1	1.08	79.82
			ZPlacebo	88	13.1	1	1.14	76.4	0	0.00	0.00
		377	SSRI	180	40.2	7	3.89	174.1	2	1.11	49.74
			ZPlacebo	95	21.4	3	3.16	139.9	0	0.00	0.00

Percentages & rates of possible suicidal behavior or ideation (outcome 4) and self injury (outcome 5), continued…

Program	Indicat.	Trial #	Tx Category	Subj.	Person Yrs	Outcome4	%	Rate 1000 y	Outcome5	%	Rate 1000 y
PARO	MDD	701	SSRI	104	15.8	3	2.88	190.3	0	0.00	0.00
			Placebo	102	16.6	1	0.98	60.3	1	0.98	60.26
	OCD	453	SSRI	96	21.9	0	0.00	0.0	0	0.00	0.00
			Placebo	98	18.9	0	0.00	0.0	0	0.00	0.00
		704	SSRI	99	18.7	2	2.02	107.0	0	0.00	0.00
			Placebo	107	22.0	0	0.00	0.0	0	0.00	0.00
REME	MDD	003-045	Atypical	170	24.0	2	1.18	83.2	0	0.00	0.00
			Placebo	89	12.7	1	1.12	78.6	0	0.00	0.00
SERT	MDD	A0501001	SSRI	97	15.5	4	4.12	257.9	0	0.00	0.00
			Placebo	91	16.2	0	0.00	0.0	0	0.00	0.00
		A0501017	SSRI	92	16.5	2	2.17	121.4	0	0.00	0.00
			Placebo	93	16.3	2	2.15	123.0	0	0.00	0.00
	OCD	90CE21-0498	SSRI	92	18.9	0	0.00	0.0	0	0.00	0.00
			Placebo	95	19.7	1	1.05	50.7	0	0.00	0.00
VENL	Anxiety	396	Atypical	80	11.3	0	0.00	0.0	0	0.00	0.00
			Placebo	84	11.6	0	0.00	0.0	0	0.00	0.00
		397	Atypical	77	10.1	1	1.30	98.6	0	0.00	0.00
			Placebo	79	9.9	1	1.27	100.6	0	0.00	0.00
	MDD	382	Atypical	80	10.9	5	6.25	458.3	0	0.00	0.00
			Placebo	85	11.6	1	1.18	85.9	0	0.00	0.00
		394	Atypical	102	14.3	7	6.86	490.2	1	0.98	70.03
			Placebo	94	13.6	0	0.00	0.0	0	0.00	0.00

16.4 Percentages & rates of discontinuation, emergence of suicidality (outcome 7), and worsening of suicidality score (outcome 6)

Program	Indicat.	Trial #	Tx Category	Person Subj.	Person Yrs	Disc cont	Disc %	Outc ome6	Outc %	Rate 1000 y	Outco me7	Outco %	Rate 1000 y
BUPR	ADHD	75	Atypical	72	5.3	9	12.50	0	0.00	0.00	0	0.00	0.0
			ZPlacebo	37	2.8	3	8.11	0	0.00	0.00	0	0.00	0.0
CITA	MDD	94404	SSRI	124	23.3	45	36.29	10	8.06	429.4	6	4.84	257.6
			ZPlacebo	120	22.2	46	38.33	18	15.00	810.1	14	11.67	630.1
		CIT_MD_18	SSRI	93	13.4	22	23.66	5	5.38	374.4	5	5.38	374.4
			ZPlacebo	85	12.0	18	21.18	12	14.12	1004	11	12.94	920.0
FLUO	MDD	HCCJ	SSRI	21	2.1	6	28.57	4	19.05	1900	4	19.05	1900
			ZPlacebo	19	2.1	4	21.05	4	21.05	1895	4	21.05	1895
		HCJE	SSRI	109	17.6	60	55.05	19	17.43	1078	17	15.60	964.9
			ZPlacebo	110	16.1	63	57.27	24	21.82	1488	22	20.00	1364
		X065	SSRI	48	6.7	15	31.25	12	25.00	1789	10	20.83	1491
			ZPlacebo	48	5.8	23	47.92	15	31.25	2575	14	29.17	2403
	OCD	HCJW	SSRI	71	15.1	22	30.99	3	4.23	198.4	2	2.82	132.3
			ZPlacebo	32	6.0	12	37.50	1	3.13	167.2	1	3.13	167.2
FLUV	OCD	RH_114_02_01	SSRI	57	9.4	19	33.33	0	0.00	0.00	0	0.00	0.0
			ZPlacebo	63	9.9	27	42.86	0	0.00	0.00	0	0.00	0.0
NEFA	MDD	CN104-141	Atypical	95	13.6	23	24.21	8	8.42	587.7	8	8.42	587.7
			ZPlacebo	95	12.5	35	36.84	10	10.53	802.6	10	10.53	802.6
		CN104-187	Atypical	184	25.4	34	18.48	21	11.41	825.8	20	10.87	786.5
			ZPlacebo	94	12.9	22	23.40	8	8.51	617.9	8	8.51	617.9
PARO	Anxiety	676	SSRI	165	50.5	42	25.45	3	1.82	59.40	2	1.21	39.6
			ZPlacebo	156	46.5	53	33.97	2	1.28	43.01	0	0.00	0.0
	MDD	329	Active control	95	12.7	42	44.21	23	24.21	1812	11	11.58	866.5
			SSRI	93	12.5	29	31.18	24	25.81	1916	19	20.43	1517
			ZPlacebo	88	13.1	30	34.09	20	22.73	1528	9	10.23	687.7
		377	SSRI	180	40.2	54	30.00	15	8.33	373.1	8	4.44	199.0
			ZPlacebo	95	21.4	26	27.37	12	12.63	559.6	6	6.32	279.8

Percentages & rates of discontinuation, emergence of suicidality (outcome 7), and worsening of suicidality score (outcome 6), continued…

Program	Indicat.	Trial #	Tx Category	Person Subj.	Person Yrs	Disc cont	Disc %	Outc ome6	Outc ome6 %	Rate 1000 y	Outco me7	Outco me7 %	Rate 1000 y
PARO	MDD	701	SSRI	104	15.8	34	32.69	15	14.42	951.5	4	3.85	253.7
			Placebo	102	16.6	23	22.55	8	7.84	482.1	1	0.98	60.3
	OCD	453	SSRI	96	21.9	54	56.25	9	9.38	411.4	9	9.38	411.4
			Placebo	98	18.9	65	66.33	14	14.29	740.7	14	14.29	740.7
		704	SSRI	99	18.7	34	34.34	0	0.00	0.00	0	0.00	0.0
			Placebo	107	22.0	27	25.23	0	0.00	0.00	0	0.00	0.0
REME	MDD	003-045	Atypical	170	24.0	32	18.82	18	10.59	748.5	17	10.00	706.9
			Placebo	89	12.7	18	20.22	11	12.36	864.9	11	12.36	864.9
SERT	MDD	A0501001	SSRI	97	15.5	32	32.99	10	10.31	644.7	10	10.31	644.7
			Placebo	91	16.2	14	15.38	9	9.89	554.2	9	9.89	554.2
		A0501017	SSRI	92	16.5	14	15.22	12	13.04	728.6	11	11.96	667.9
			Placebo	93	16.3	14	15.05	13	13.98	799.5	12	12.90	738.0
	OCD	90CE21-0498	SSRI	92	18.9	18	19.57	0	0.00	0.00	0	0.00	0.0
			Placebo	95	19.7	13	13.68	0	0.00	0.00	0	0.00	0.0
VENL	Anxiety	396	Atypical	80	11.3	18	22.50	0	0.00	0.00	0	0.00	0.0
			Placebo	84	11.6	16	19.05	0	0.00	0.00	0	0.00	0.0
		397	Atypical	77	10.1	19	24.68	0	0.00	0.00	0	0.00	0.0
			Placebo	79	9.9	25	31.65	0	0.00	0.00	0	0.00	0.0
	MDD	382	Atypical	80	10.9	31	38.75	13	16.25	1192	12	15.00	1100
			Placebo	85	11.6	31	36.47	7	8.24	601.0	7	8.24	601.0
		394	Atypical	102	14.3	28	27.45	10	9.80	700.3	10	9.80	700.3
			Placebo	94	13.6	17	18.09	12	12.77	883.5	11	11.70	809.9

17 APPENDIX X: Relationship between sponsors and expert panel assessment of AE's

17.1 Overall relationship between original events provided by sponsors (suievent) and Columbia University expert panel's classification (final)

FINAL SUIEVENT(OLD-Suicide-related event)

Frequency	No	Yes	Total
no event	4418	17	4435
suicide attempt, code 1	1	26	27
preparatory actions, code 2	0	6	6
injury/int unkn, code 3	4	20	24
injury, code 4	1	1	2
injury, code 5	0	5	5
suicidal ideation, code 6	10	35	45
not enough information, code 10	7	0	7
injury, code 11	1	3	4
Total	4442	113	4555

FINAL SUIATT(OLD-Suicide attempt)

Frequency	No	Yes	Total
no event	4423	12	4435
suicide attempt, code 1	1	26	27
preparatory actions, code 2	2	4	6
injury/int unkn, code 3	5	19	24
injury, code 4	1	1	2
injury, code 5	0	5	5
suicidal ideation, code 6	37	8	45
not enough information, code 10	7	0	7
injury, code 11	1	3	4
Total	4477	78	4555

17.2 Overall relationship between outcomes 6 (suithres) & 7 (suiworse) and Columbia University classification (final)

FINAL SUITHRES(Emergence of sui.)

Frequency	No	Yes	Total
no event	4117	318	4435
suicide attempt, code 1	23	4	27
preparatory acti ons, code 2	3	3	6
injury/int unkn, code 3	21	3	24
injury, code 4	2	0	2
injury, code 5	3	2	5
suicidal ideatio n, code 6	29	16	45
not enough infor mation, code 10	6	1	7
injury, code 11	2	2	4
Total	4206	349	4555

FINAL SUIWORSE(Worsening of sui.score)

Frequency	No	Yes	Total
no event	4044	391	4435
suicide attempt, code 1	16	11	27
preparatory acti ons, code 2	1	5	6
injury/int unkn, code 3	20	4	24
injury, code 4	2	0	2
injury, code 5	3	2	5
suicidal ideatio n, code 6	27	18	45
not enough infor mation, code 10	6	1	7
injury, code 11	2	2	4
Total	4121	434	4555

17.3 Relationship between the primary outcome (outcome 3) and outcome 6 by drug, trial, and indication

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Development program CITA
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Development program FLUO
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,                  , Worsening of  ,
,                  ,   sui.score   ,
,                  ‡fffffff…fffffff‰
,                  ,  No   ,  Yes  ,
,                  ‡fff…fff^fff…fff‰
,                  , # , % , # , % ,
‡fffff…fffff…ffffff^fff^fff^fff^fff‰
,Indi-,TRIAL,Suici-,   ,   ,   ,   ,
,cati-,     ,dal   ,   ,   ,   ,   ,
,on   ,     ,behav-,   ,   ,   ,   ,
‡fffff^fffff‰ior or,   ,   ,   ,   ,
,MDD  ,HCCJ ,ideat-,   ,   ,   ,   ,
,     ,     ‡ffffff‰   ,   ,   ,   ,
,     ,     ,No    , 32, 82,  7, 18,
,     ,     ‡ffffff^fff^fff^fff^fff‰
,     ,     ,Yes   ,  0,  0,  1,100,
,     ‡fffff^ffffff^fff^fff^fff^fff‰
,     ,HCJE ,No    ,173, 84, 34, 16,
,     ,     ‡ffffff^fff^fff^fff^fff‰
,     ,     ,Yes   ,  3, 25,  9, 75,
,     ‡fffff^ffffff^fff^fff^fff^fff‰
,     ,X065 ,No    , 65, 71, 27, 29,
,     ,     ‡ffffff^fff^fff^fff^fff‰
,     ,     ,Yes   ,  4,100,  0,  0,
‡fffff^fffff^ffffff^fff^fff^fff^fff‰
,OCD  ,HCJW ,No    , 99, 97,  3,  3,
,     ,     ‡ffffff^fff^fff^fff^fff‰
,     ,     ,Yes   ,  0,  0,  1,100,
Šfffff‹fffff‹ffffff‹fff‹fff‹fff‹fffŒ
Development program PARO
„ffffffffffffffff…ffffffffffffff†
,                  , Worsening of  ,
```

```
 ,                  ,   sui.score   ,
 ,                  ‡fffffff…fffffff‰
 ,                  ,  No   ,  Yes  ,
 ,                  ‡fff…fff^fff…fff‰
 ,                  , # , % , # , % ,
 ‡fffff…fffff…ffffff^fff^fff^fff^fff‰
 ,Indi-,TRIAL,Suici-,   ,   ,   ,   ,
 ,cati-,     ,dal   ,   ,   ,   ,   ,
 ,on   ,     ,behav-,   ,   ,   ,   ,
 ‡fffff^fffff‰ior or,   ,   ,   ,   ,
 ,MDD  ,329  ,ideat-,   ,   ,   ,   ,
 ,     ,     ,ion   ,   ,   ,   ,   ,
 ,     ,     ‡ffffff‰   ,   ,   ,   ,
 ,     ,     ,No    ,206, 77, 63, 23,
 ,     ,     ‡fffffff^fff^fff^fff^fff‰
 ,     ,     ,Yes   ,  3, 43,  4, 57,
 ,     ‡fffff^ffffff^fff^fff^fff^fff‰
 ,     ,377  ,No    ,243, 91, 24,  9,
 ,     ,     ‡fffffff^fff^fff^fff^fff‰
 ,     ,     ,Yes   ,  5, 63,  3, 38,
 ,     ‡fffff^ffffff^fff^fff^fff^fff‰
 ,     ,701  ,No    ,181, 89, 22, 11,
 ,     ,     ‡fffffff^fff^fff^fff^fff‰
 ,     ,     ,Yes   ,  2, 67,  1, 33,
 ‡fffff^fffff^ffffff^fff^fff^fff^fff‰
 ,OCD  ,453  ,No    ,171, 88, 23, 12,
 ,     ‡fffff^ffffff^fff^fff^fff^fff‰
 ,     ,704  ,No    ,205,100,  0,  0,
 ,     ,     ‡fffffff^fff^fff^fff^fff‰
 ,     ,     ,Yes   ,  1,100,  0,  0,
 ‡fffff^fffff^ffffff^fff^fff^fff^fff‰
 ,Anxi-,676  ,No    ,313, 98,  5,  2,
 ,ety  ,     ‡fffffff^fff^fff^fff^fff‰
 ,     ,     ,Yes   ,  3,100,  0,  0,
 Šfffff‹fffff‹ffffff‹fff‹fff‹fff‹fffŒ
Development program REME
 „fffffffffffffffff…ffffffffffffff†
 ,                  , Worsening of  ,
 ,                  ,   sui.score   ,
 ,                  ‡fffffff…fffffff‰
 ,                  ,  No   ,  Yes  ,
 ,                  ‡fff…fff^fff…fff‰
 ,                  , # , % , # , % ,
 ‡fffff…fffff…ffffff^fff^fff^fff^fff‰
 ,Indi-,TRIAL,Suici-,   ,   ,   ,   ,
 ,cati-,     ,dal   ,   ,   ,   ,   ,
 ,on   ,     ,behav-,   ,   ,   ,   ,
 ‡fffff^fffff‰ior or,   ,   ,   ,   ,
 ,MDD  ,045  ,ideat-,   ,   ,   ,   ,
 ,     ,     ‡ffffff‰   ,   ,   ,   ,
 ,     ,     ,No    ,230, 89, 28, 11,
 ,     ,     ‡fffffff^fff^fff^fff^fff‰
 ,     ,     ,Yes   ,  0,  0,  1,100,
 Šfffff‹fffff‹ffffff‹fff‹fff‹fff‹fffŒ
Development program SERT
 „fffffffffffffffff…ffffffffffffff†
 ,                  , Worsening of  ,
 ,                  ,   sui.score   ,
 ,                  ‡fffffff…fffffff‰
 ,                  ,  No   ,  Yes  ,
 ,                  ‡fff…fff^fff…fff‰
```

```
,                  , # , % , # , % ,
‡fffff…fffff…ffffff^fff^fff^fff^fff‰
,Indi-,TRIAL,Suici-,   ,   ,   ,   ,
,cati-,     ,dal   ,   ,   ,   ,   ,
,on   ,     ,behav-,   ,   ,   ,   ,
‡fffff^fffff‰ior or,   ,   ,   ,   ,
,MDD  ,A050-,ideat-,   ,   ,   ,   ,
,     ,1001 ,ion   ,   ,   ,   ,   ,
,     ,     ‡ffffff‰   ,   ,   ,   ,
,     ,     ,No    ,168, 91, 17,  9,
,     ,     ‡ffffff^fff^fff^fff^fff‰
,     ,     ,Yes   ,  1, 33,  2, 67,
,     ‡fffff^ffffff^fff^fff^fff^fff‰
,     ,A050-,No    ,158, 87, 23, 13,
,     ,1017 ‡ffffff^fff^fff^fff^fff‰
,     ,     ,Yes   ,  2, 50,  2, 50,
‡fffff^fffff^ffffff^fff^fff^fff^fff‰
,OCD  ,90CE-,No    ,186,100,  0,  0,
,     ,21-  ‡ffffff^fff^fff^fff^fff‰
,     ,0498 ,Yes   ,  1,100,  0,  0,
Šfffff‹fffff‹ffffff‹fff‹fff‹fff‹fffŒ
```

```
Development program VENL
„ffffffffffffffff…ffffffffffffff†
,                  , Worsening of  ,
,                  ,   sui.score   ,
,                  ‡fffffff…fffffff‰
,                  ,  No   ,  Yes  ,
,                  ‡fff…fff^fff…fff‰
,                  , # , % , # , % ,
‡fffff…fffff…ffffff^fff^fff^fff^fff‰
,Indi-,TRIAL,Suici-,   ,   ,   ,   ,
,cati-,     ,dal   ,   ,   ,   ,   ,
,on   ,     ,behav-,   ,   ,   ,   ,
‡fffff^fffff‰ior or,   ,   ,   ,   ,
,MDD  ,382  ,ideat-,   ,   ,   ,   ,
,     ,     ‡ffffff‰   ,   ,   ,   ,
,     ,     ,No    ,144, 89, 18, 11,
,     ,     ‡ffffff^fff^fff^fff^fff‰
,     ,     ,Yes   ,  1, 33,  2, 67,
,     ‡fffff^ffffff^fff^fff^fff^fff‰
,     ,394  ,No    ,170, 89, 21, 11,
,     ,     ‡ffffff^fff^fff^fff^fff‰
,     ,     ,Yes   ,  4, 80,  1, 20,
‡fffff^fffff^ffffff^fff^fff^fff^fff‰
,Anxi-,396  ,No    ,164,100,  0,  0,
,ety  ‡fffff^ffffff^fff^fff^fff^fff‰
,     ,397  ,No    ,154,100,  0,  0,
,     ,     ‡ffffff^fff^fff^fff^fff‰
,     ,     ,Yes   ,  2,100,  0,  0,
Šfffff‹fffff‹ffffff‹fff‹fff‹fff‹fffŒ
```

17.4 Listing of patients (n=26) with a discrepancy between sponsors' and expert panel's classifications during the double-blind (phase 1).

Drug	Trial	Old * classification	New $ classification	Unique ID
BUPR	75	0	10	75_18
CITA	94404	0	10	94404864
CITA	94404	0	11	94404841
FLUO	HCJE	0	6	HCJE1605
FLUO	HCJE	0	6	HCJE1652
FLUO	HCJE	0	6	HCJE2207
FLUO	HCJE	0	6	HCJE2210
FLUO	HCJE	0	6	HCJE2212
FLUO	HCJE	0	6	HCJE2214
FLUO	HCJE	0	6	HCJE2220
FLUO	HCJE	0	10	HCJE0133
FLUO	HCJE	0	10	HCJE1217
FLUV	RH_114_02_01	0	6	RH_114_02_0165265
PARO	329	0	3	329.006.00039
PARO	329	0	6	329.003.00089
PARO	329	1	8	329.001.00065
PARO	377	0	3	377.042.00554
PARO	377	0	6	377.040.00298
PARO	676	0	4	676.100.24708
PARO	676	0	10	676.209.24966
PARO	701	0	1	701.185.25965
PARO	701	0	3	701.192.25869
PARO	704	0	10	704.016.27018
REME	003-045	0	3	003-0450801
VENL	382	1	8	38202036
VENL	394	0	10	39400447

* Old classification based on sponsors submission: 1=suicide-related event, 0=no event.
$ New classification based on Columbia expert panel's classification codes
The two highlighted events are not included in the analysis because of their code

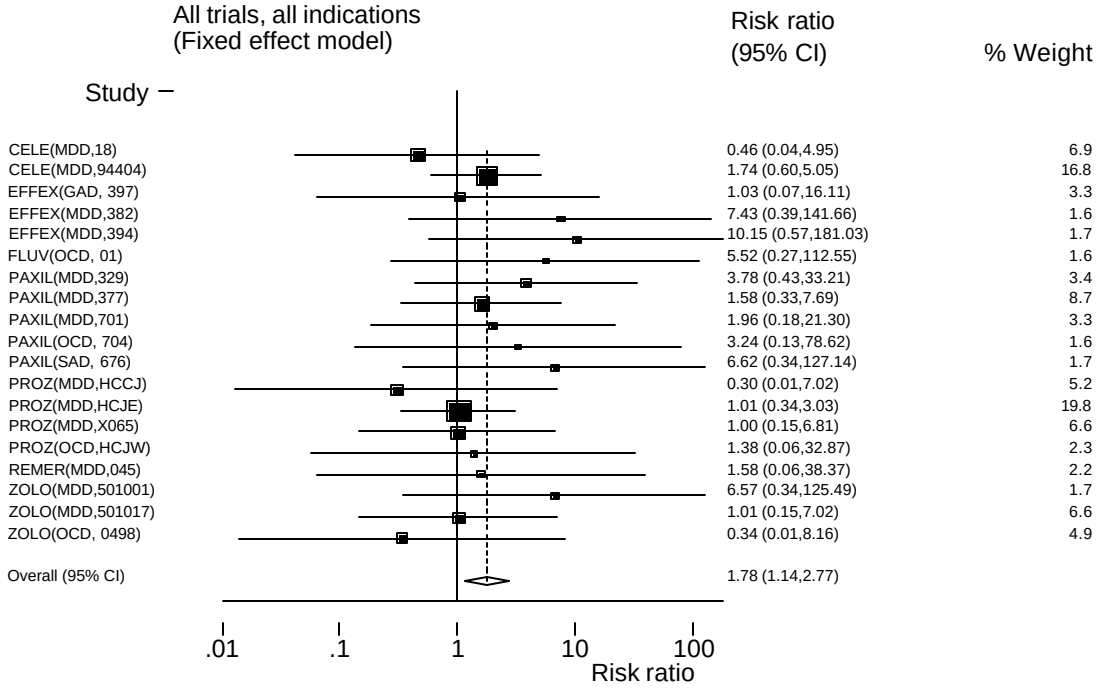
17.5 Listing of patients (n=20) with a discrepancy between sponsors' and expert panel's classifications after the double-blind (phases 2 to 6).

Drug	Trial	Old * classification	New $ classification	Unique ID
CITA	94404	1	1	94404007
CITA	94404	1	1	94404121
CITA	94404	1	6	94404152
FLUO	HCJE	0	6	HCJE1510
FLUO	HCJE	1	1	HCJE0804
FLUO	HCJE	1	5	HCJE0901
FLUO	HCJE	1	6	HCJE0419
FLUV	RH_114_02_01	0	5	RH_114_02_0166069
FLUV	RH_114_02_01	0	6	RH_114_02_0165855
NEFA	CN104-187	0	6	104187-18-231
NEFA	CN104-187	1	1	104187-18-322
NEFA	CN104-187	1	6	104187-17-405
PARO	329	1	6	329.002.00106
PARO	377	1	1	377.041.00294
PARO	377	1	3	377.042.00315
PARO	377	1	6	377.049.00479
PARO	701	0	2	701.185.25963
PARO	701	1	1	701.180.25639
PARO	701	1	6	701.183.27620
VENL	382	1	6	38207008

* Old classification based on sponsors submission: 1=suicide-related event, 0=no event.
$ New classification based on Columbia expert panel's classification codes

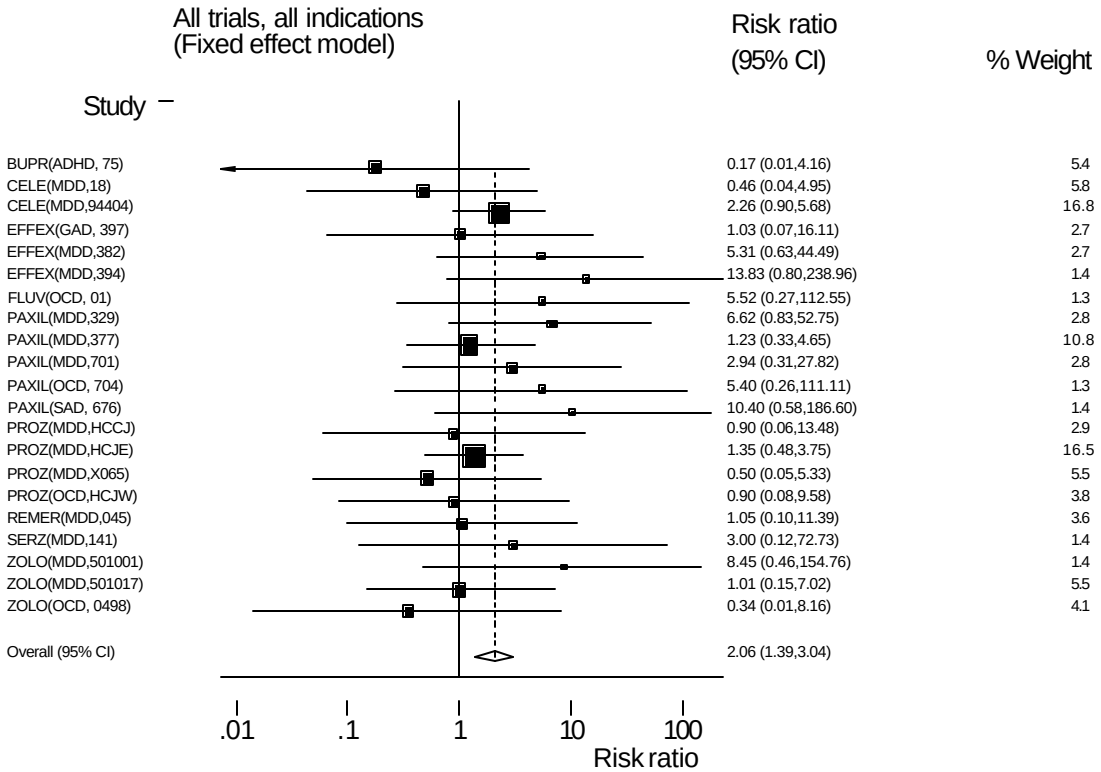
18 APPENDIX XI: RRs and 95% CI for various outcomes overall and by indication

18.1 The primary outcome (outcome 3), all trials, all indications

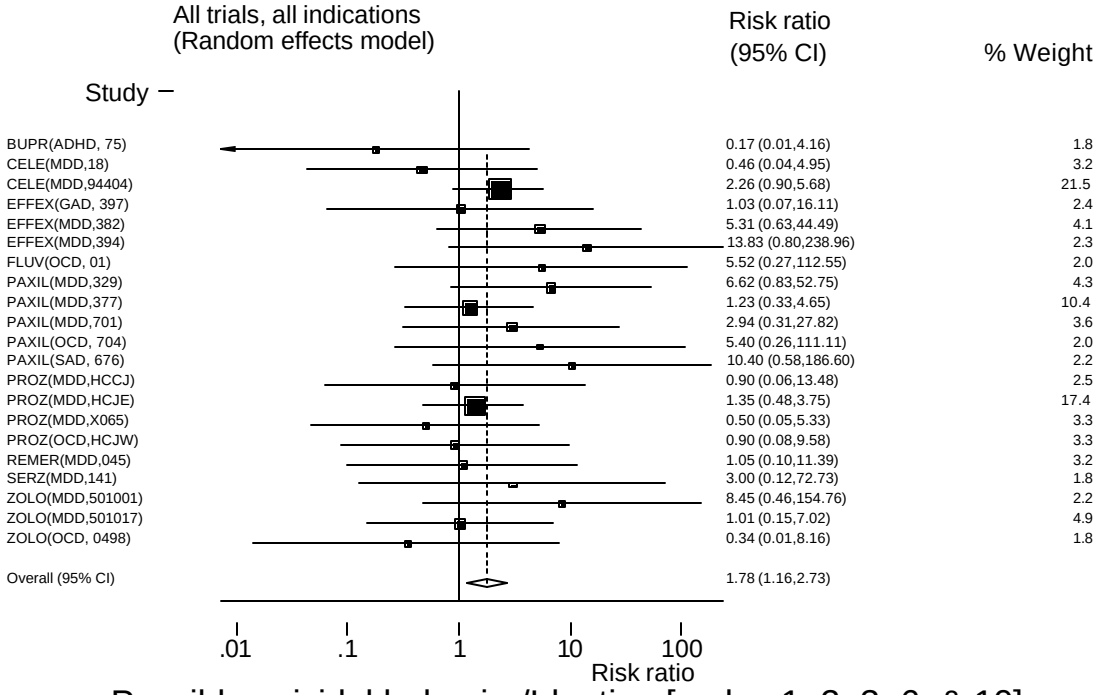


Suicide Behavior or Ideation [codes 1, 2, & 6]

18.2 Outcome 4, all trials, all indications

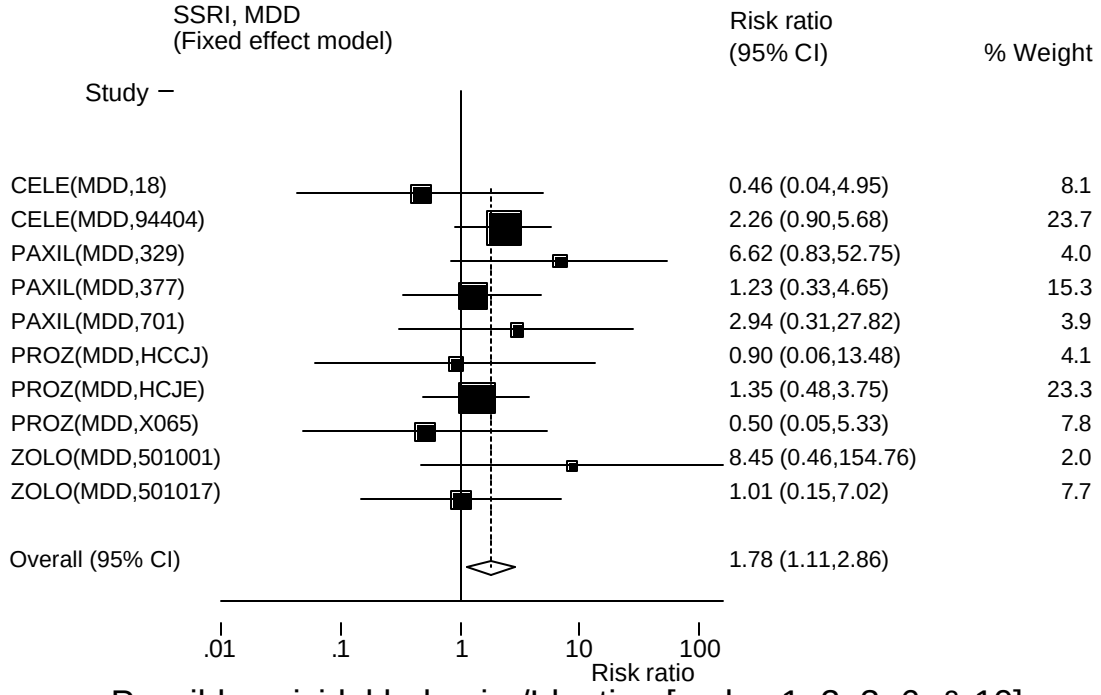


Possible suicidal behavior/Ideation [codes 1, 2, 3, 6, & 10]

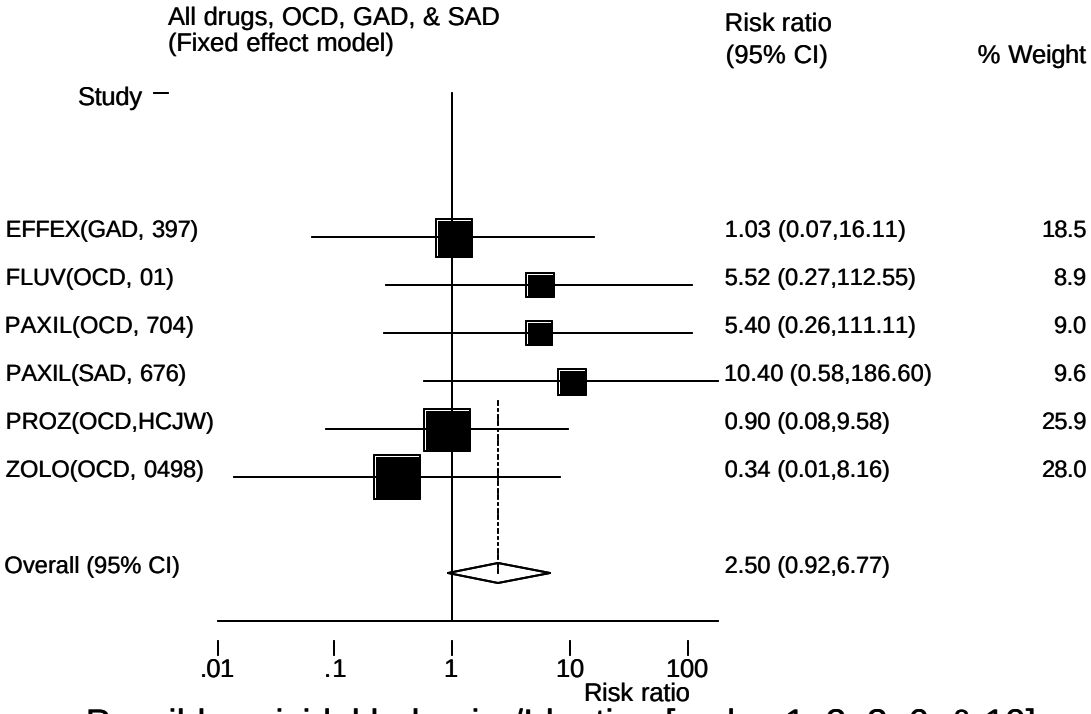


Possible suicidal behavior/Ideation [codes 1, 2, 3, 6, & 10]

18.3 Outcome 4, by indication

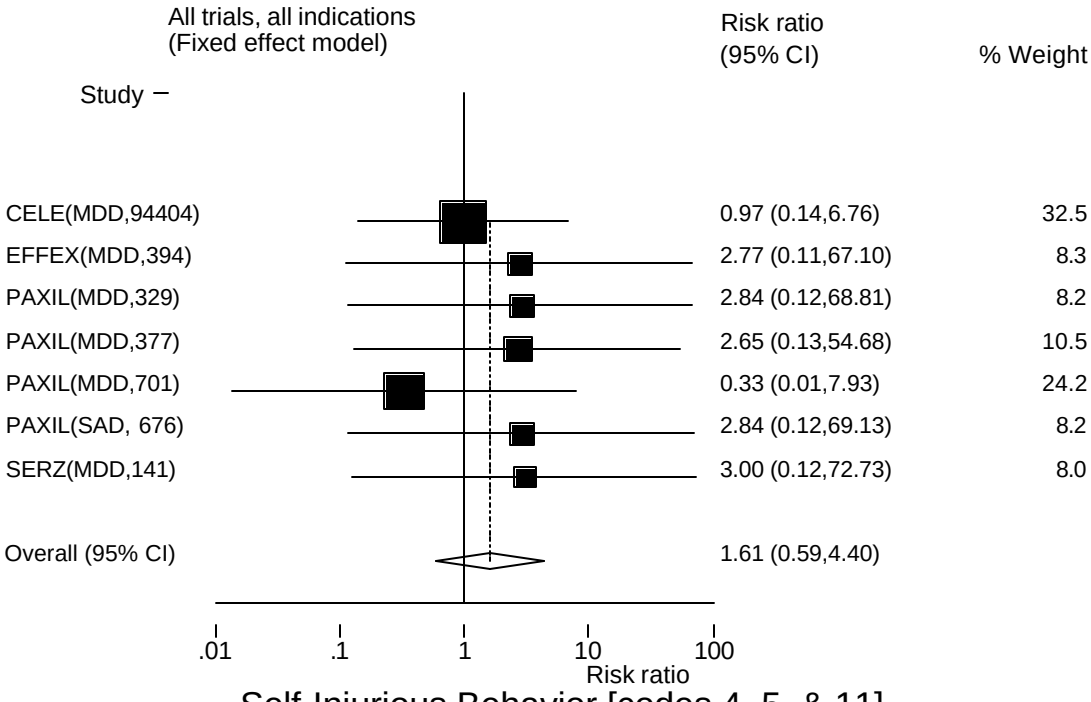


Possible suicidal behavior/Ideation [codes 1, 2, 3, 6, & 10]



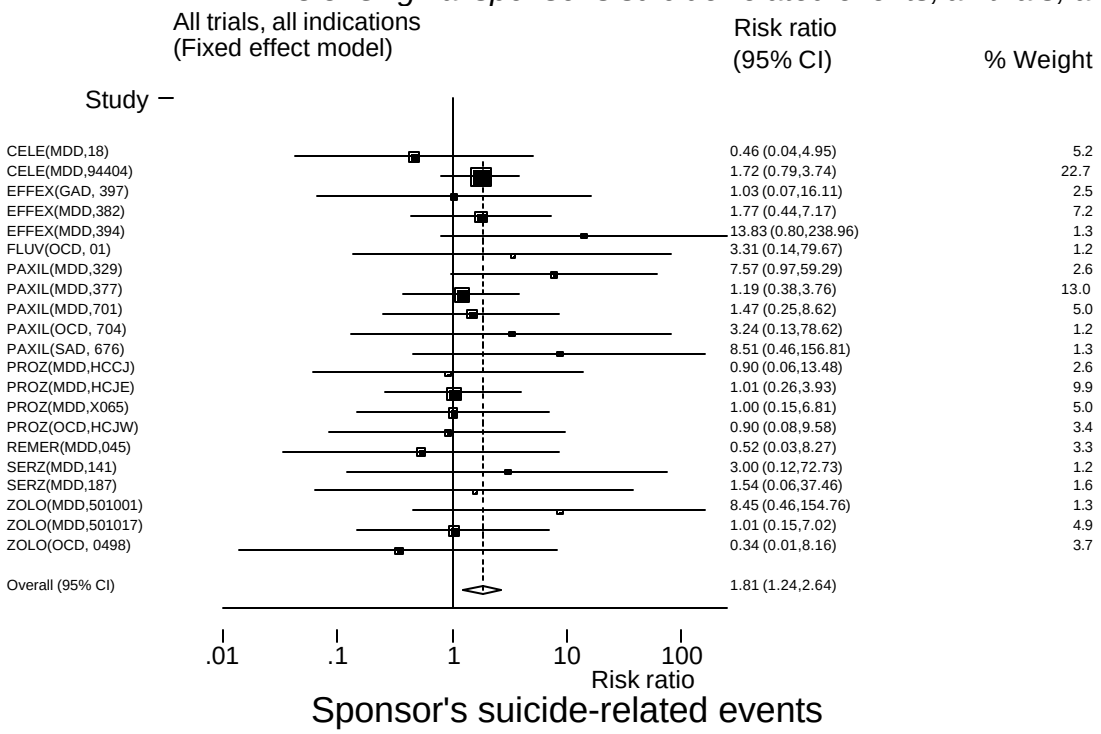
Possible suicidal behavior/Ideation [codes 1, 2, 3, 6, & 10]

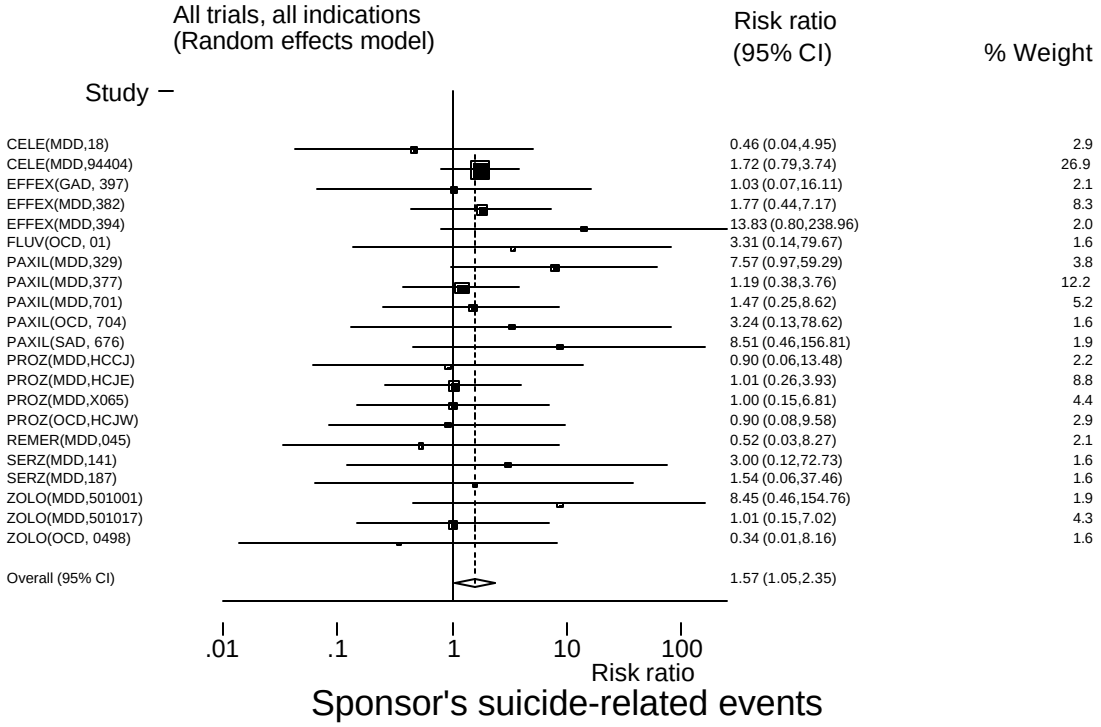
18.4 Outcome 5, all trials, all indications



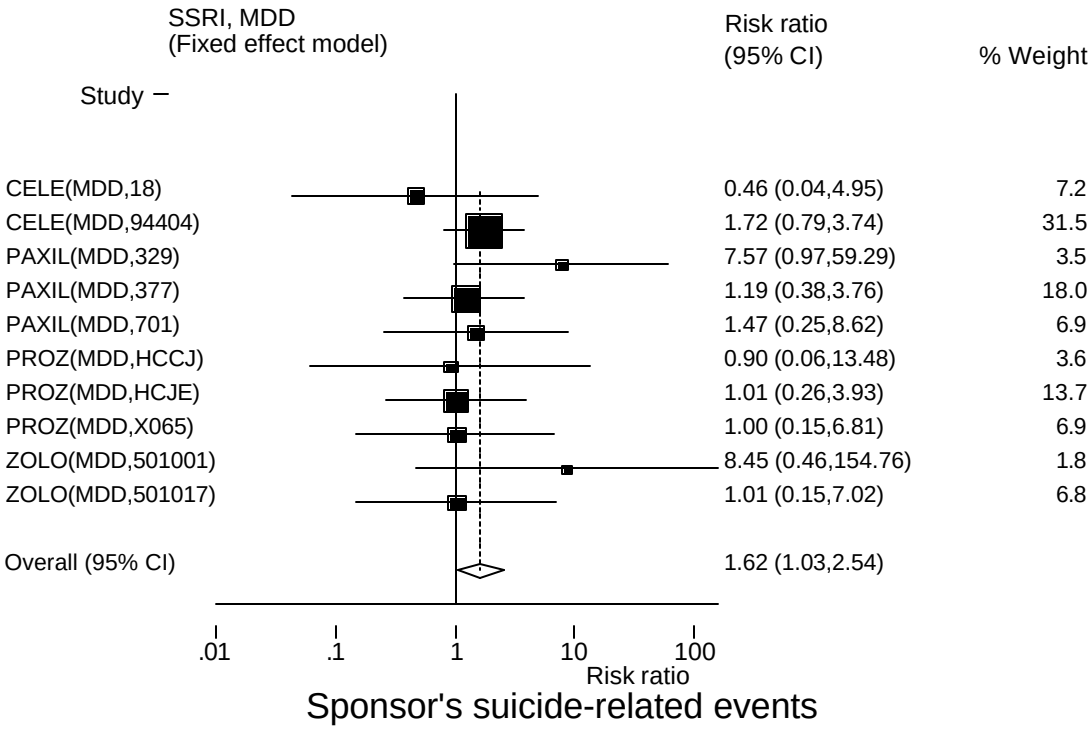
Self-Injurious Behavior [codes 4, 5, & 11]

18.5 Original sponsor's suicide-related events, all trials, all indications

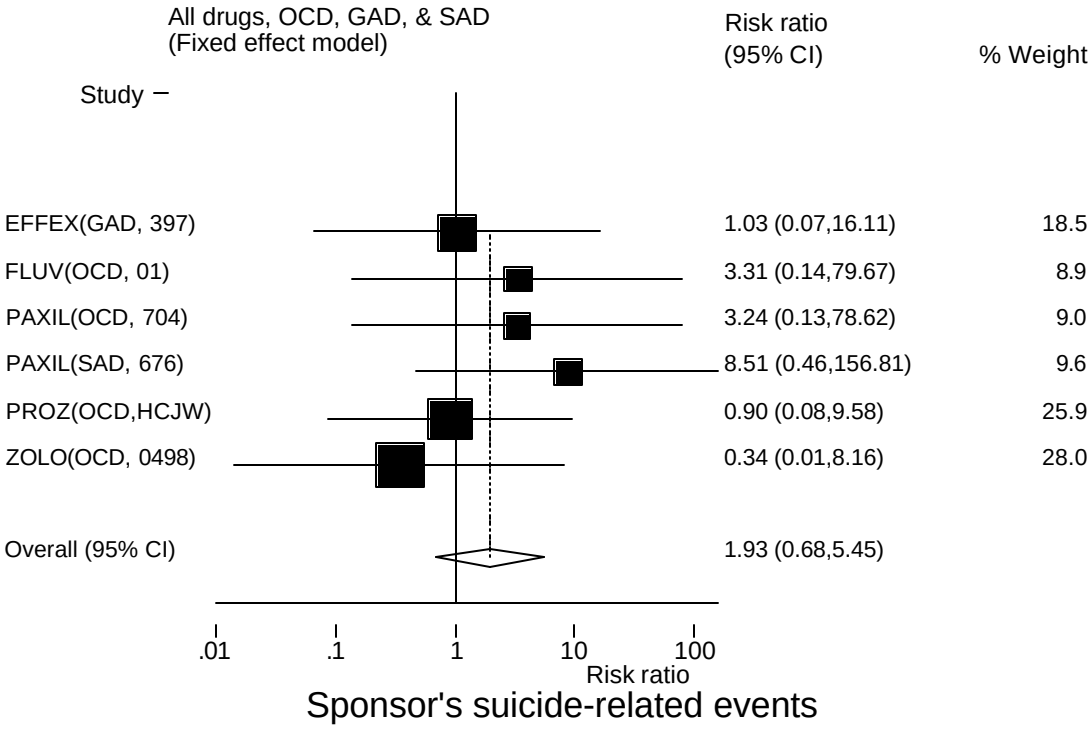




18.6 Original sponsor's suicide-related events, by indication

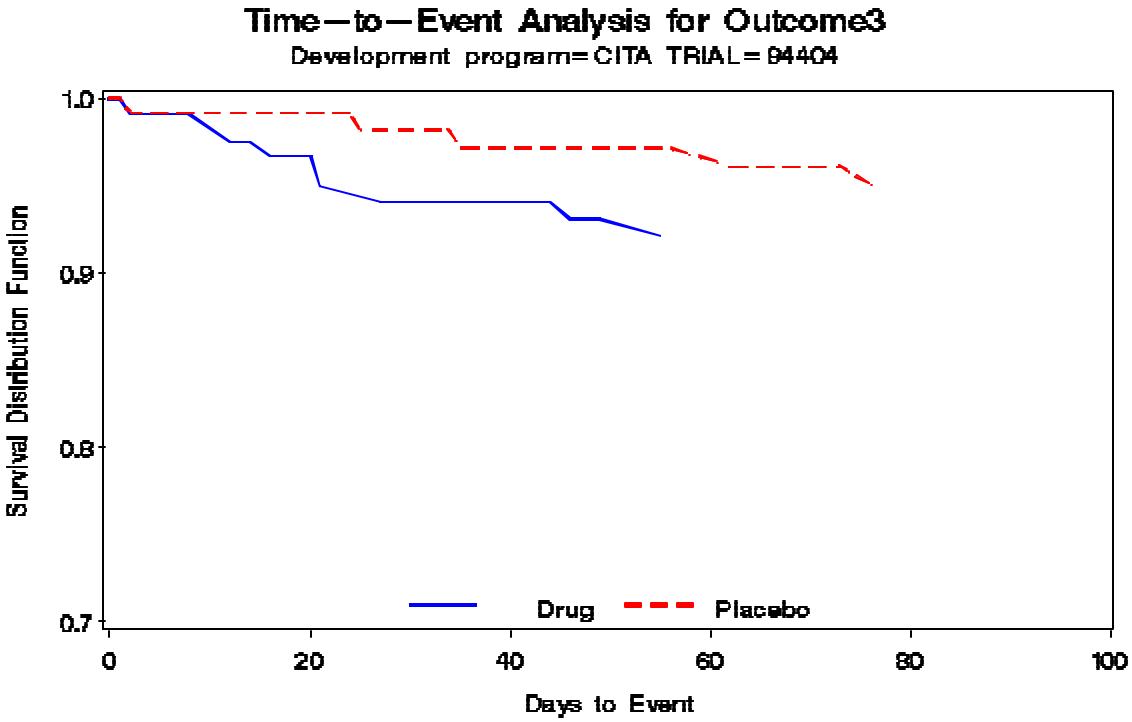


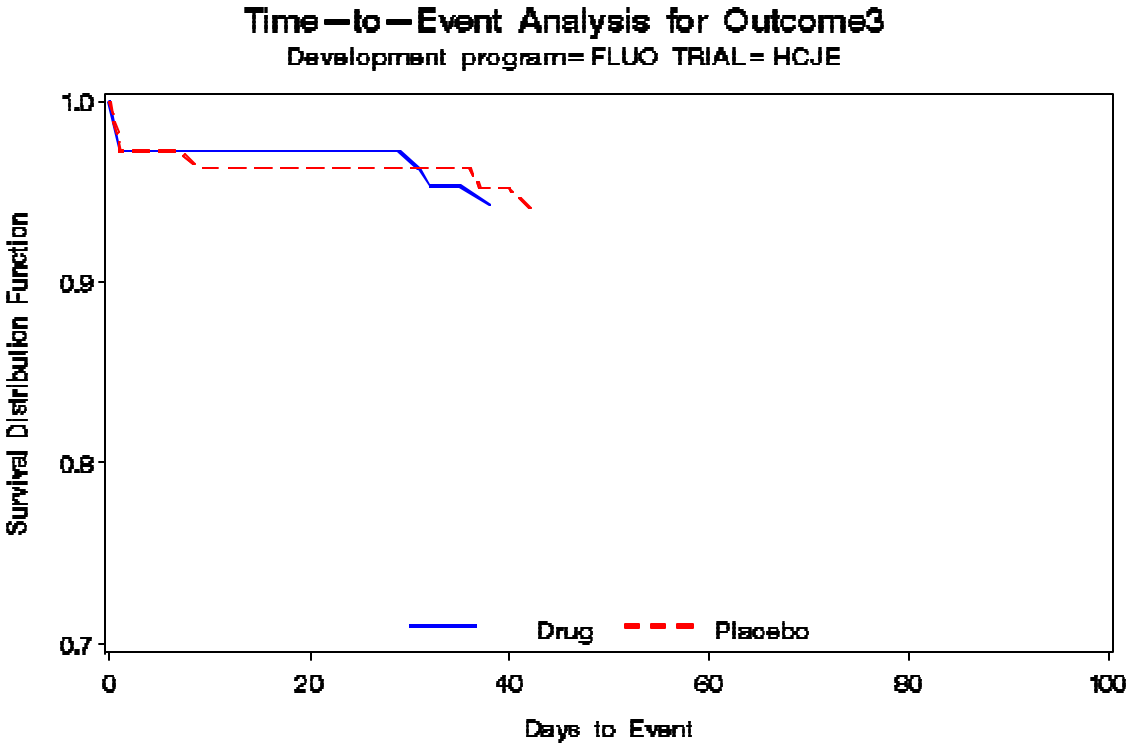
Sponsor's suicide-related events

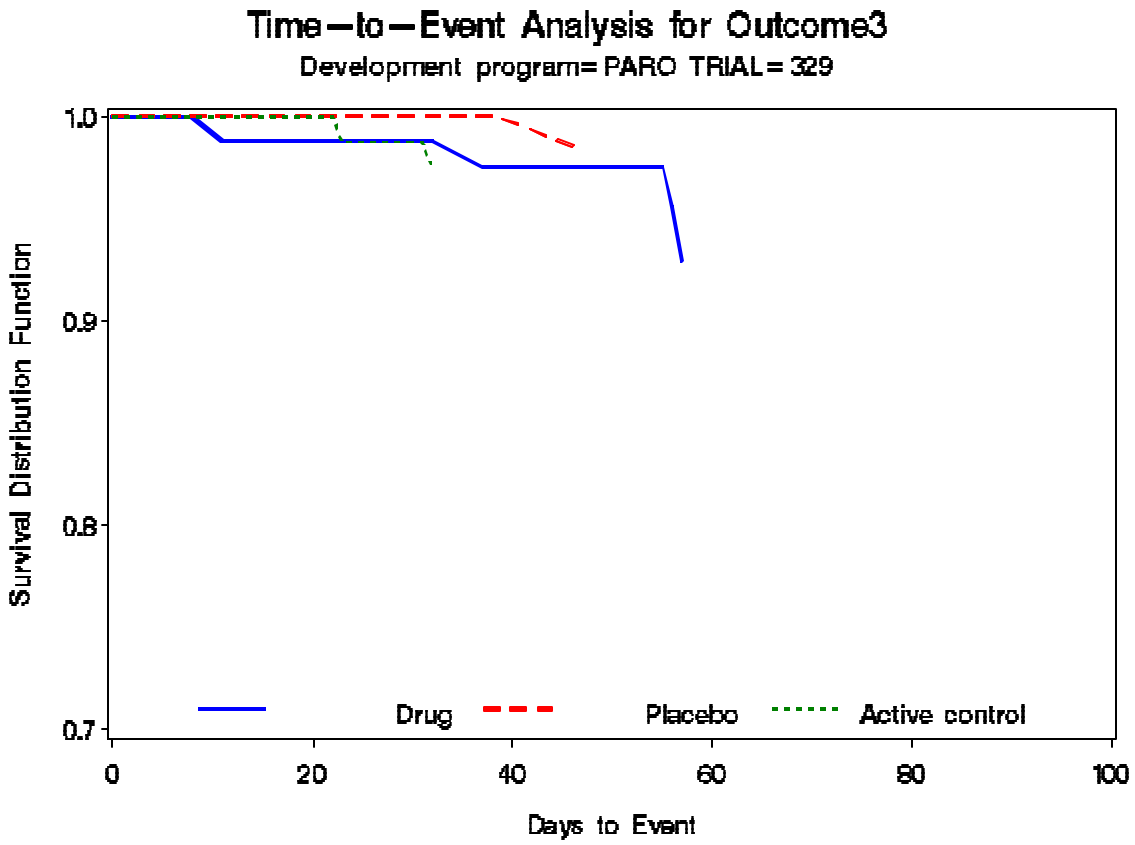


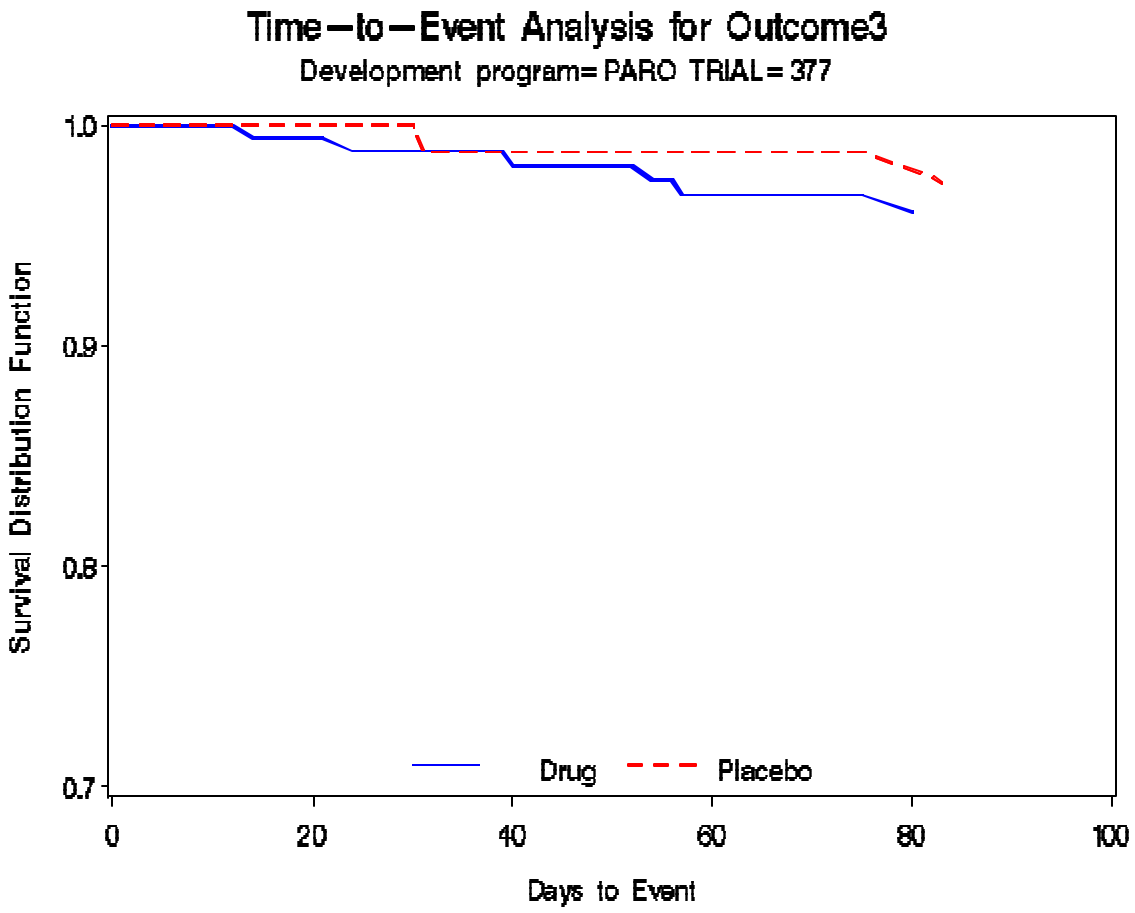
Sponsor's suicide-related events

19 Appendix XII: Graphs for time-to-event analysis for trials 94404, HCJE, 329, and 377

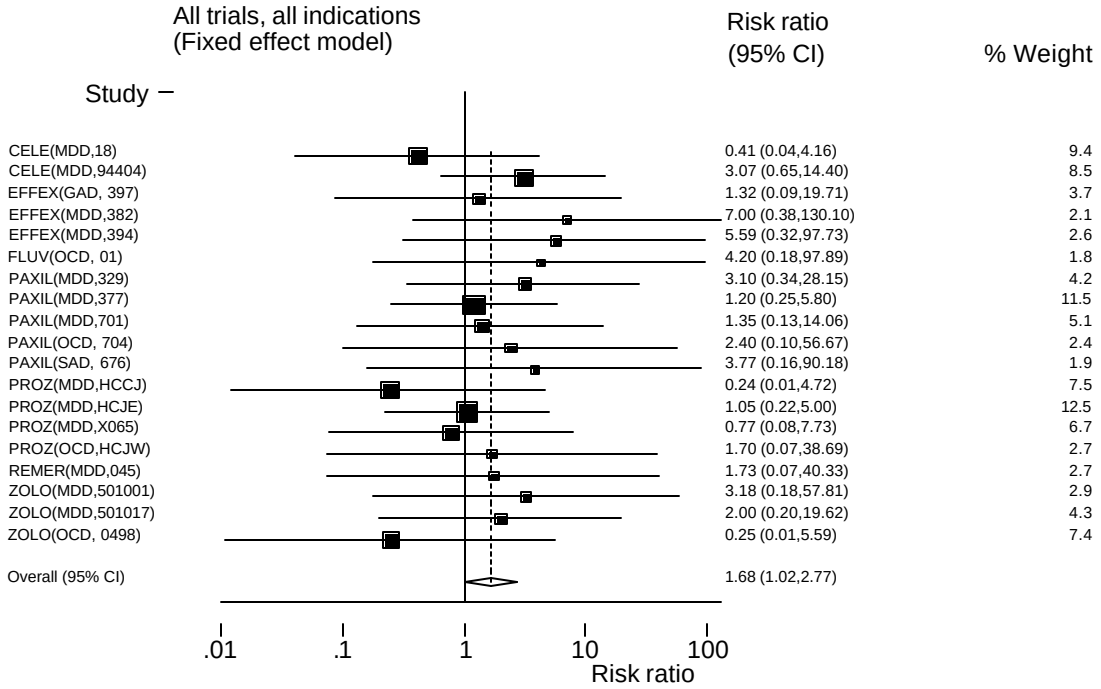




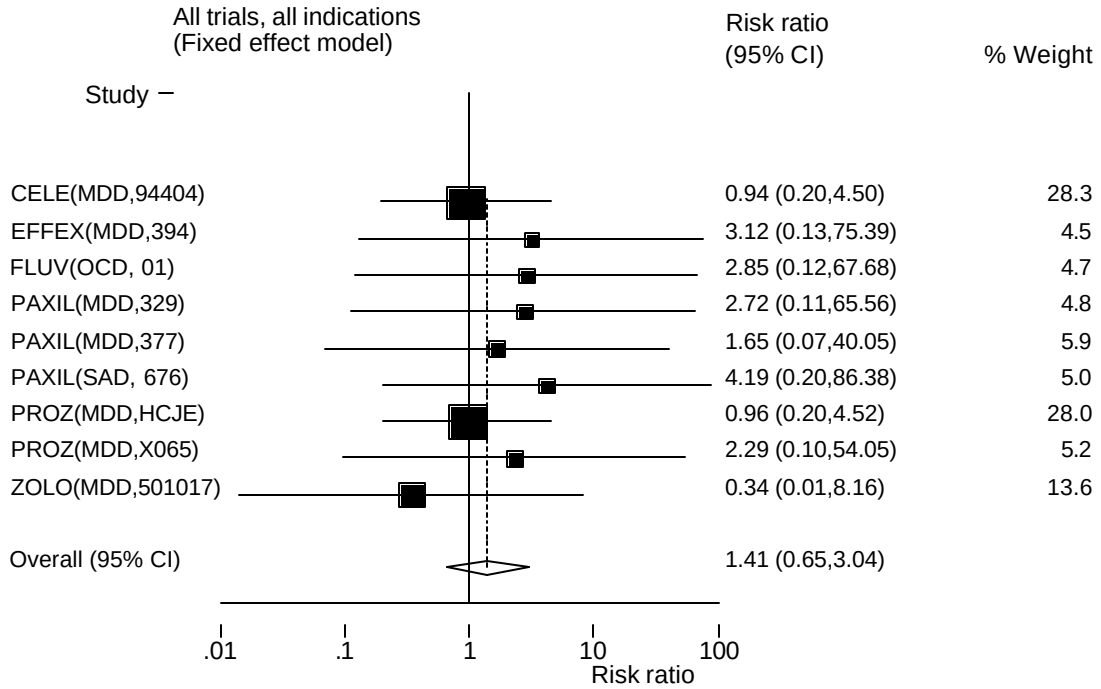

Time–to–Event Analysis for Outcome3
Development program= PARO TRIAL= 329
Survival Distribution Function
1.0
0.9
0.8
0.7
Drug
Placebo
Active control
0
20
40
60
80
100
Days to Event


Time–to–Event Analysis for Outcome3
Development program= PARO TRIAL= 377
Survival Distribution Function
1.0
0.9
0.8
0.7
Drug
Placebo
0
20
40
60
80
100
Days to Event

20 Appendix XIII: The primary outcome (outcome 3) stratified by premature discontinuation



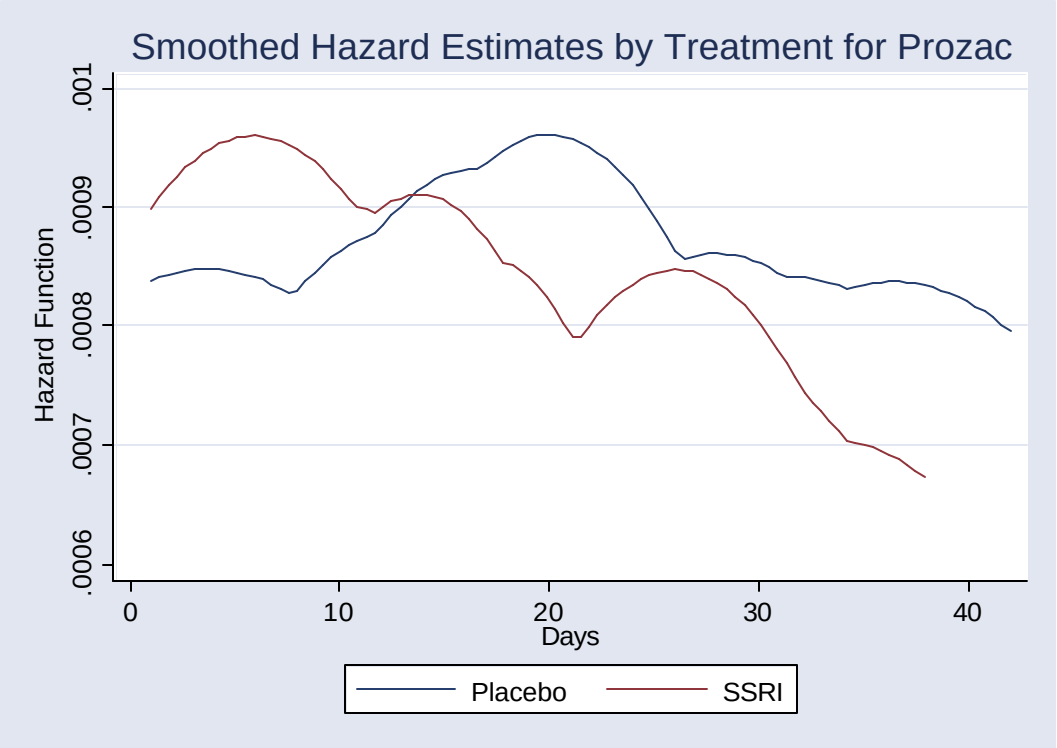
Suicide Behavior or Ideation [1, 2, 6]/discont



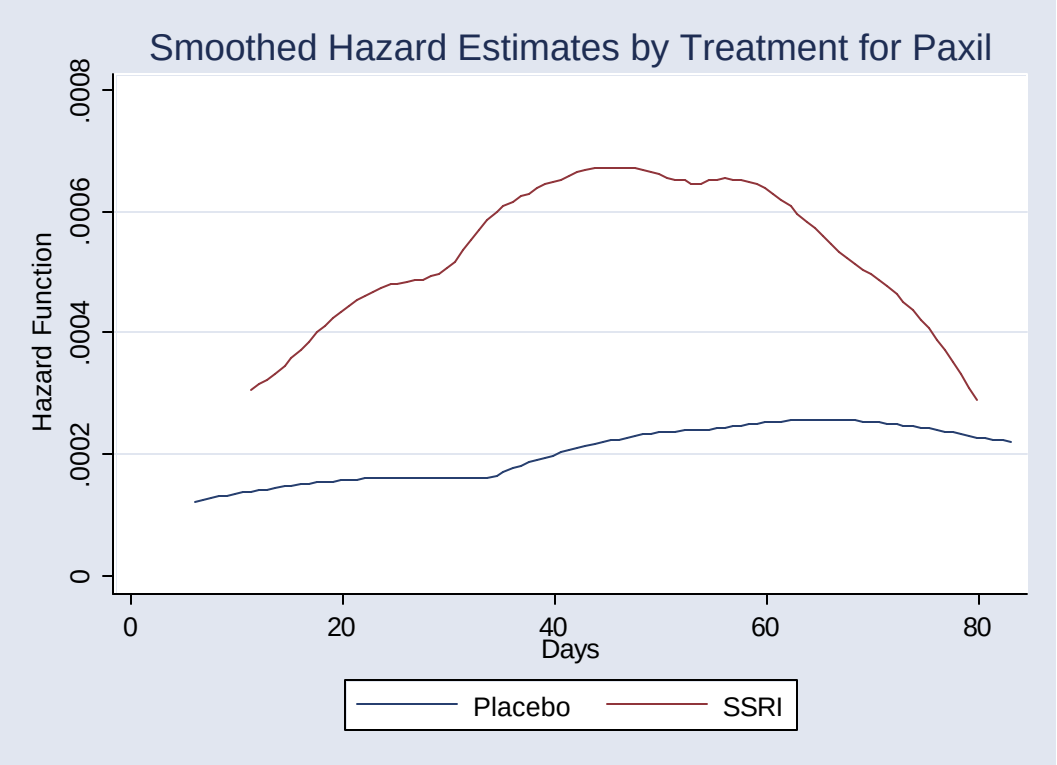
Suicide Behavior or Ideation [1, 2, 6]/No discont

21 Appendix XIV: Smoothed hazard estimates, by drug

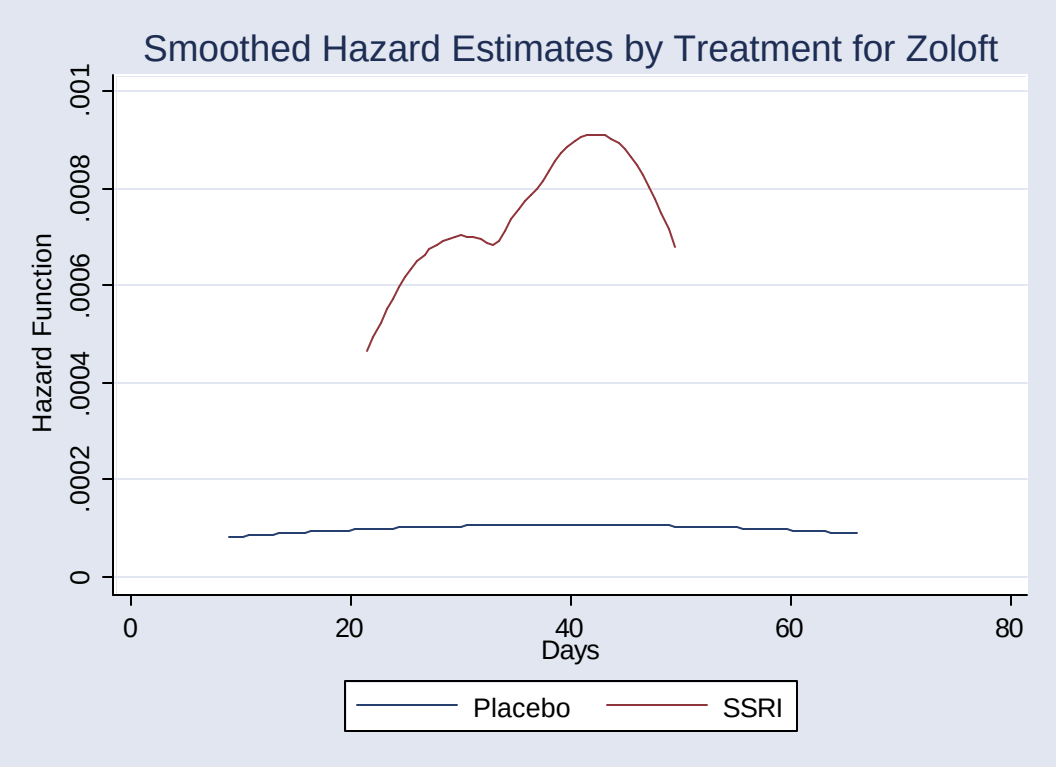
Prozac: HR 0.86 (0.33, 2.23) –stratified by trial



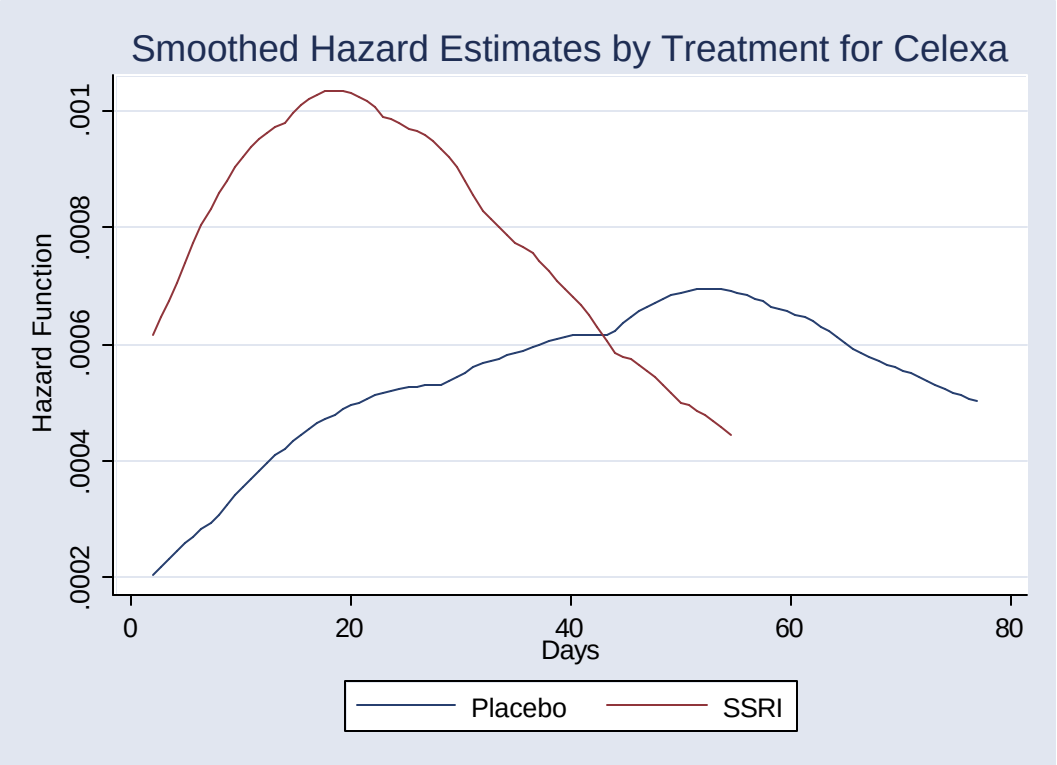
Paxil: HR 2.37 (0.75-7.45) –stratified by trial



Zoloft: HR 2.54 (0.49-13.10) –stratified by trial

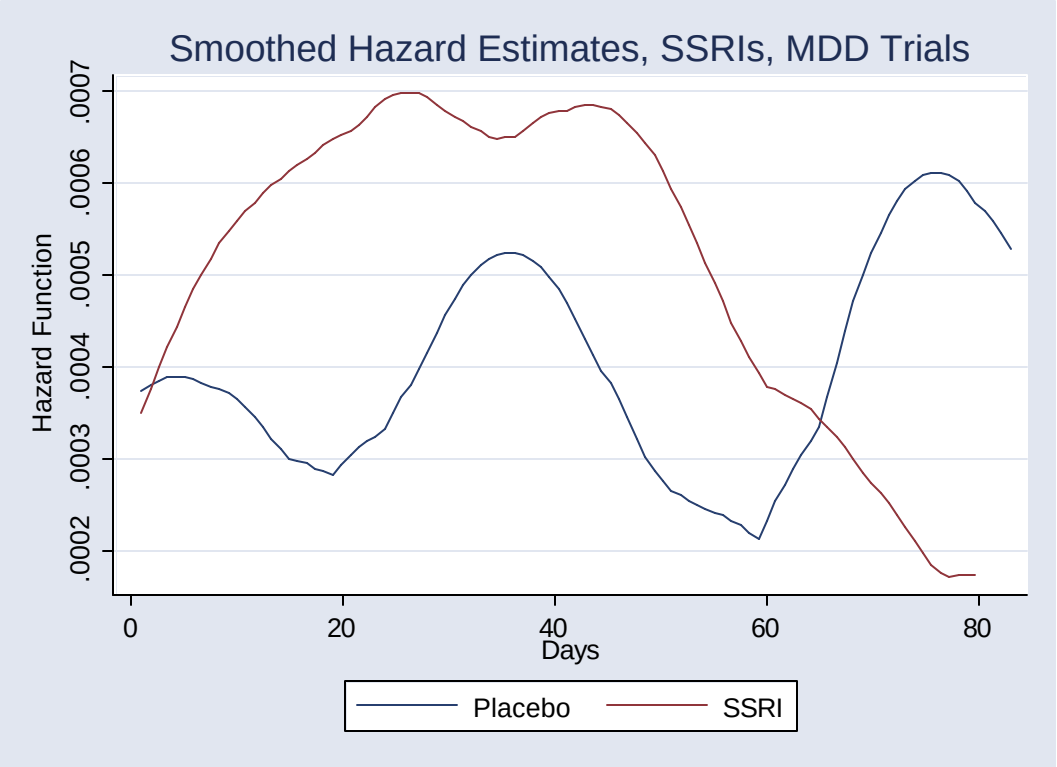


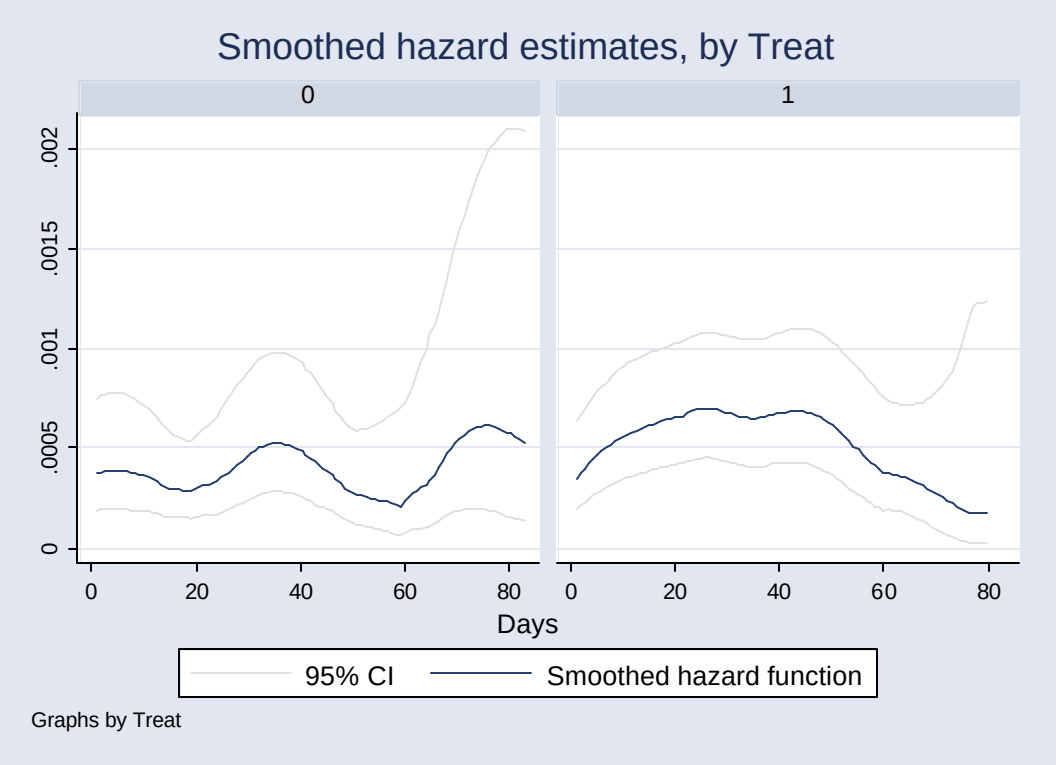
Celexa: HR 1.36 (0.52-3.56) –stratified by trial



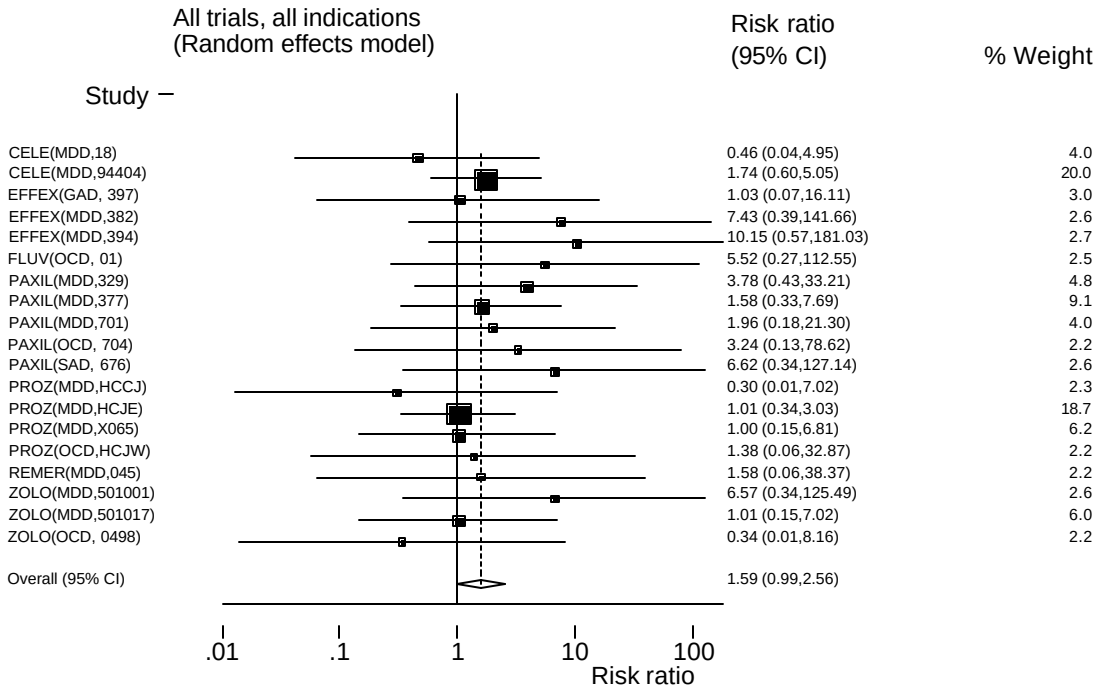
21.1 Overall drug effect of SSRIs in MDD trials

HR 1.45 (0.85, 2.48)

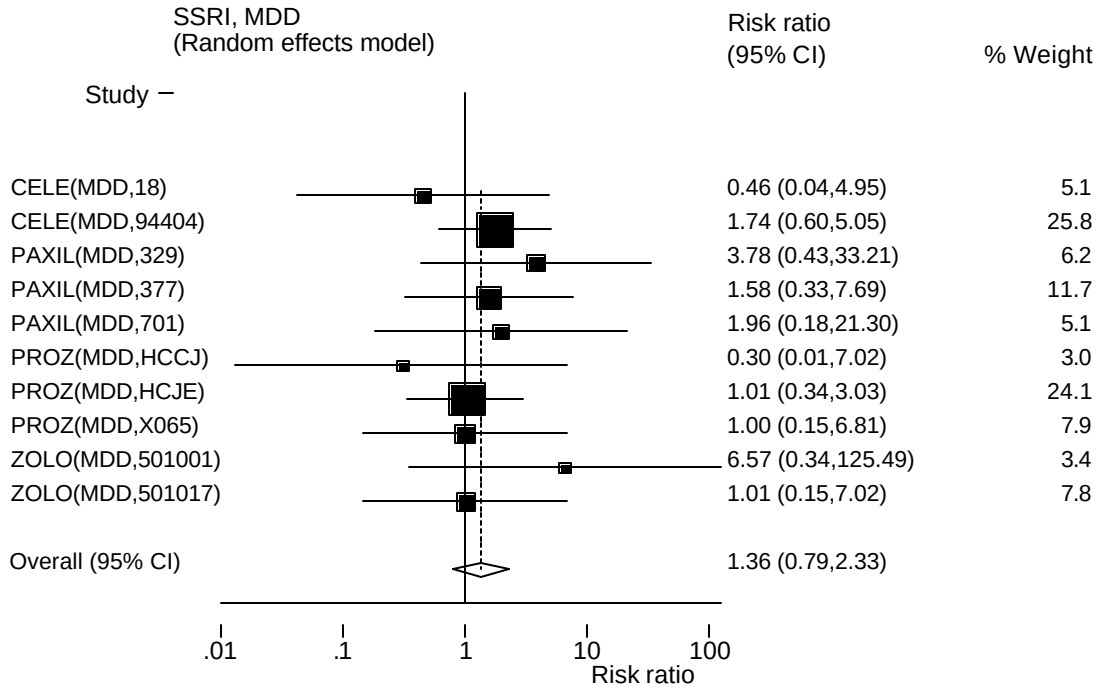




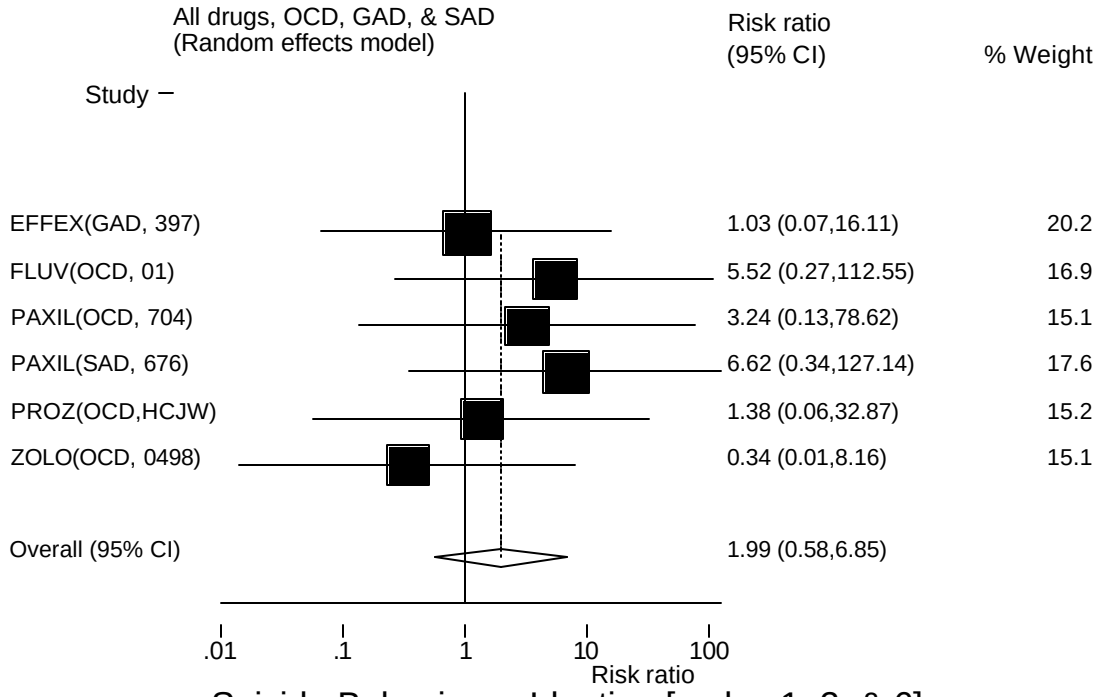
22 Appendix XV: Results of random-effects models



Suicide Behavior or Ideation [codes 1, 2, & 6]

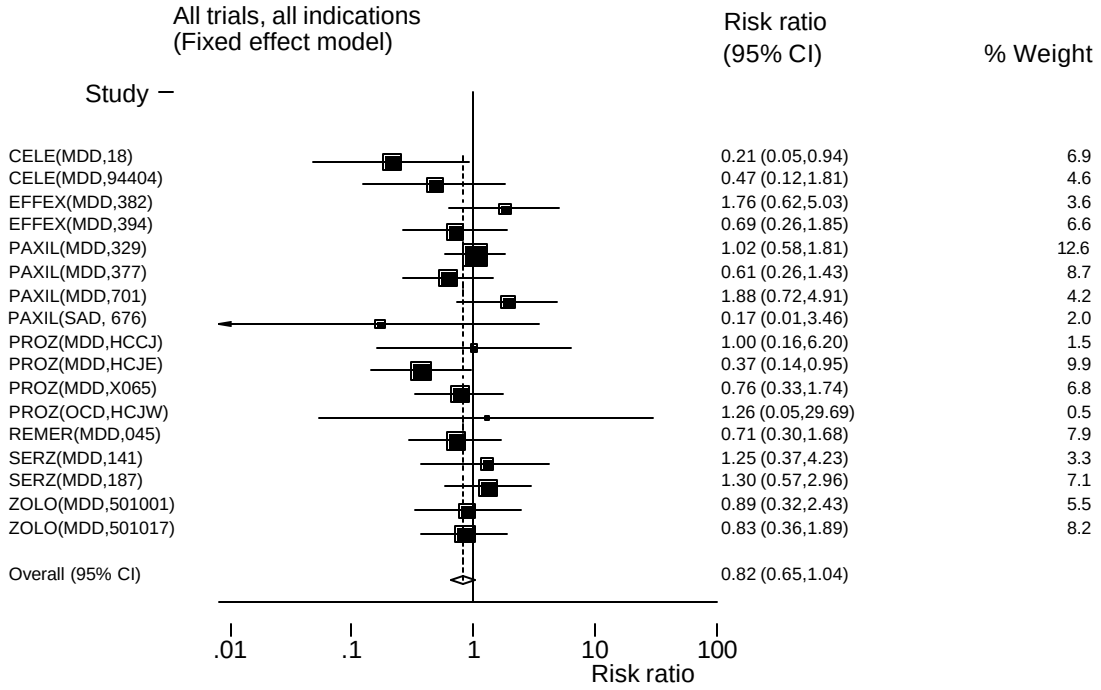


Suicide Behavior or Ideation [codes 1, 2, & 6]

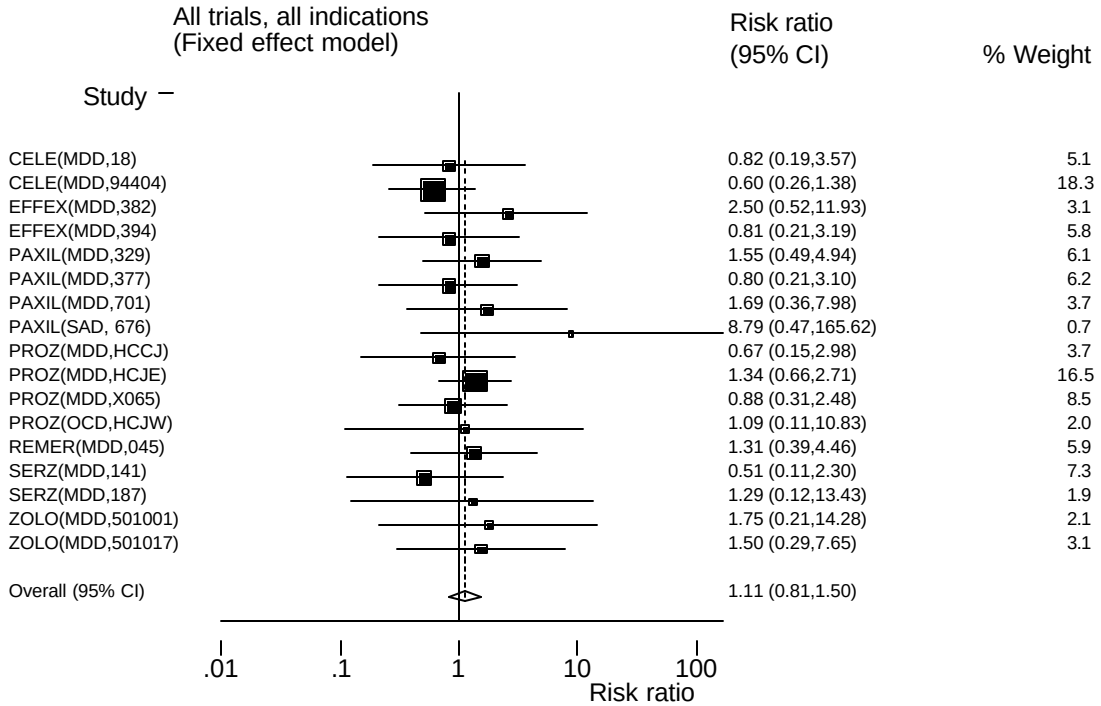


Suicide Behavior or Ideation [codes 1, 2, & 6]

23 Appendix XVI: Stratification of worsening (outcome 6) by premature discontinuation



Worsening/Emergence of Suicidality/No discont



Worsening/Emergence of Suicidality/discont

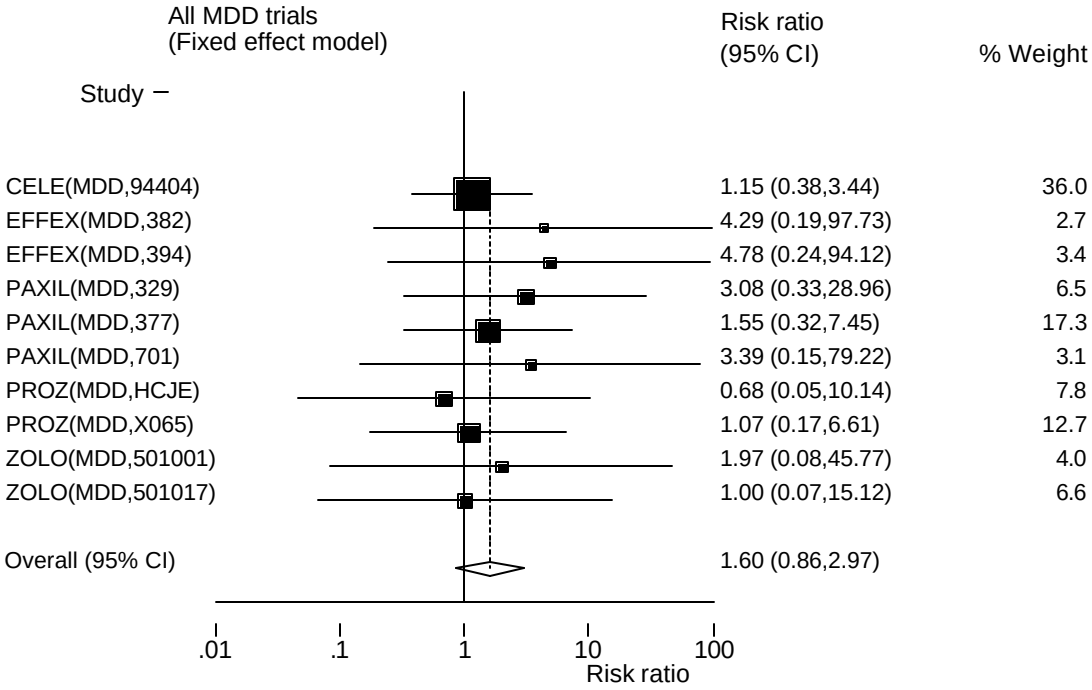
24 Appendix XVII: Treatment-emergent hostility or agitation

24.1 Frequency of treatment emergent hostility or agitation by drug, indication, and trial

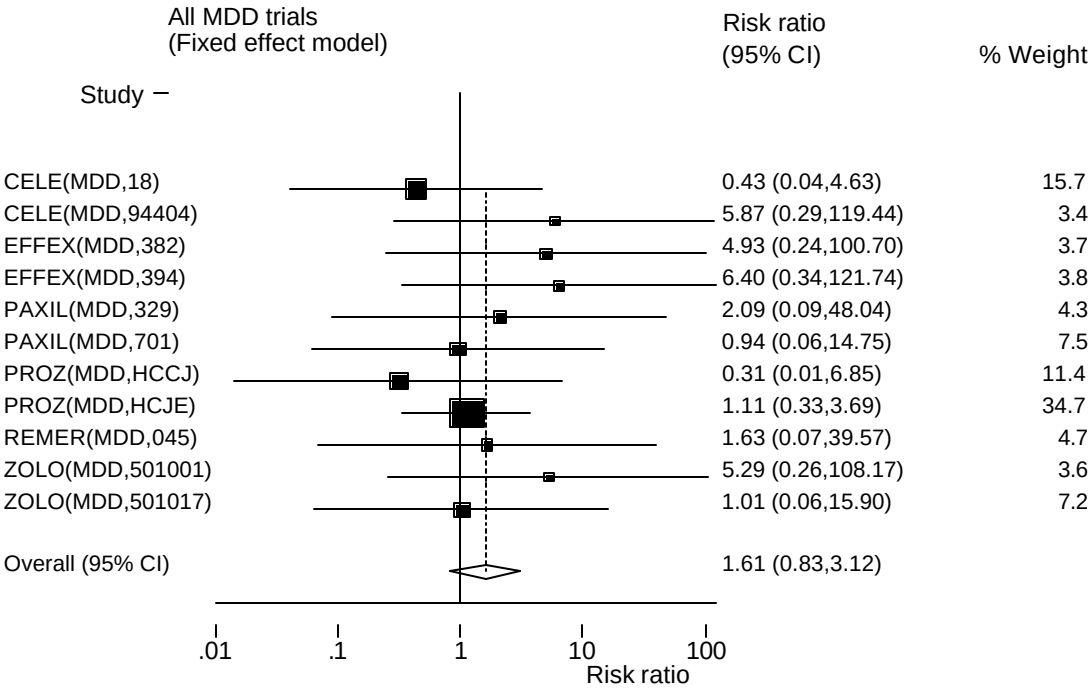
Program	Indicat.	Trial #	Tx Category	Subj.	Activation symptoms	%
CITA	MDD	94404	SSRI	124	1	0.81
			ZPlacebo	120	1	0.83
		CIT_MD_18	SSRI	93	3	3.23
			ZPlacebo	85	1	1.18
FLUO	MDD	HCCJ	SSRI	21	0	0.00
			ZPlacebo	19	0	0.00
		HCJE	SSRI	109	8	7.34
			ZPlacebo	110	5	4.55
		X065	SSRI	48	0	0.00
			ZPlacebo	48	3	6.25
NEFA	MDD	CN104-141	Atypical	95	8	8.42
			ZPlacebo	95	5	5.26
		CN104-187	Atypical	184	9	4.89
			ZPlacebo	94	6	6.38
PARO	MDD	329	Active control	95	5	5.26
			SSRI	93	8	8.60
			ZPlacebo	88	0	0.00
		377	SSRI	180	6	3.33
			ZPlacebo	95	0	0.00
		701	SSRI	104	4	3.85
			ZPlacebo	102	1	0.98
REME	MDD	003-045	Atypical	170	1	0.59
			ZPlacebo	89	1	1.12
SERT	MDD	A0501001	SSRI	97	1	1.03
			ZPlacebo	91	0	0.00
		A0501017	SSRI	92	1	1.09

			ZPlacebo	93	0	0.00
Program	Indicat.	Trial #	Tx Category	Subj.	Activation symptoms	%
VENL	MDD	382	Atypical	80	1	1.25
			ZPlacebo	85	1	1.18
		394	Atypical	102	8	7.84
			ZPlacebo	94	2	2.13

25 Appendix XVIII: Stratification of the primary outcome (outcome 3) by history of suicide attempt at baseline



Suicide Behavior or Ideation [1, 2, 6]/History



Suicide Behavior or Ideation [1, 2, 6]/No History

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/s/

Tarek Hammad
8/16/04 03:46:48 PM
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Judith Racoosin
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