

## MEMORANDUM

DATE: June 12, 2008

FROM: Russell Katz, M.D.  
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TO: Members of the Peripheral and Central Nervous Systems (PCNS)  
and Psychiatric Drugs (PD) Advisory Committees (PDAC)

SUBJECT: Briefing Document for the July 10, 2008 Advisory Committee  
Meeting to Discuss Antiepileptic Drugs (AEDs) and Suicidality

As you know, the PCNS and PD Advisory Committees will meet on July 10, 2008 to consider the results of analyses performed by FDA staff on placebo controlled trials of 11 AEDs. These analyses examined the comparative rates of suicidality (between active treatment and placebo), defined as episodes of suicidal ideation, suicidal behavior, or completed suicide, and are analogous to analyses performed in the recent past on controlled trials of antidepressant drug products. In the case of the AEDs analyzed, a meta-analysis of 199 controlled trials yielded an overall Odds Ratio (OR) for suicidality of 1.80, indicating a statistically significant increase in episodes of suicidality on treatment compared to placebo. When these results were obtained, the Agency published a notification of the findings in January, 2008.

In this memo, I will present a brief overview of the analyses performed and the results obtained (the reviews included in this package describe the analyses and results in great detail). I will also address some questions raised by the results, and briefly raise the issues we would like the committee to discuss at the July 10 meeting.

This background package includes, in addition to this memo, the following documents:

- 1) statistical review of the data by Dr. Mark Levenson of the Agency's Quantitative Safety and Pharmacoepidemiology Group
- 2) clinical review by Dr. Evelyn Mentari of the Division's Safety Group
- 3) the Agency's proposed labeling changes for AEDs
- 4) the information sheet published by the Agency in January, 2008
- 5) an article describing the C-CASA rating system (briefly referred to below)

### **Background and Results**

The Agency decided to investigate the question of suicidality for AEDs in early 2005, when the manufacturer of a particular AED presented analyses that they

believed indicated an increased incidence of suicidality in controlled trials of their drug compared to placebo. At that point, the Agency decided to examine appropriate controlled trials for all AEDs, using systematic analyses analogous to those performed, and being performed at that time, for the antidepressant drug products.

Specifically, the Agency asked sponsors of AEDs to examine those controlled trials for any indication that met the following criteria:

- 1) Randomized, parallel arm, placebo controlled
- 2) At least 20 patients in all treatment arms
- 3) Duration of at least 7 days
- 4) Subjects had to be at least 5 years old
- 5) No randomized withdrawal designs

The Agency subsequently received data from studies that met these criteria for the following 11 AEDs:

- 1) Carbamazepine
- 2) Divalproex sodium
- 3) Felbamate
- 4) Gabapentin
- 5) Lamotrigine
- 6) Levetiracetam
- 7) Oxcarbazepine
- 8) Pregabalin
- 9) Tiagabine
- 10) Topiramate
- 11) Zonisamide

Sponsors were asked to identify potential suicidality events by screening these trials for events coded with specific text strings that might identify such events (e.g., “suic”, “cut”, “self inflict”, etc.) as well as all serious adverse events and deaths. For each possible event, a narrative description of the event was constructed that was purged of any information that might have introduced a potential bias. These narratives were classified by a blinded reviewer according to the following Columbia Classification Algorithm of Suicide Assessment (C-CASA):

- |   |  |
|---|--|
| 0 | No event   |
| 1 | Completed suicide                                  |
| 2 | Suicide attempt                                    |
| 3 | Preparatory acts toward imminent suicidal behavior |
| 4 | Suicidal ideation                                  |
| 5 | Self-injurious behavior, intent unknown            |
| 6 | Not enough information, fatal                      |

## 7 Not enough information, non-fatal

Events that occurred during the double-blind phase and within 1 day after treatment discontinuation were included in the analyses.

A total of 199 studies were identified that met the trial inclusion criteria, involving 27,863 patients on active treatment and 16,029 on placebo. Of these 199 studies, 62 (31%) were in epilepsy, 56 (28%) were in 8 psychiatric indications, and 81 (41%) were in 11 other indications. The overall OR for suicidality events was 1.80 (0.22% on placebo compared to 0.37% on active drug), which reached nominal statistical significance. Of the 11 drugs included, the ORs for 8 were greater than 1, varying for these 8 drugs from 1.57 to 2.75 (with the OR for one drug being infinity [2 events on drug, 0 on placebo]). The ORs for 2 drugs were less than 1 (favoring treatment); one, carbamazepine had the second fewest patients of any of the drugs studied. The OR for one drug, felbamate, was undefined, with no events on either drug or placebo; the number of patients in trials for felbamate was the smallest of any drug included in the analyses.

The primary analysis performed was the exact method for a stratified odds ratio, the odds ratio being in terms of patient units. The stratification factor was the trial. The analyses assumed that all trials had a common treatment effect and included only those trials in which there was at least one suicidality event; this included about 1/3 of the trials identified. The results of additional analyses that included all trials gave similar results. In addition, other sensitivity analyses (including relative risks, risk differences, analyses that allowed for heterogeneity of treatment effect, analyses utilizing person-time, time-to-event analyses) all gave consistent results. Further, analyses were performed by: drug group defined by specific mechanisms of action, indication (epilepsy, psychiatric, other), type of event (suicidal behavior vs ideation), age, gender, race, setting (in-patient vs out-patient), and location (North America, non-North America). In general, there were no obvious differences in outcomes within these groupings, although with regard to indication and location, the following differences were seen:

INDICATION	Odds Ratio
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Epilepsy	3.53
Psychiatric	1.51
Other	1.87

LOCATION	
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North America	1.38
Non-North America	4.53

## Comments

Based on these data, the Agency has concluded that there is a signal for increased suicidality for the class of AEDs, and plans to propose that product labeling for all chronically used AEDs describe this increased risk; it is our intention to ask sponsors to include a description of these findings in a Boxed Warning, as well as in the Warnings and Precautions sections. In addition, we expect that patients will receive a medication guide describing this risk each time a prescription for an AED is filled.

At this point, it is worth discussing briefly how we came to the conclusion that this signal applies to all drugs in the class, given that there was no signal detected for 3 of the 11 drugs studied.

It is, of course, reasonable to ask why it is appropriate to consider these drugs (and the others not studied but to which we believe the results apply) as constituting a class at all. Although some of the drugs studied are considered to share at least one common (primary?) pharmacologic action, as a whole they clearly do not appear to have an obvious common pharmacologic mechanism or mechanisms. Nonetheless, although these drugs are used to treat a myriad of medical conditions, they do all share the ability to decrease the frequency of seizures (in addition to whatever other effects they may have); perhaps this can be considered to constitute a common mechanism, and serve as the basis for considering them as a class. In any event, it is typical for the Agency to consider all drugs approved for a similar indication to constitute a therapeutic class. This is important because (adverse) findings included in product labeling for only one (or a few) member(s) of a therapeutic class have the potential to drive prescribers to choose an alternative member of that class, all other things being equal. For this reason, it is very important, in many cases, to determine if a given adverse finding occurs with all or some of the other members of that therapeutic class as well, so that prescribers can make informed judgments when choosing between drugs used to treat a particular indication. It is for this reason that we consider AEDs a therapeutic class, and why it was important to examine the potential for suicidality of all of the drugs in that class (for which there were appropriately designed trials).

It then becomes important to explain why, given the results seen, we have concluded that the signal should be considered to apply to all drugs in the class. The question arises for two reasons: 1) the finding was not seen for all drugs, and 2) given the disparate pharmacologies of the drugs, there is no obvious explanation for why there should be a common finding of an increase in suicidality.

Regarding the first concern, the lack of complete uniformity in the finding would not be especially surprising if the true state of nature was that all AEDs increase suicidality. It is important to note that there **was** a numerical increase in the OR

for 8 of the 11 drugs studied, which reached nominal statistical significance for 2 of those 8. The lack of nominal significance for the other 6 drugs is not surprising, given the relatively small number of relevant events. The three drugs for which the OR was not greater than one included the two drugs with the fewest number of patients studied, so it is not surprising that the estimate of the treatment effects for these drugs might not represent a true or stable estimate. And it would not be surprising, if the finding is real, that, by chance, there would be one drug (in this case divalproex sodium) out of the 9 with an adequate sample size with an estimate of the OR of less than one.

Regarding the second concern, it must be acknowledged that we do not have a clear understanding of, or explanation for, the observation that there appears to be an increase in suicidality for multiple drugs with multiple pharmacologic mechanisms (although, as noted above, it must be remembered that at least one pharmacologic effect of these drugs, namely the capacity to decrease seizure frequency, is common to them all). The wide variety of pharmacologic actions represented by these drugs might reasonably raise questions about our interpretation of the observation itself; that is, the lack of an obvious underlying biological explanation might argue for dismissing the conclusion that these disparate treatments all cause an increase in suicidality, because it simply is not “plausible”. On the other hand, one could consider this observation to provide **support** for the conclusion that the finding is both real and should apply to all AEDs (including those studied for which there was no signal, and those not studied). If we take the signal at face value, the observation that so many different drugs are associated with this increase in suicidality strongly suggests that the finding is independent of mechanism, and it is therefore reasonable to conclude that all drugs of the “class” can cause this increase. In this regard, in the recent example of an observed increase in suicidality with antidepressants, there were drugs in those analyses that did not show an increase in suicidality. Nonetheless, the decision was made to attribute this effect to all antidepressants (one could, I suppose, argue that those drugs had more similar mechanisms than do the AEDs, thereby making the generalization to all members of that “class” more reasonable than in the current case. However, whether the antidepressants, as a “class”, actually do share common mechanisms is an arguable point). In any event, in our estimation, there seems to be no compelling reason to: 1) ignore what appears to be a very clear **empirical** finding of an increase in suicidality, despite no obvious explanation for this finding, or 2) not generalize the conclusion to other AEDs. This is the Agency’s current view.

In recent weeks, we have become aware that at least one sponsor has performed additional analyses of the data for their own drugs, and has come to a different conclusion than the Agency. At the time of this writing, we have not yet had the opportunity to examine those analyses in detail. We expect that this sponsor, as well as perhaps others, may present their findings at the July 10 meeting. In addition, this sponsor, as well as perhaps others, may submit their

own documents for the committee to review. If so, those documents will be sent to you at a later date.

At this time, we are not including a detailed list of questions that we would like you to discuss and/or vote on at the meeting; this list will be sent to you at a later date. However, we will be interested in your views about the analyses we have performed and the results we have obtained. In particular, of course, we are very interested in whether you believe the conclusions should be applied to any, only some, or, as we have concluded, all of the AEDs studied and all AEDs to be taken chronically. Further, we are interested in your thoughts and comments about the changes to the product labeling that we have proposed.

I would like to thank you in advance for all the work you will have done prior to and during the meeting, and I look forward to seeing you on July 10.



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

## STATISTICAL REVIEW AND EVALUATION

### ANTIEPILEPTIC DRUGS AND SUICIDALITY

**Drug Class:** Antiepileptic drugs

**Drug Names (NDA Numbers):** Carbamazepine (21-710)  
Divalproex (18-723, 19-680, 21-168)  
Felbamate (20-189)  
Gabapentin (20-235, 20-882, 21-129, 21-216)  
Lamotrigine (20-241, 20-764)  
Levetiracetam (21-035, 21-505, 21-872)  
Oxcarbazepine (21-014, 21-285)  
Pregabalin (21-446)  
Tiagabine (20-646)  
Topiramate (20-505, 20-844)  
Zonisamide (20-789)

**Indication(s):** Epilepsy, psychiatric disorders, other

**Date:** 23 May 2008

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**Keywords:** Epilepsy, psychiatric, bipolar, suicide, suicidality, meta-analysis

## TABLE OF CONTENTS

List of Tables .....	3
List of Figures .....	4
Executive Summary .....	5
1.1 Overview .....	5
1.2 Findings .....	5
1.3 Conclusions .....	6
2 Introduction .....	7
2.1 Background .....	7
2.2 Review Objectives .....	7
3 Data Sources .....	7
3.1 Data Requests .....	7
3.2 Trial Summary .....	9
4 Methods .....	12
4.1 Endpoints .....	12
4.2 Analysis Population .....	13
4.3 Subgroups and Special Populations .....	13
4.4 Statistical Methods .....	14
5 Patient Summary .....	16
5.1 Drugs and Demographics .....	16
5.2 Discontinuation and Duration .....	20
6 Findings .....	22
6.1 Suicidal Behavior or Ideation .....	22
6.2 Suicidal Behavior and Suicidal Ideation .....	26
6.3 Sensitivity Analysis .....	27
6.4 Exploratory Analysis .....	32
7 Findings in Special/Subgroup Populations .....	35
7.1 Drug Groups .....	35
7.2 Trial Indication .....	37
7.3 Demographics .....	39
8 Post-Hoc Analyses .....	45
8.1 Lamotrigine Additional Data .....	45
8.2 Alternative Age Subgroups .....	47
9 Summary and Conclusions .....	47
9.1 Review Summary .....	47
9.2 Conclusions .....	49
10 References .....	49



## LIST OF TABLES

Table 1: Suicidality Events and Codes. ....	8
Table 2: Antiepileptic Drugs under Review. ....	9
Table 3: Indication Categories. ....	10
Table 4: Trials by Comparator Type and Drug.....	11
Table 5: Trials by Indication Group and Therapy (Monotherapy, Adjunctive Therapy, Other). ....	12
Table 6: Patients by Treatment Arm and Comparator Type.....	16
Table 7: Patients by Treatment Arm and Drug, Placebo-Controlled Trials. ....	17
Table 8: Patients by Indication Group and Drug, Placebo-Controlled Trials.....	18
Table 9: Demographics by Treatment Arm, Placebo-Controlled Trials.....	19
Table 10: Patients by Drug Class and Treatment Arm, Placebo-Controlled Trials.....	20
Table 11: Patient Treatment Discontinuation and Duration by Treatment Arm, Placebo-Controlled Trials. ....	21
Table 12: Events by Type and Treatment Arm, Placebo-Controlled Trials. ....	22
Table 13: Suicidal Behavior or Ideation Events and Patients by Drug, Placebo-Controlled Trials. ....	23
Table 14: Suicidal Behavior or Ideation Hazard Estimates by Treatment Arm, Placebo-Controlled Trials. ....	32
Table 15: Events from Patients with Multiple Events, Placebo-Controlled Trials.....	34
Table 16: Placebo and Drug Suicidal Behavior or Ideation Event Rates and Risk Difference by Indication, Placebo-Controlled Trials.....	38

## LIST OF FIGURES

Figure 1: Mean Trial Duration by Treatment Arm, Placebo-Controlled Trials.....	21
Figure 2: Suicidal Behavior or Ideation Odds Ratio Estimates, Placebo-Controlled Trials. .....	25
Figure 3: Suicidal Behavior versus Suicidal Ideation Odds Ratio Estimates, Placebo- Controlled Trials. ....	26
Figure 4: Suicidal Behavior or Ideation Risk Difference Estimates, Placebo-Controlled Trials. ....	28
Figure 5: Suicidal Behavior or Ideation Rate Ratio Estimates, Placebo-Controlled Trials. .....	31
Figure 6: Kaplan-Meier Suicidal Behavior or Ideation Incidence Curves by Treatment Arm, Placebo-Controlled Trials.....	33
Figure 7: Suicidal Behavior or Ideation Odds Ratio Estimates by Drug Group, Placebo- Controlled Trials. ....	36
Figure 8: Suicidal Behavior or Ideation Odds Ratio Estimates by Indication Group, Placebo-Controlled Trials. ....	37
Figure 9: Suicidal Behavior or Ideation Odds Ratio Estimates by Age Group, Placebo- Controlled Trials. ....	40
Figure 10: Suicidal Behavior or Ideation Odds Ratio Estimates by Gender, Placebo- Controlled Trials. ....	41
Figure 11: Suicidal Behavior or Ideation Odds Ratio Estimates by Race Group, Placebo- Controlled Trials. ....	42
Figure 12: Suicidal Behavior or Ideation Odds Ratio Estimates by Setting, Placebo- Controlled Trials. ....	43
Figure 13: Suicidal Behavior or Ideation Odds Ratio Estimates by Location, Placebo- Controlled Trials. ....	44
Figure 14: Suicidal Behavior or Ideation Odds Ratio Estimates, Placebo-Controlled and Low-Dose-Controlled Trials. ....	45
Figure 15: Suicidal Behavior or Ideation Odds Ratio Estimates with Additional Lamotrigine Data, Placebo-Controlled Trials.....	46
Figure 16: Suicidal Behavior or Ideation Odds Ratio Estimates by Post-Hoc Age Group, Placebo-Controlled Trials. ....	47

## **EXECUTIVE SUMMARY<sup>1</sup>**

### **1.1 Overview**

The Food and Drug Administration (FDA) concerned about the potential for elevated risk of suicidality (suicidal behavior or ideation) from the use of antiepileptic drugs carried out a meta-analysis of 11 drugs. Antiepileptic drugs are also used for indications other than epilepsy including psychiatric disorders.

In March 2005, FDA sent letters to sponsors of antiepileptic drugs requesting that they submit data from placebo-controlled trials for the FDA to review the possible association of suicidality events and antiepileptic drugs. Letters in July 2005, May 2006, and January 2007 requested additional information to obtain the data necessary for the review. The letters specified detailed instructions for the identification of suicidality events and the format of the data to be submitted.

Prior to the analysis of the data, medical reviewers in the Division of Neurology and statistical reviewers in the Quantitative Safety and Pharmacoepidemiology Group agreed upon the definition of the research objectives, endpoints, study population, and subgroups and upon the specification of the statistical methods. These elements were incorporated into a statistical analysis plan prior to the review. The statistical methods maintained the integrity of placebo-controlled trials. This allowed for trials to have different background rates of events.

### **1.2 Findings**

There were 199 placebo-controlled trials consisting of 27,863 patients in drug arms and 16,029 patients in placebo arms from 11 drugs that formed the primary analysis population.

The average age of patients was 42 years. The majority of patients were female (55%), white (79%), and from North American locations (61%). The placebo patients had statistically higher treatment duration (77 days for placebo versus 73 days for drug). There were no statistical differences among the baseline characteristics of the drug and placebo patients for age, gender, race, and location.

There were 4 completed suicides among drug patients and none among placebo patients. The majority of suicidality events for both drug and placebo patients were Suicidal Ideation. The second most frequent type of event was Suicide Attempt. Without adjusting for differences among trials, 0.37% of the drug patients had a Suicidal Behavior or Ideation event versus 0.24% of the placebo patients.

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<sup>1</sup> This review replaces the March 5, 2008 version. Two small discrepancies in the data have been corrected for this version.

Overall, patients who received an antiepileptic drug had statistically significant increased risk of Suicidal Behavior or Ideation relative to placebo patients. The estimated overall odds ratio (OR) of a drug patient experiencing a Suicidal Behavior or Ideation event versus a placebo patient was 1.80 (95% CI: 1.24, 2.66). The results for individual drugs were generally consistent with the overall result. Suicidal Behavior had a larger estimated odds ratio [2.92 (95% CI: 1.44, 6.47)] than Suicidal Ideation [1.45 (95% CI: 0.93, 2.30)]. Sensitivity analyses showed that the results were robust to statistical methods and differences in the treatment durations between the treatment groups.

Indication and location appeared to have the largest effects on the odds ratio among the subgroups considered. The epilepsy indication subgroup had the largest estimated odds ratio [3.53 (95% CI: 1.28, 12.10)] compared to the psychiatric indication subgroup [1.51 (95% CI: 0.95, 2.45)] and the other indication subgroup [1.87 (95% CI: 0.81, 4.76)]. However, the psychiatric indication subgroup had the largest placebo risk and the risk difference for the psychiatric indications subgroup was the largest. The estimated odds ratio for the Non-North American subgroup [4.53 (95% CI: 1.86, 13.18)] was notably larger than that of the North American subgroup [1.38 (95% CI: 0.90, 2.13)].

The higher risk of events for the drug-treated patients was observed as early as 1 week from initiating treatment until at least 24 weeks. After 24 weeks, it was not possible to draw conclusions due to the scarcity of data beyond 24 weeks.

There was no obvious pattern in the drug effect with respect to age subgroups. Likewise, there were no patterns with respect to subgroups based on gender, race, setting, and prespecified drug groups (sodium channel blocking, GABAergic and GABA-mimetic, and carbonic anhydrase inhibitors).

### **1.3 Conclusions**

In conclusion, antiepileptic drugs are associated with increased risk of suicidality relative to placebo in randomized placebo-controlled trials. The effect appears consistent among the group of 11 drugs. There are 1.9 per 1000 (95% CI: 0.6, 3.9) more antiepileptic drug patients than placebo patients who experience Suicidal Behavior or Ideation. In terms of adjusted risk estimates for the treatment groups, 0.43% of the drug patients experience Suicidal Behavior or Ideation compared to 0.24% of the placebo patients.

There is no obvious subgroup of patients to which the increased risk is specifically attributed. The increased risk was seen in almost all subgroups, although epileptic and Non-North American patients may have higher relative risks.

## **2 INTRODUCTION**

### **2.1 Background**

The Food and Drug Administration (FDA) concerned about the potential for elevated risk of suicidality (suicidal behavior or ideation) from the use of antiepileptic drugs carried out a meta-analysis of 11 drugs. Antiepileptic drugs are also used for indications other than epilepsy including psychiatric disorders. In March 2005 FDA initiated requests to the sponsors of antiepileptic drugs for data to address the suicidality concern.

Prior to the analysis of the antiepileptic data, medical reviewers in the Division of Neurology and statistical reviewers in the Quantitative Safety and Pharmacoepidemiology Group agreed upon the definition of the research objectives, endpoints, study population, and subgroups and upon the specification of the statistical methods. These elements were incorporated into a statistical analysis plan prior to the review.

This review replaces the March 5, 2008 version. Two small discrepancies in the data have been corrected for this version.

### **2.2 Review Objectives**

1. Examine whether 11 antiepileptic drugs as a group are associated with increased risk of suicidality relative to placebo in randomized placebo-controlled trials.
2. Examine whether the risk of suicidality varies by (a) individual drug, (b) drug subgroups, (c) indication subgroups, and (d) demographic subgroups.

## **3 DATA SOURCES**

### **3.1 Data Requests**

In March 2005, FDA sent letters to sponsors of antiepileptic drugs requesting that they submit data from placebo-controlled trials for the FDA to review the possible association of suicidality events and antiepileptic drugs. Sponsors of all drugs with available registration trials were contacted. Letters in July 2005, May 2006, and January 2007 requested additional information to obtain the data necessary for the review. The letters specified detailed instructions for the identification of suicidality events and the format of the data to be submitted.

#### *3.1.1 Trial Inclusion Criteria*

The final directions to the sponsors called for the submission of data for all randomized parallel-arm, placebo-controlled trials, regardless of indication and duration, with at least 30 patients total. Trials may have had active-control arms as well. In addition to parallel-arm trials, data from the first period of cross-over trials that otherwise met the trial inclusion criteria were also included. In addition to placebo-controlled trials, trials with subtherapeutic comparator arms, known as “low-dose placebo” were to be included. The low-dose controlled studies were not included in the primary analysis. The July 2005

FDA letter specified that studies with ongoing blinded treatment phases should not be included.

### 3.1.2 Identification of Suicidality Events

FDA specified the procedure for the identification of suicidality events. The procedure called for a search of “possibly suicide-related” adverse events (PSRAEs). The search was to be strictly limited to events that occurred during the double-blind phase of treatment, or within 1 day of stopping randomized treatment. All deaths and serious adverse events (SAEs) were to be included as PSRAEs. In addition, events were identified through a search of specified text-strings in the adverse event data. For each PSRAE, a narrative was to be prepared.

Based on blinded versions of the narratives, the PSRAEs were to be classified into mutually exclusive suicidality events using the approach employed in classification of outcomes as implemented in the pediatric antidepressant analysis (Posner et al. 2007). Table 1 gives the suicidality events. Sponsors were responsible for the classification of events.

Table 1: Suicidality Events and Codes.

Event Code	Event
0	No Event
1	Completed suicide
2	Suicide attempt
3	Preparatory acts toward imminent suicidal behavior
4	Suicidal ideation
5	Self-injurious behavior, intent unknown
6	Not enough information, fatal
7	Not enough information, non-fatal

### 3.1.3 Dataset Definition

FDA specified the format of patient-level and trial-level datasets to be submitted. The patient-level dataset was to have one record per event. Patients with multiple events were to have multiple records in the dataset corresponding to each event. Patients without events were to be assigned an event code of 0. The patient-level dataset included variables for trial identification, patient identification, age, gender, race, setting of trial (inpatient, outpatient, both), location of trial (North America, Non-North America), treatment drug, event code, day of event, and discontinuation status. For location, FDA did not specify the meaning of North America.

The trial-level dataset summarized and characterized the trial. This information included indication, nominal duration, treatment arm sizes, inclusion and exclusion criteria, dosage, and design features.

### 3.2 Trial Summary

Sponsors submitted datasets from 12 drug programs. One of these drugs, vigabatrin, is not currently approved in the United States and was not part of the review. Table 2 gives the names of the 11 drugs that were included in the review.

Table 2: Antiepileptic Drugs under Review.

Drug	NDA Number
Carbamazepine	21-710
Divalproex	18-723, 19-680, 21-168
Felbamate	20-189
Gabapentin	20-235, 20-882, 21-129, 21-216
Lamotrigine	20-241, 20-764
Levetiracetam	21-035, 21-505, 21-872
Oxcarbazepine	21-014, 21-285
Pregabalin	21-446
Tiagabine	20-646
Topiramate	20-505, 20-844
Zonisamide	20-789

The medical officer, Dr. Evelyn Mentari, Division of Neurology Products, performed some initial data processing of the submitted patient-level datasets including:

1. Checking the correctness of the data submission to the FDA instructions
2. Concatenating the data from the 11 drug programs into a single dataset
3. Removing trials based on exclusion criteria (described below)
4. Reducing multiple events in a single day to a single event (described below)
5. Removing patients under the age of 5
6. Creating indication categories (described below)

Trials were excluded if the duration was less than 7 days, there were fewer than 20 patients in any arm, all patients were less than 5-years old, or the trial had a randomized withdrawal design (including withdrawal to placebo).

For patients with multiple events on a single day, only the most critical event (based on the event codes shown in Table 1) on the day was retained.

The medical officer categorized the numerous indications into 21 indication categories. These 21 indication categories were further categorized into three categories: (1) epilepsy, (2) psychiatric, and (3) other. Table 3 gives the 21 indication categories and their further classification into three categories.

Table 3: Indication Categories.

Epilepsy	Psychiatric	Other
Epilepsy	Anxiety	Agitation
	Binge eating disorder	Chronic pain
	Bipolar disorder	Fibromyalgia
	Depression	Impaired cognition
	Panic disorder	Insomnia
	Post-Traumatic Stress Disorder	Migraine
	Schizophrenia	Neuropathy
	Social phobia	Obesity
		Radiculopathy
		Spasticity
		Tremor

Note: The other indication category included volunteer studies.

The review was based on the datasets prepared by Dr. Mentari and provided on 7 November 2007.



Table 4 gives the number of trials by comparator type and drug. There were 210 trials. Of these, 199 were placebo controlled and 11 were low-dose controlled. No study had both a placebo arm and a low-dose arm. There were 23 trials that also had an active-control arm.

Table 4: Trials by Comparator Type and Drug.

Drug	Number of Trials		Total
	Placebo-Controlled	Low-Dose Controlled	
Carbamazepine	3	0	3
Divalproex	13	1	14
Felbamate	6	3	9
Gabapentin	28	0	28
Lamotrigine	27	2	29
Levetiracetam	21	0	21
Oxcarbazepine	10	1	11
Pregabalin	38	1	39
Tiagabine	6	0	6
Topiramate	42	3	45
Zonisamide	5	0	5
Total	199	11	210

Table 5 gives the number of trials by indication group and therapy (monotherapy, adjunctive therapy, and other). In the majority of epilepsy trials (81%), the drug was used in combination with other therapies as adjunctive therapy. In contrast, in the majority of psychiatric trials (86%), the drug was used as monotherapy.

Table 5: Trials by Indication Group and Therapy (Monotherapy, Adjunctive Therapy, Other).

Therapy	Indication Group			Total N=210 n (%)
	Epilepsy N=73 n (%)	Psychiatric N=56 n (%)	Other N=81 n (%)	
Monotherapy	14 (19)	48 (86)	61 (75)	123 (59)
Adjunctive Therapy	59 (81)	8 (14)	12 (15)	79 (38)
Other	0 (0)	0 (0)	8 (10)	8 (4)

Note: Other therapy includes trials with optional adjunctive therapy and a trial in which one patient cohort received adjunctive therapy and one patient cohort did not receive adjunctive therapy.

## 4 METHODS

The statistical analysis plan (SAP) including the definitions of the endpoints, study population, subgroups, and statistical methods were prespecified prior to conducting the review. As stated above, these definitions and specifications were chosen by medical reviewers in the Division of Neurology and statistical reviewers in the Quantitative Safety and Pharmacoepidemiology Group. Deviations from and additions to the SAP are noted.

### 4.1 Endpoints

#### 4.1.1 Primary Endpoint

The primary endpoint was *Suicidal Behavior or Ideation*. A patient had this endpoint if the patient had any of the following suicidality events:

- Completed suicide
- Suicide attempt
- Preparatory acts toward imminent suicidal behavior
- Suicidal ideation

#### 4.1.2 Secondary Endpoint

There were two secondary endpoints. A patient had the endpoint *Suicidal Behavior* if the patient had any of the following suicidality events:

- Completed suicide
- Suicide attempt

- Preparatory acts toward imminent suicidal behavior

A patient had the endpoint *Suicidal Ideation* if the patient had only a Suicidal Ideation event. Note that the endpoint *Suicidal Ideation* was not part of the SAP.

## **4.2 Analysis Population**

The primary analysis population was all patients in test drug and placebo arms from placebo-controlled trials that met the trial and patient inclusion criteria described in Section 3.2.

## **4.3 Subgroups and Special Populations**

### *4.3.1 Drugs*

Each drug was considered separately

### *4.3.2 Drug Groups*

Three groups of drugs were considered. These groupings were chosen by the medical officers from the Division of Neurology. Each group of drugs was compared to the complementary group of drugs. Note that the drug groups are not mutually exclusive or exhaustive.

1. Sodium Channel Blocking Drugs
  - Carbamazepine
  - Lamotrigine
  - Oxcarbazepine
  - Topiramate
  - Zonisamide
2. GABAergic Drugs and GABAmimetic Drugs
  - Divalproex
  - Gabapentin
  - Pregabalin
  - Tiagabine
  - Topiramate
3. Carbonic Anhydrase Inhibitors
  - Topiramate
  - Zonisamide

### *4.3.3 Trial Indication*

Three indication groups were considered as defined in Table 3:

1. Epilepsy
2. Psychiatric Indications
3. Other Indications

### *4.3.4 Demographics*

The following subgroup classes were considered:

1. Age
  - 5-17

- 18-24
- 25-30
- 31-64
- $\geq 65$
- 2. Gender
  - Male
  - Female
- 3. Race
  - White Caucasian
  - Other
- 4. Setting
  - Inpatient or Inpatient/Outpatient Combined
  - Outpatient
- 5. Location
  - North America
  - Non-North America

The age subgroups were chosen to be the same as used in FDA analysis of the antidepressant suicidality. Only two race subgroups were used because the overwhelming majority of patients were white. “Other” for race included African American, Hispanic, Asian, and other. For location, FDA did not specify the meaning of North America.

#### *4.3.5 Comparator Type*

The group of patients from low-dose-controlled trials was considered. This group was compared to the primary analysis group of placebo-control trial patients and the group of patients from both placebo-controlled and low-dose-controlled trials. For the analysis of patients from both types of trials, the test drug patients were compared to the patients in the corresponding trial control arm patients (placebo or low-dose).

### **4.4 Statistical Methods**

#### *4.4.1 Primary Method*

The primary analysis method was the exact method for a stratified odds ratio and associated 95% confidence interval (Cytel 2005, Ch. 19). The odds ratio was in terms of patient units. The stratification factor was the trial.

#### *4.4.2 Sensitivity Methods*

Three sensitivity analyses were employed to examine the robustness of the primary method.

##### *4.4.2.1 Zero-Event Trials*

The first sensitivity analysis examined the consequences of the fact that a large number of the trials were expected to have no events. The exact method for a stratified odds ratio does not make use of these trials. The Mantel-Haenszel risk difference and associated confidence interval (Greenland and Robins 1985), which makes use of these trials, was

used for this sensitivity analysis. However, if there are no events for any trials, for example in a subgroup, then the estimated variance will be zero. In this case, it is not appropriate to use the variance estimate, and no estimate and confidence intervals were presented.

#### 4.4.2.2 Trial Heterogeneity

The second sensitivity analysis examined between-trial heterogeneity of the effect measure. Zelen's test (Cytel 2005, Ch. 19), an exact test, was used to test the hypothesis of a common odds ratio. However, because of the small number of events, it was expected that there would be little power to detect heterogeneity of the odds ratio across trials. The result of the test was intended for qualitative purposes.

The trial weight of the Mantel-Haenszel odds ratio estimator was used to quantitatively identify trials with large influence. The weight was equal to  $(\text{control patients with events}) * (\text{test patients without events}) / (\text{total patients})$ . Trials with no events had a weight of zero. For trials with events in one arm only, the weight was equal to  $(\text{control patients with events} + 0.5) * (\text{test patients without events} + 0.5) / (\text{total patients} + 2)$ . Note that the SAP incorrectly specified "+1" rather than "+2" in the denominator.

A generalized linear mixed model (GLMM) (McCulloch and Searle 2001) was used to estimate the overall odds ratio in the presence of trial heterogeneity of the odds ratio. The model used the binomial error distribution and logit link function. The model included fixed effects for the trial and treatment effects and a random effect on the trial-level for the treatment-trial interaction. The estimate and the 95% confidence interval of the treatment effect were qualitatively compared to those from the primary method to examine the effect of trial heterogeneity. The confidence interval of the variance component of the random effect was also examined to evaluate trial heterogeneity.

#### 4.4.2.3 Duration Differences

The third sensitivity method, which was not part of the SAP, examined the consequences of the observed difference in treatment duration between the treatment arms. The method was similar to the primary method, but used person-time rather than patients as the unit of analysis (Cytel 2005, Ch. 15). Because the duration difference was small, an assumption of constant hazards was not key.

### 4.4.3 Exploratory Methods

#### 4.4.3.1 Time Pattern

Kaplan-Meier incidence curves were used to examine the time-pattern (hazard function) of the *Suicidal Behavior or Ideation* events. For patients with multiple events, only the most critical event was used. No stratification was employed in the analysis.

#### 4.4.3.2 Demographics, Duration and Discontinuation

Differences in treatment arms within trials of demographics, treatment duration, and premature discontinuation of patients were examined. For categorical variables, p-values for differences between treatment groups were based on the Cochran-Mantel-Haenszel test stratifying on trial. For continuous variables, p-values and least-squares means were based on a 2-way ANOVA controlling for trial.

#### 4.4.3.3 Multiple Events

For each patient that had multiple events, the events were summarized.

#### 4.4.4 Missing values

There were no missing values allowed for trial, treatment arm, and event codes. Therefore, the primary analysis was not be affected by missing values. For each subgroup analysis, all patients with the necessary information to determine the subgroup membership were used.

#### 4.4.5 Statistical Significance

Statistical significance refers to a two-sided type 1 error of 0.05. Because the analysis was exploratory in nature, no adjustments for multiplicity were be made.

## 5 PATIENT SUMMARY

### 5.1 Drugs and Demographics

Table 6 gives the number of patients by treatment arm and comparator type (placebo-controlled versus low-dose-controlled). Overall, there were 43,892 patients in the placebo and the drug arms from placebo-controlled trials. There were more patients in the drug arms (27,863) than in the placebo arms (16,029) for these trials. There were 1,587 patients from low-dose-controlled trials. Not included in the table were an additional 1,997 patients from active-control arms among the placebo-controlled and low-dose-controlled trials.

Table 6: Patients by Treatment Arm and Comparator Type.

Comparator Type	Treatment Arm			Total
	Drug	Placebo	Low-Dose Placebo	
Placebo-Controlled	27863	16029	0	43892
Low-Dose Controlled	788	0	799	1587
Total	28651	16029	799	45479

Table 7 gives the number of patients by treatment arm and drug for placebo-controlled trials. The drugs topiramate and pregabalin accounted for approximately half of the overall patients: 27% for topiramate and 24% for pregabalin.

Table 7: Patients by Treatment Arm and Drug, Placebo-Controlled Trials.

Drug	Treatment Group		
	Drug N = 27863 n (%)	Placebo N = 16029 n (%)	Total N = 43892 n (%)
Carbamazepine	252 (1)	250 (2)	502 (1)
Divalproex	1327 (5)	992 (6)	2319 (5)
Felbamate	170 (1)	170 (1)	340 (1)
Gabapentin	2903 (10)	2029 (13)	4932 (11)
Lamotrigine	2865 (10)	2070 (13)	4935 (11)
Levetiracetam	2554 (9)	1549 (10)	4103 (9)
Oxcarbazepine	1342 (5)	827 (5)	2169 (5)
Pregabalin	7201 (26)	3125 (19)	10326 (24)
Tiagabine	835 (3)	608 (4)	1443 (3)
Topiramate	7742 (28)	3971 (25)	11713 (27)
Zonisamide	672 (2)	438 (3)	1110 (3)

Table 8 gives the number of patients by indication group and drug. Seven of the 11 drugs had patients in all three indication groups. Large percentages of gabapentin and topiramate patients were in the Other Indication group (non-epilepsy, non-psychiatric). Overall, the Other Indication group had the most patients with 48% of the patients. The Epilepsy and Psychiatric Indication groups had similar percentages of the patients to each other with roughly 25% of the patients each.

Table 8: Patients by Indication Group and Drug, Placebo-Controlled Trials.

Drug	Indication Group			Total N
	Epilepsy n (n/N%)	Psychiatric n (n/N%)	Other n (n/N%)	
Carbamazepine	0 (0)	502 (100)	0 (0)	502
Divalproex	147 (6)	1285 (55)	887 (38)	2319
Felbamate	340 (100)	0 (0)	0 (0)	340
Gabapentin	1485 (30)	331 (7)	3116 (63)	4932
Lamotrigine	1408 (29)	2313 (47)	1214 (25)	4935
Levetiracetam	1634 (40)	1609 (39)	860 (21)	4103
Oxcarbazepine	1110 (51)	115 (5)	944 (44)	2169
Pregabalin	1685 (16)	3204 (31)	5437 (53)	10326
Tiagabine	939 (65)	504 (35)	0 (0)	1443
Topiramate	1346 (11)	1933 (17)	8434 (72)	11713
Zonisamide	848 (76)	0 (0)	262 (24)	1110
Total	10942 (25)	11796 (27)	21154 (48)	43892

Table 9 gives the demographics of the patients by treatment arm. For age, gender, race, and location there were no statistically significant differences between the treatment arms. P-value for setting could not be calculated due to the sparseness of the data, but the observed percentages were similar between the treatment arms.

The least-squares means for age was 42 for both treatment arms. The least-squares means control for differences among the trials and are more appropriate measures than the ordinary means in the context of the meta-analysis, which controls for differences among the trials. Roughly 5% of the patients were under the age of 18 and 13% of the patients were age 65 or older. A majority of the patients were female (55%). A large majority of the patients were white Caucasian (79%). A large majority of patients had out-patient treatment only (92%) and a majority of the patients were in North America (61%).



Table 9: Demographics by Treatment Arm, Placebo-Controlled Trials.

Characteristic		Drug N=27863	Placebo N=16029	Total N=43892	P-Value
Age (Years)	5-17	1292 (5)	1119 (7)	2411 (5)	0.2745
	18-24	2126 (8)	1296 (8)	3422 (8)	
	25-30	2633 (9)	1568 (10)	4201 (10)	
	31-64	18157 (65)	9990 (62)	28147 (64)	
	≥ 65	3653 (13)	2056 (13)	5709 (13)	
	Missing	2 (0)	0 (0)	2 (0)	
	Mean (Std.)	45 (17)	43 (18)	44 (17)	0.2184
	Least-Squares Mean	42	42		
	Range (Min – Max)	(5 -100)	(5 – 99)	(5 – 100)	
Gender	Female	15586 (56)	8686 (54)	24272 (55)	0.6557
	Male	12276 (44)	7343 (46)	19619 (45)	
	Missing	1 (0)	0 (0)	1 (0)	
Race	White Caucasian	22302 (80)	12541 (78)	34843 (79)	0.1703
	Other	3588 (13)	2264 (14)	5852 (13)	
	Missing	1973 (7)	1224 (8)	3197 (7)	
Setting	Inpatient or Both	1893 (7)	1411 (9)	3304 (8)	NA
	Outpatient	25970 (93)	14618 (91)	40588 (92)	
	Missing	0 (0)	0 (0)	0 (0)	
Location	North America	16841 (60)	9941 (62)	26782 (61)	0.9523
	Non-North America	11022 (40)	6088 (38)	17110 (39)	
	Missing	0 (0)	0 (0)	0 (0)	

Notes: Results for categorical variables are expressed as counts and percentages of treatment arm. P-values for categorical variables are based on Cochran-Mantel-Haenszel test controlling for trial. P-values and least-squares means for continuous variables are based on 2-way ANOVA controlling for trial. P-value for setting could not be calculated due to the sparseness of the data.

Table 10 gives the number of patients for the three drug groups. No p-values are available because drug class does not vary within a trial. As stated in Section 4.3, the three drug groups are not mutually exclusive. Drugs and therefore patients appear in multiple drug groups.

Table 10: Patients by Drug Class and Treatment Arm, Placebo-Controlled Trials.

Drug Group		Drug N=27863	Placebo N=16029	Total N=43892
Sodium Channel Blocking	Yes	12873 (46)	7556 (47)	20429 (47)
	No	14990 (54)	8473 (53)	23463 (53)
GABAergic and GABAmimetic	Yes	20008 (72)	10725 (67)	30733 (70)
	No	7855 (28)	5304 (33)	13159 (30)
Carbonic Anhydrase Inhibitors	Yes	8414 (30)	4409 (28)	12823 (29)
	No	19449 (70)	11620 (72)	31069 (71)

## 5.2 Discontinuation and Duration

Table 11 gives the treatment discontinuation status and the duration by treatment arm. A statistically significant larger percentage of drug patients discontinued prematurely than placebo patients. The placebo patients had a statistically significant larger least-squares mean for duration than drug patients. However, the drug patients had a larger ordinary mean for duration than the placebo patients.

The difference in results between the least-squares means and the ordinary means is influenced by a single trial. Figure 1 plots for each trial, the mean placebo duration versus the mean drug duration. The overall consistency of the durations within trials is seen by the fact that most trials fall near the 45-degree line. The trial with the largest durations (topiramate OBES002) had a large imbalance of patients between the arms: 960 drug patients and 322 placebo patients. This imbalance in arm sizes had large influence on the ordinary means. Removing this trial, the ordinary means were more similar, 82 days for each arm. Overall, for 131 of the 199 trials, the placebo arm had a higher duration than the drug arm.

Since the meta-analysis controlled for differences in trials, the least-squares means are more appropriate to examine differences in duration. The least-squares means show that the placebo patients had larger durations (77 days for placebo versus 73 days for drug). If events were related to duration, the placebo patients may be expected to have more events independent of any treatment effect. The person-time analysis described in Section 4.4, which was not part of the Statistical Analysis Plan, was performed to account for the possibility of a duration effect.

Table 11: Patient Treatment Discontinuation and Duration by Treatment Arm, Placebo-Controlled Trials.

Characteristic		Drug N=27863	Placebo N=16029	Total N=43892	P-Value
Discontinue	No	17889 (64)	11118 (69)	29007 (66)	<.0001
	Yes	9974 (36)	4911 (31)	14885 (34)	
	Missing	0 (0)	0 (0)	0 (0)	
Duration (Days)	Mean (Std.)	90 (89)	87 (78)	89 (85)	<.0001
	Least-Squares Mean	73	77		
	Range (Min – Max)	(0 – 575)	(1 – 582)	(0 – 582)	
	Missing	9	8	17	

Notes: Results for categorical variables are expressed as counts and percentages of treatment arm. P-values for categorical variables are based on Cochran-Mantel-Haenszel test controlling for trial. P-values and least-squares means for continuous variables are based on 2-way ANOVA controlling for trial.

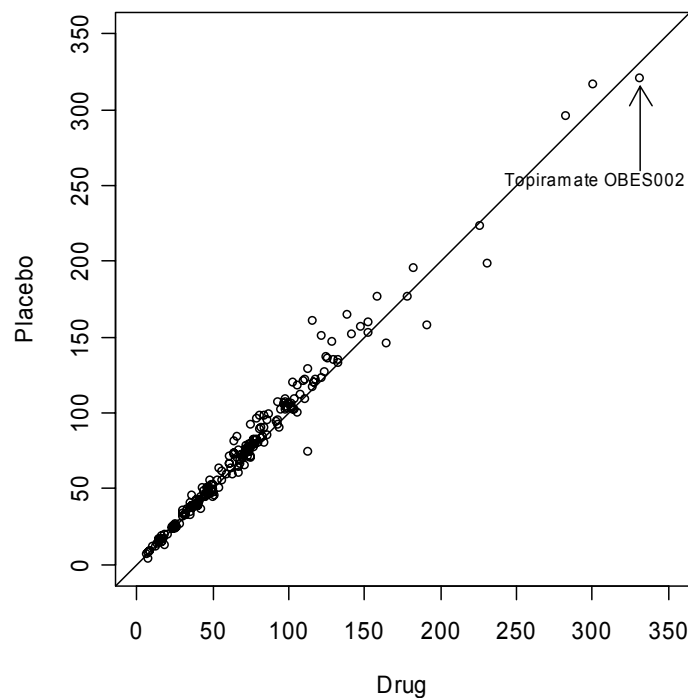


Figure 1: Mean Trial Duration by Treatment Arm, Placebo-Controlled Trials.

## 6 FINDINGS

### 6.1 Suicidal Behavior or Ideation

Table 12 gives the number of patients with a Suicidal Behavior or Ideation event by type of event and treatment arm. There were 4 completed suicides among patients in the drug arms and none among patients in the placebo arms. Of the 4 completed suicides, 2 were in the Epilepsy Indication subgroup and 2 were in the Psychiatric Indication subgroup. The majority of events for both arms were Suicidal ideation. The second most frequent type of event for both arms was Suicide Attempt. Note that as seen on Table 6, there were more drug patients than placebo patients. Without adjusting for differences among trials, 0.37% of the drug patients had a Suicidal Behavior or Ideation event versus 0.24% of the placebo patients. Of the 199 placebo-controlled trials, 66 (33%) had at least one Suicidal Behavior or Ideation event in the test drug or placebo arms.

Table 12: Events by Type and Treatment Arm, Placebo-Controlled Trials.

Event	Drug	Placebo	Total
Completed suicide	4	0	4
Suicide attempt	30	8	38
Preparatory acts	3	1	4
Suicidal ideation	67	29	96
Total	104	38	142

Notes: Events include only the most critical event for each patient.

Table 13 gives the number of patients with a Suicidal Behavior or Ideation event, the number of patients, and the crude odds ratios by drug. The drug felbamate had no events and therefore the odds ratio for the drug is not defined. The drug tiagabine had events only in the drug arm and therefore the odds ratios for this drug was infinity. No drug had events only in the placebo arm. The range of the finite crude odds ratios was from 0.66 to 2.57.

Table 13: Suicidal Behavior or Ideation Events and Patients by Drug, Placebo-Controlled Trials.

Drug	Drug Events/Patients	Placebo Events/Patients	Crude OR
Carbamazepine	2/252	3/250	0.66
Divalproex	11/1327	9/992	0.91
Felbamate	0/170	0/170	ND
Gabapentin	2/2903	1/2029	1.40
Lamotrigine	27/2865	11/2070	1.78
Levetiracetam	8/2554	2/1549	2.43
Oxcarbazepine	2/1342	1/827	1.23
Pregabalin	7/7201	2/3125	1.52
Tiagabine	2/835	0/608	Inf.
Topiramate	40/7742	8/3971	2.57
Zonisamide	3/672	1/438	1.96
Total	104/27863	38/16029	1.58

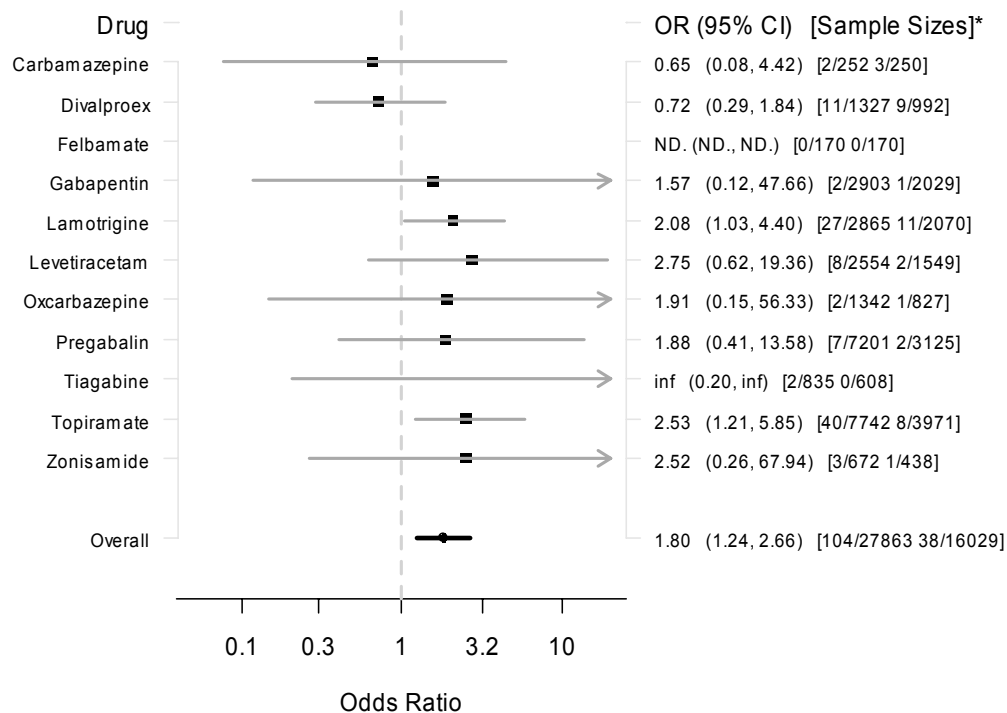
Notes: Events include only most critical event for each patient.

ND: Not defined. Inf.: Infinity.

Figure 2 gives a forest plot of the estimated odds ratios and 95% confidence intervals for Suicidal Behavior or Ideation by drug and overall. The estimated overall odds ratio was 1.80 (95% CI: 1.24, 2.66). The odds ratio was greater than 1 and the confidence interval did not contain the value of 1. Therefore, the drugs were associated with statistically significant increased risk of Suicidal Behavior or Ideation events relative to placebo.

Based on the overall odds ratio estimate and the observed rate of 0.24% for Suicidal Behavior or Ideation events among placebo patients, there was an estimated 1.9 per 1000 (95% CI: 0.6, 3.9) more antiepileptic drug patients than placebo patients who experienced Suicidal Behavior or Ideation in placebo-controlled trials. In terms of adjusted risk estimates for the treatment groups, 0.43% of the drug patients experienced Suicidal Behavior or Ideation compared to the 0.24% of placebo patients.

Among the 10 drugs with any events, the estimated odds ratios for 8 drugs were greater than 1. For 2 of these 8 drugs, the confidence interval did not contain the value of 1.



\*[Treat. Events/Treat. n Plac. Events/Placebo n]

Figure 2: Suicidal Behavior or Ideation Odds Ratio Estimates, Placebo-Controlled Trials.

## 6.2 Suicidal Behavior and Suicidal Ideation

Figure 3 gives the overall odds ratio estimates for the two endpoints: (1) Suicidal Behavior and (2) Suicidal Ideation. The odds ratio estimate for Suicidal Behavior was greater than the odds ratio for Suicidal Ideation. The confidence interval for Suicidal Behavior did not contain the value of 1, whereas the confidence interval for Suicidal Ideation contained the value of 1.

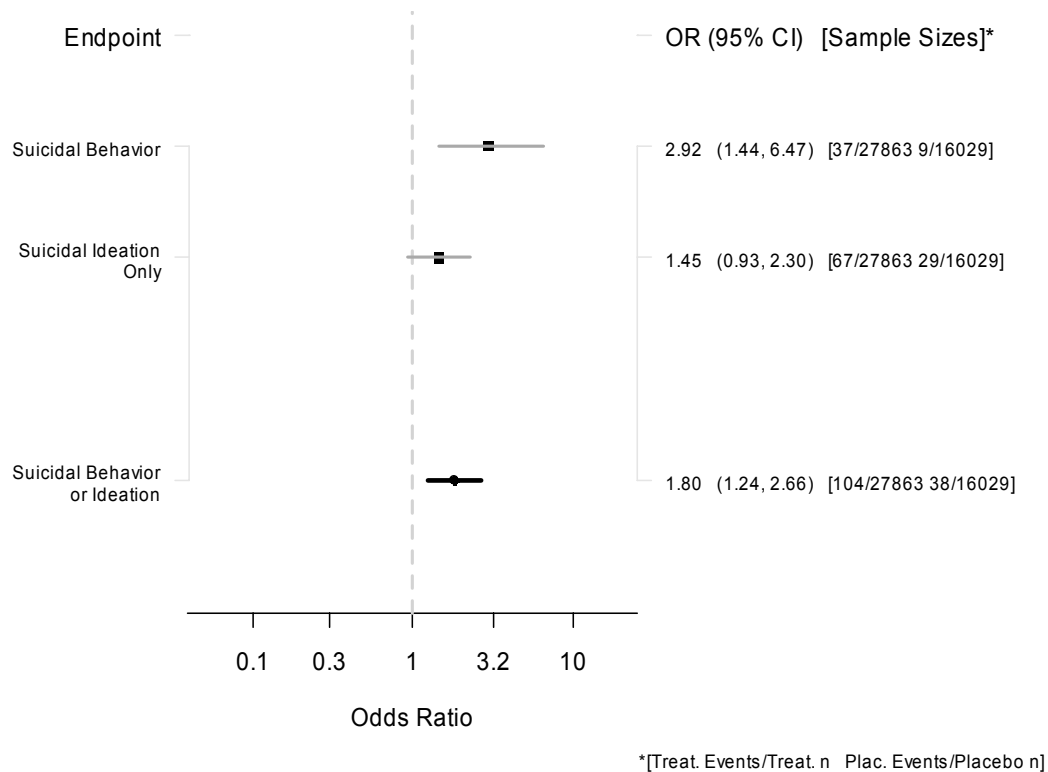


Figure 3: Suicidal Behavior versus Suicidal Ideation Odds Ratio Estimates, Placebo-Controlled Trials.

## 6.3 Sensitivity Analysis

### 6.3.1 Zero-Event Trials

Figure 4 gives the estimated risk differences and 95% confidence intervals for Suicidal Behavior or Ideation by drug and overall. Unlike the odds ratio analysis, this risk difference analysis makes use of trials without any events.

The overall risk difference was 1.79 (95% CI: 0.70, 2.87) per 1000 patients. The risk difference was greater than 0 and the confidence interval did not contain the value of 0. As was the case, for the odds ratio analysis, this result supports the finding that the drugs were associated with statistically significant increased risk of Suicidal Behavior or Ideation events relative to placebo. For each of the 11 drugs, the risk difference estimate had the same direction as the odds ratio estimate relative to the null value of no effect.

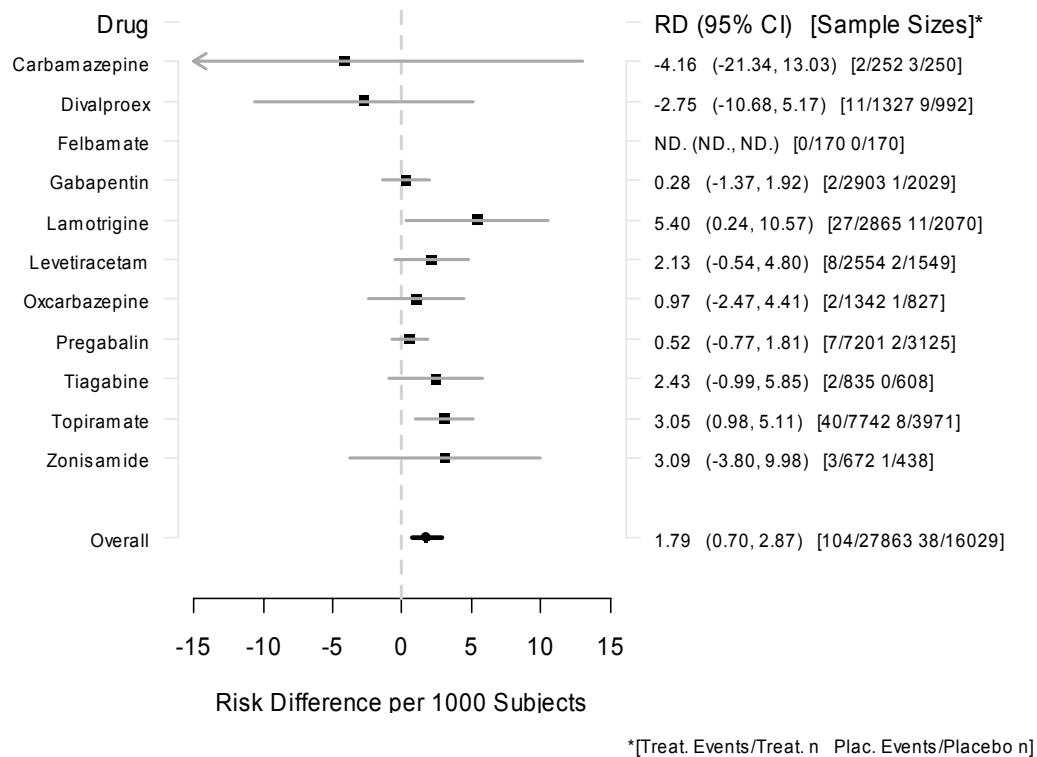


Figure 4: Suicidal Behavior or Ideation Risk Difference Estimates, Placebo-Controlled Trials.

### 6.3.2 Trial Heterogeneity

The primary analysis method was a fixed-effect method. Fixed effect methods assume that all the trials had a common treatment effect. The p-value based on Zelen's test for the null hypothesis that all trials had a common odds ratio test was 0.735. This value does not provide evidence for trial heterogeneity in the odds ratio. However, the lack evidence does not imply that there was no trial heterogeneity.

The general linear mixed model (GLMM) that allows for trial heterogeneity produced an overall odds ratio estimate of 1.86 (95% CI: 1.24, 2.78). Both the estimate and the



confidence interval were very similar to those from the primary analysis method. The similarity implies that trial heterogeneity was not a major concern. The variance component estimate for the trial heterogeneity effect from the GLLM was 0.13 with a standard error of 0.26. The scale of the component is complex. However, the fact that the estimate was small relative to its standard error again does not provide evidence for trial heterogeneity.

The Mantel-Haenszel odds ratio weights were calculated to examine if there were trials with large influence on the overall odds ratio estimate. On a normalized scale such that the weights add to one, the largest five weights were 0.060, 0.020, 0.019, 0.017, and 0.016. The weight of 0.06 corresponded to the trial divalproex M92822. Except for this trial, no trial accounted for more than one fiftieth of the total weight. The overall odds ratio estimated using the exact method and excluding this trial was 2.12 (95% CI: 1.42, 3.25). This estimate was slightly larger than the estimate with all the trials. However, the two sets of estimates and confidence intervals were qualitatively similar.

### 6.3.3 Person-Time Analysis

Based on the finding that there was a statistically significant difference in treatment duration between the treatment arms (least-squares means 77 days for placebo versus 73 days for drug), an analysis that adjusts for differences in duration was performed. Figure 5 gives the estimated rate ratio and 95% confidence intervals from this analysis for Suicidal Behavior or Ideation by drug and overall. The overall rate ratio was 1.82 (95% CI: 1.25, 2.68). This result was very similar to the overall odds ratio result, which does not adjusted for difference in treatment duration. Additionally, for each of the 11 drugs, the rate estimate was very similar to the odds ratio estimate.

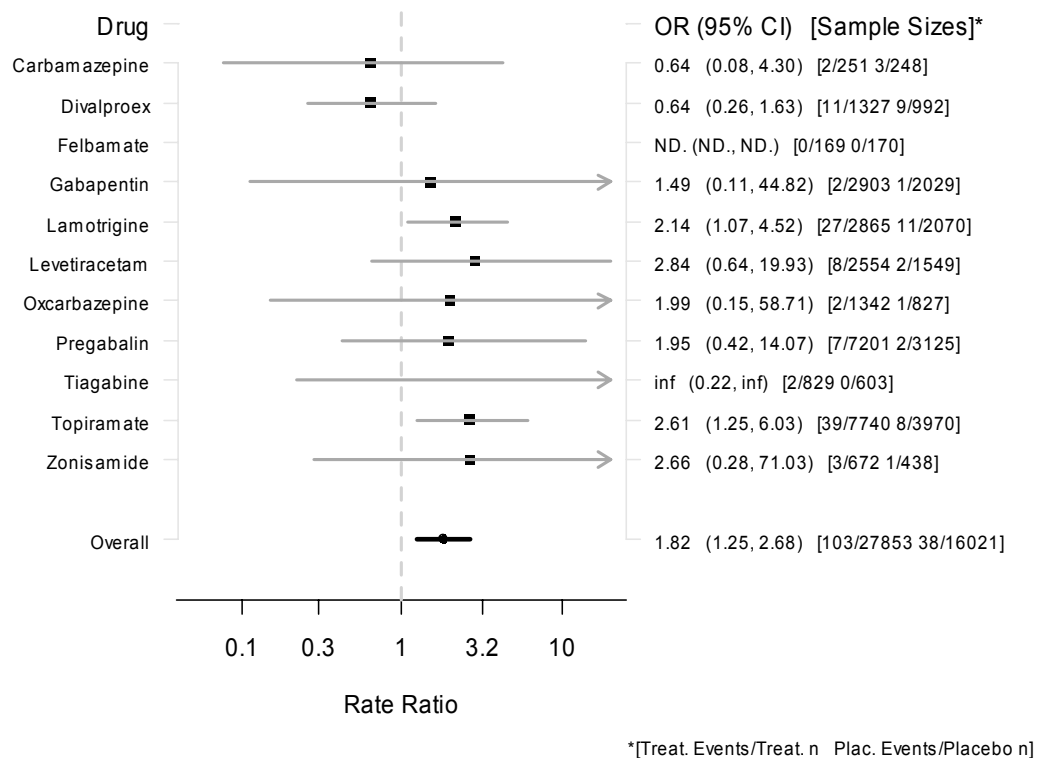


Figure 5: Suicidal Behavior or Ideation Rate Ratio Estimates, Placebo-Controlled Trials.  
Note: 18 Patients with missing or zero duration were not included in this analysis.

## 6.4 Exploratory Analysis

### 6.4.1 Time-to-Event Analysis

Table 14 shows the number of patients with a Suicidal Behavior or Ideation event and the estimated hazards by disjoint time intervals. The higher hazard of events for the drug-treated patients was observed as early as 1 week from initiating treatment until at least 24 weeks. After 24 weeks, it was not possible to draw conclusions due to the scarcity of data beyond 24 weeks. It appears that the drug effect existed over an extended period and not, for example, just at the initiation of the treatment.

Figure 6 plots Kaplan-Meier incidence curves for the Suicidal Behavior or Ideation events by treatment arm. The spreading of the two curves, at least up to 24 weeks, shows that the higher hazard for the drug patients existed over a period of time.

For the time-to-event analysis as in the other analyses, the first most critical event was used. For all but one patient, this was the first event as well. One patient had a lesser critical event 2 days earlier than the most critical event.

Table 14: Suicidal Behavior or Ideation Hazard Estimates by Treatment Arm, Placebo-Controlled Trials.

Week	Events	Drug		Events	Placebo	
		Patients	Hazard		Patients	Hazard
< 1	10	27337	0.37	5	15780	0.32
1 - 2	13	26077	0.50	4	15192	0.26
2 - 4	27	23979	0.56	11	14029	0.39
4 - 12	34	17591	0.24	14	10312	0.17
12 - 24	12	8139	0.12	3	4592	0.05
≥ 24	7	1862	0.05	1	886	0.02

Notes: Events include only the most critical event for each patient. Patients are “effective sample size” which is the estimated number of patients at the midpoint of interval. Hazard is expressed as events per 1000 patient-weeks. For details see Klein and Moeschberger (2003, p. 152).

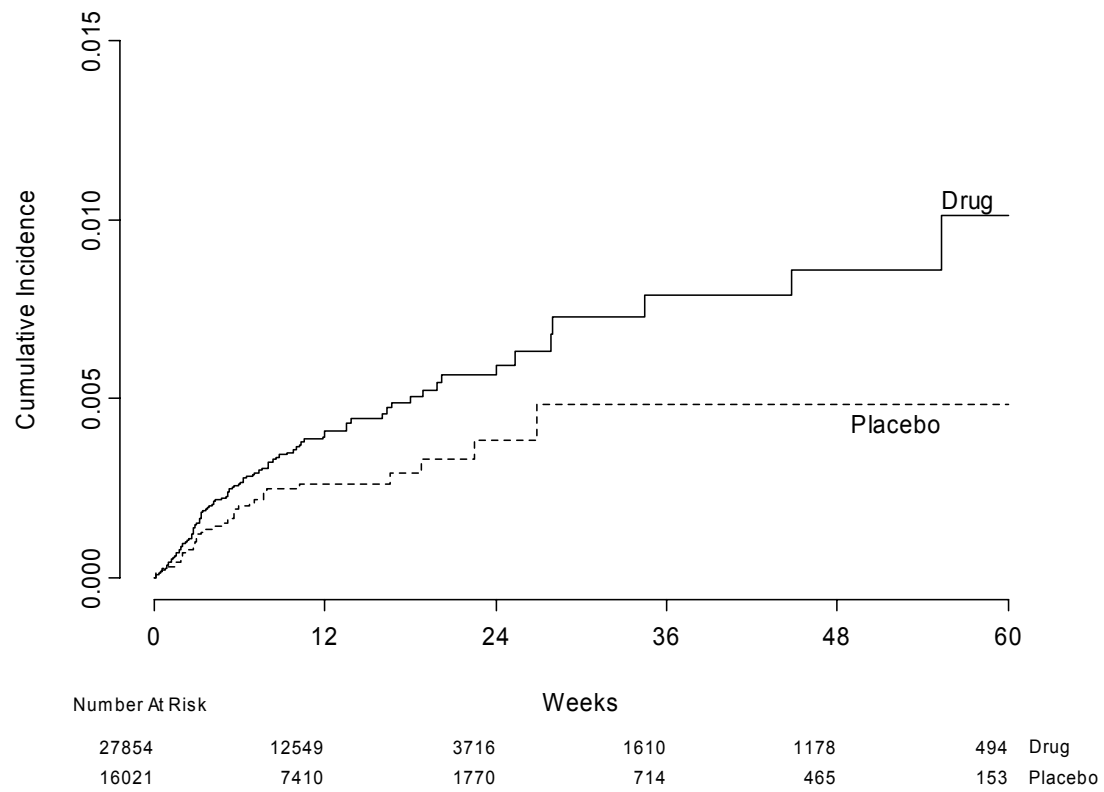


Figure 6: Kaplan-Meier Suicidal Behavior or Ideation Incidence Curves by Treatment Arm, Placebo-Controlled Trials.

#### 6.4.2 Multiple Events

Among the placebo-controlled trials, 9 patients had more than one Suicidal Behavior or Ideation event. Table 15 lists the events for these patients. One patient had two suicide attempts. Another patient had one suicide attempt. The events of the remaining 7 patients were all suicidal ideation.

Table 15: Events from Patients with Multiple Events, Placebo-Controlled Trials.

Patient	Event	Event Day
Carbamazepine 105.301 004004	Ideation	11
	Ideation	12
Divalproex M92822 13709	Ideation	44
	Ideation	234
Divalproex M96493 20101	Ideation	17
	Suicide attempt	19
Lamotrigine P42040 37004	Ideation	5
	Ideation	75
	Ideation	83
	Ideation	88
Lamotrigine SCA3092/0946 63307	Ideation	56
	Ideation	78
Lamotrigine SCAA2010 03168	Suicide attempt	23
	Suicide attempt	30
Topiramate CAPSS168 00013403	Ideation	25
	Ideation	56
Topiramate OBES002 7123	Ideation	51
	Ideation	82
Topiramate PDMD005 10004	Ideation	1
	Ideation	11

## 7 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 7.1 Drug Groups

Figure 7 gives the estimated odds ratios and 95% confidence intervals for Suicidal Behavior or Ideation by drug group. The estimated odds ratio for each drug group and its complement were all greater than one. Except for the group made of drugs that are not in the Sodium Channel Blocking group, the confidence intervals for all drug groups did not contain the value of 1. As stated above, the three drug groups are not disjoint. Topiramate is in all three drugs groups, and there were a large number of patients from topiramate trials. Therefore, treatment effects of topiramate can be expected to have large influence on all three drugs classes.

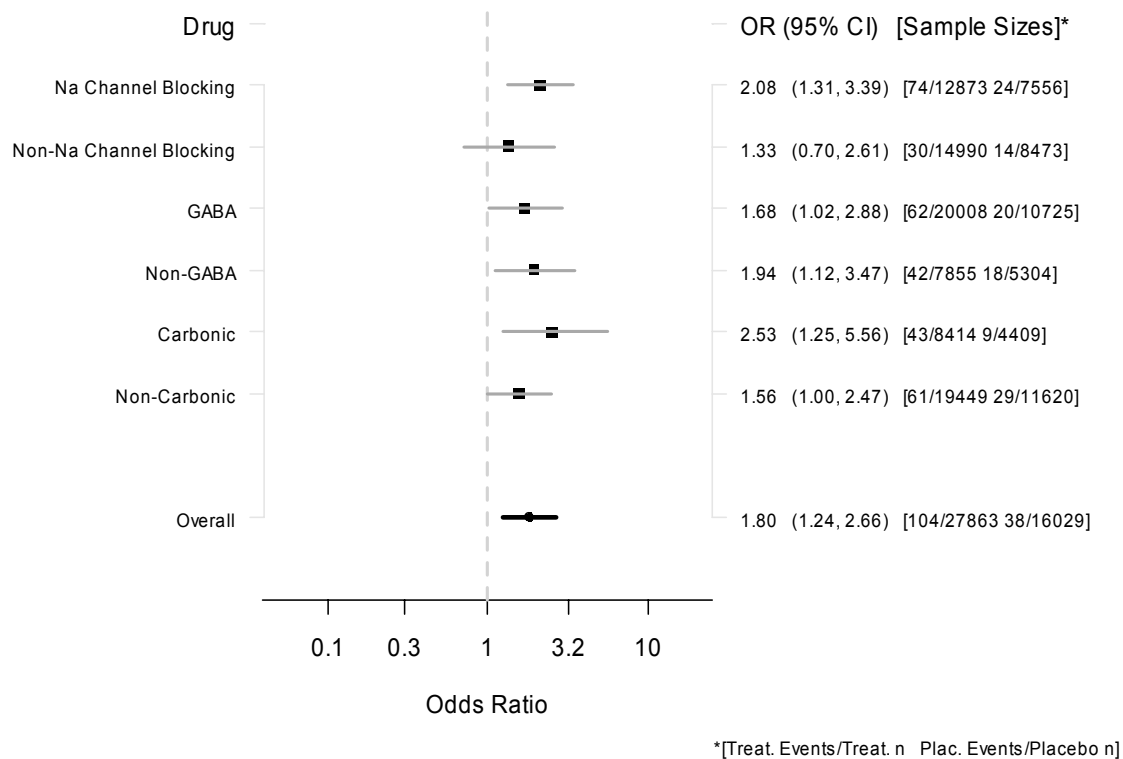


Figure 7: Suicidal Behavior or Ideation Odds Ratio Estimates by Drug Group, Placebo-Controlled Trials.

## 7.2 Trial Indication

Figure 8 gives the estimated odds ratios and 95% confidence intervals for Suicidal Behavior or Ideation by indication group. The epilepsy indication group had the highest estimated odds ratio and its confidence interval did not contain the value of 1. The odds ratios for the other two indication groups, psychiatric and other, were greater than 1, but the lower end of the confidence intervals were slightly below 1.

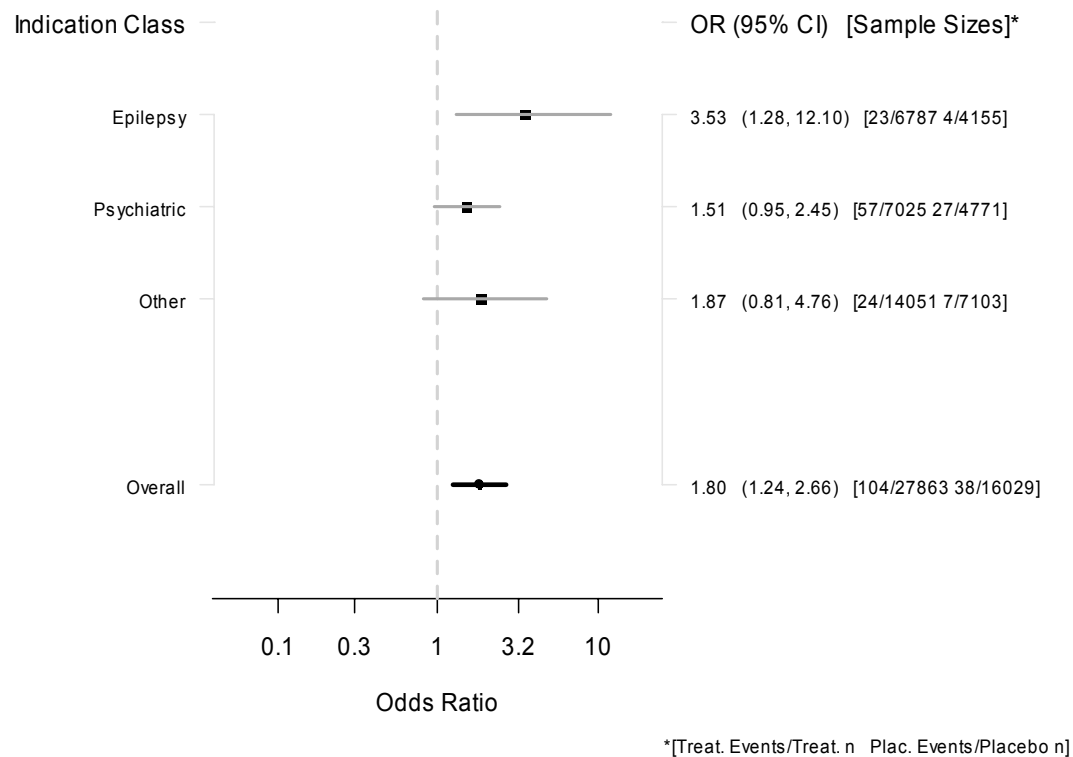


Figure 8: Suicidal Behavior or Ideation Odds Ratio Estimates by Indication Group, Placebo-Controlled Trials.

Although the estimated odds ratio was higher in the epilepsy indication group than in the psychiatric indication group, the excess drug risks in the two indication groups were similar. Table 16 gives estimates of the placebo and drug event rates and the risk difference risk by indication group. The psychiatric indication group had a notably higher placebo event rate than the other indication groups and had the highest risk difference, whereas, the epilepsy indication group had the highest odds ratio.

Table 16: Placebo and Drug Suicidal Behavior or Ideation Event Rates and Risk Difference by Indication, Placebo-Controlled Trials.

Indication	Odds Ratio	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients	Risk Ratio
Epilepsy	3.53	1.0	3.4	2.4	3.5
Psychiatric	1.51	5.7	8.5	2.9	1.5
Other	1.87	1.0	1.8	0.9	1.9
Total	1.80	2.4	4.3	1.9	1.8

Notes: Drug event rate was calculated as the product of the placebo event rate and estimated odds ratio. Risk difference was calculated as the drug event rate minus the placebo event rate. Risk ratio was calculated as the ratio of the drug event rate to the placebo event rate.



## 7.3 Demographics

### 7.3.1 Age

Figure 9 gives the estimated odds ratios and 95% confidence intervals for Suicidal Behavior or Ideation by age group. For all but the 25 – 30 age group, the estimated odds ratios were greater than 1. Only the 31 – 64 age group had a confidence interval that did not contain the value of 1. However, the other age-groups had smaller numbers of patients resulting in wider confidence intervals. Overall, there was no clear pattern across age groups.

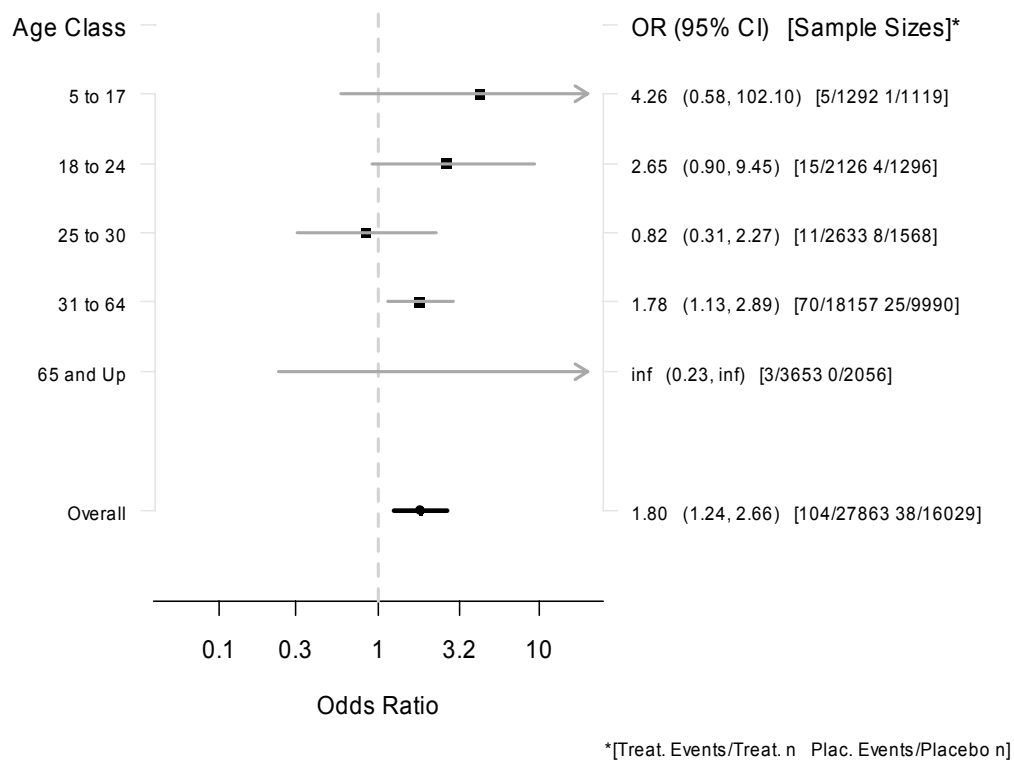


Figure 9: Suicidal Behavior or Ideation Odds Ratio Estimates by Age Group, Placebo-Controlled Trials.

### 7.3.2 Gender

Figure 10 gives the estimated odds ratios and 95% confidence intervals for Suicidal Behavior or Ideation trials by gender. For both females and males, the estimated odds ratios were greater than 1. The confidence interval for males did not contain the value of 1, whereas the confidence interval for females did contain the value of 1.

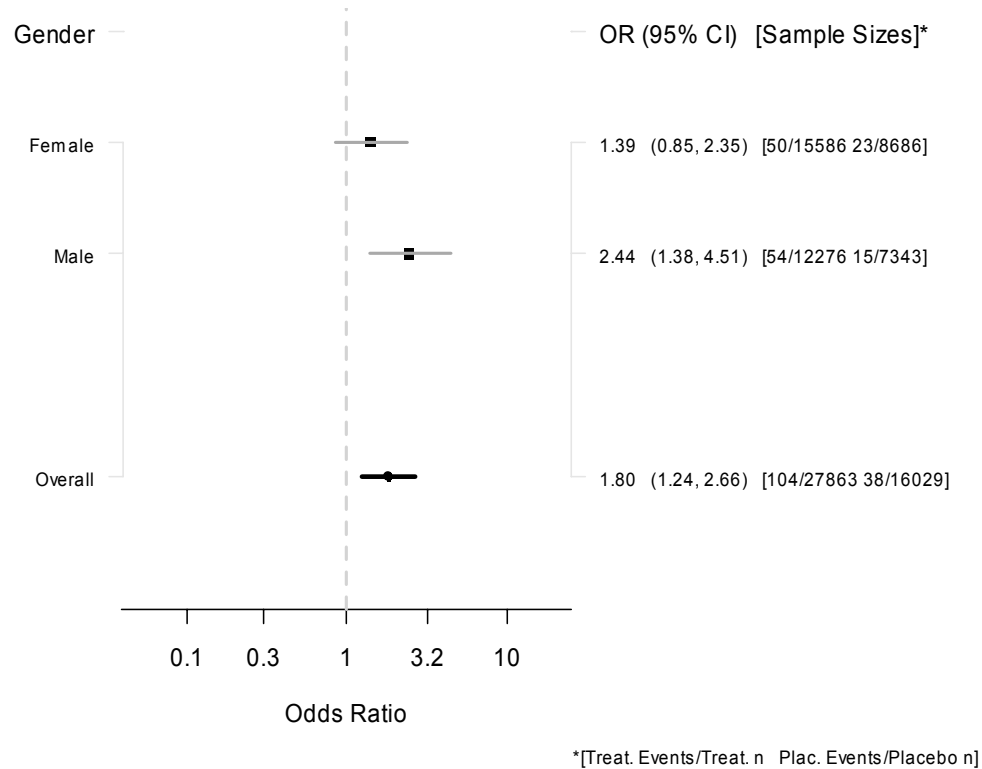


Figure 10: Suicidal Behavior or Ideation Odds Ratio Estimates by Gender, Placebo-Controlled Trials.

### 7.3.3 Race

Figure 11 gives the estimated odds ratios and 95% confidence intervals for Suicidal Behavior or Ideation by race. For both the white and other subgroups, the estimated odds ratios were greater than 1. The estimate for the other subgroup was higher than that for white subgroup. The confidence interval for the white subgroup did not contain the value of 1. The confidence interval for other subgroup contained the value of 1, but because of the small number of patients in this group, the confidence interval was wide.

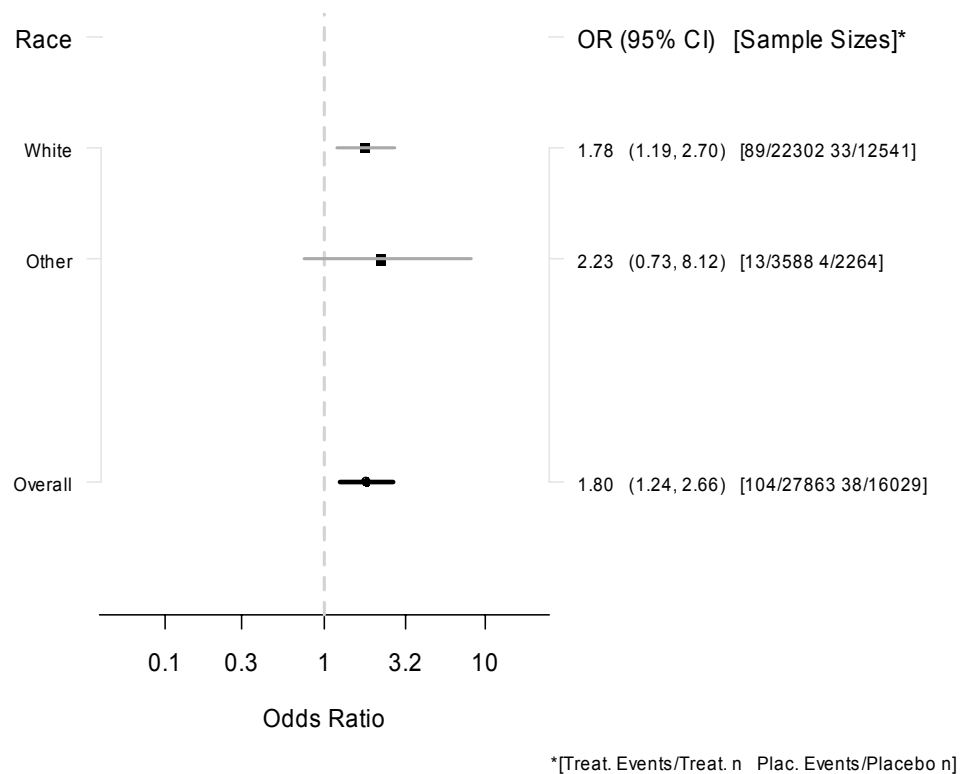


Figure 11: Suicidal Behavior or Ideation Odds Ratio Estimates by Race Group, Placebo-Controlled Trials.

#### 7.3.4 Setting

Figure 12 gives the estimated odds ratios and 95% confidence intervals for Suicidal Behavior or Ideation by setting. For both settings, the estimated odds ratios were greater than 1. The confidence interval for outpatient setting did not contain the value of 1. The confidence interval for the inpatient or both setting contained the value of 1, but because of the small number of patients in this group, the confidence interval was very wide.

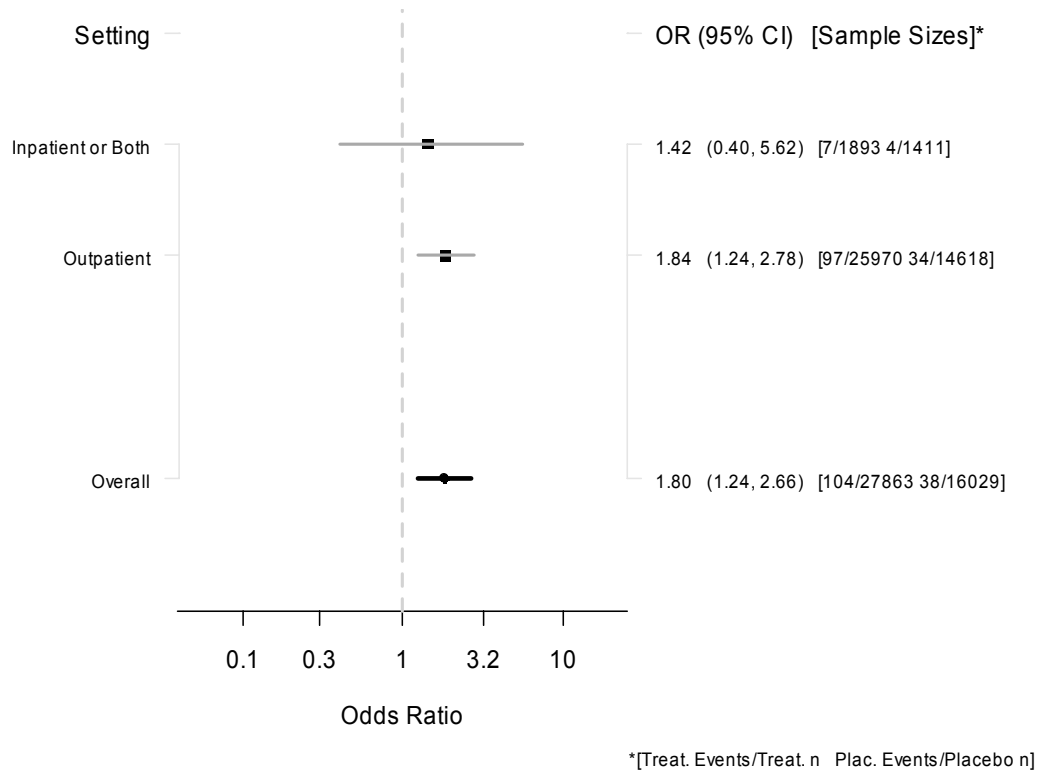


Figure 12: Suicidal Behavior or Ideation Odds Ratio Estimates by Setting, Placebo-Controlled Trials.

### 7.3.5 Location

Figure 13 gives the estimated odds ratios and 95% confidence intervals for Suicidal Behavior or Ideation by location. For both North America and Non-North America locations, the estimated odds ratios were greater than 1. However, the estimate for the Non-North America location was notably larger. The confidence interval for Non-North America location did not contain the value of 1. The lower end of the confidence interval for North America location was slightly below the value of 1.

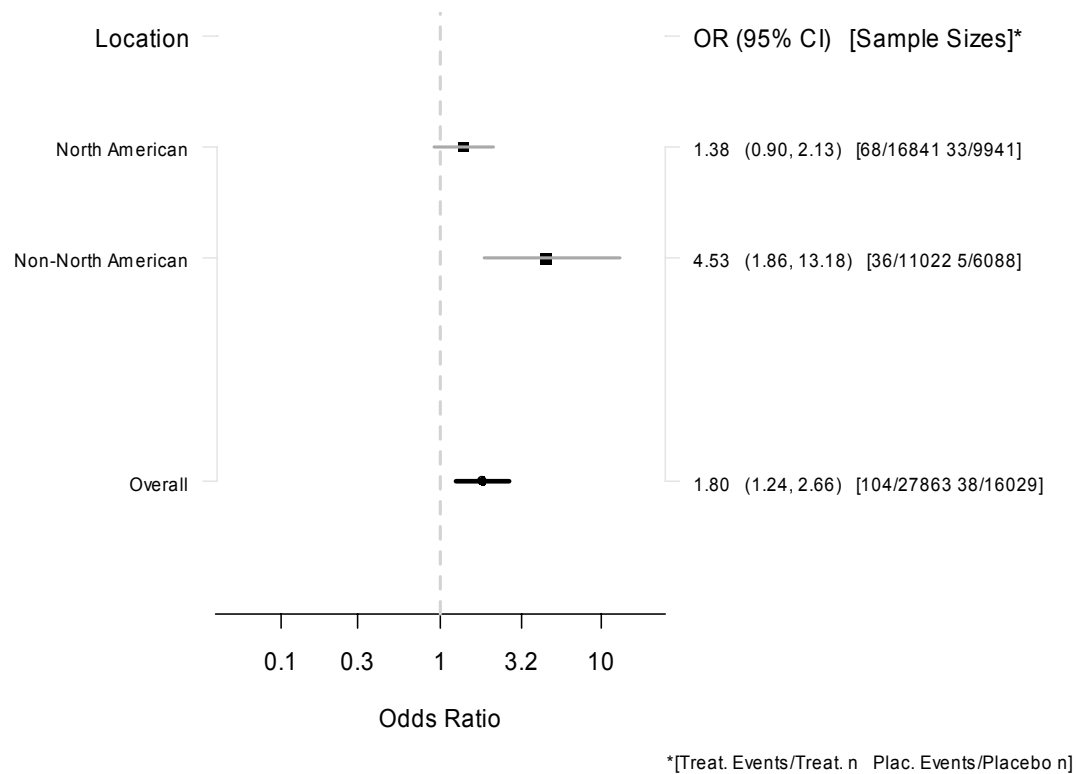


Figure 13: Suicidal Behavior or Ideation Odds Ratio Estimates by Location, Placebo-Controlled Trials.

### 7.3.6 Comparator Type

Figure 14 gives the estimated overall odds ratios and 95% confidence intervals for Suicidal Behavior or Ideation for placebo-controlled, low-dose-controlled trials, and all trials. The estimated odds ratio was 1.83 (95% CI: 1.26, 2.69) for all controlled trials. This result was very similar to the result for placebo-controlled trial, since most trials were placebo-controlled. The estimated odds ratio for low-dose-controlled trials was 3.09 (95% CI: 0.33, 81.51). The large confidence interval indicates that the result was not precise.

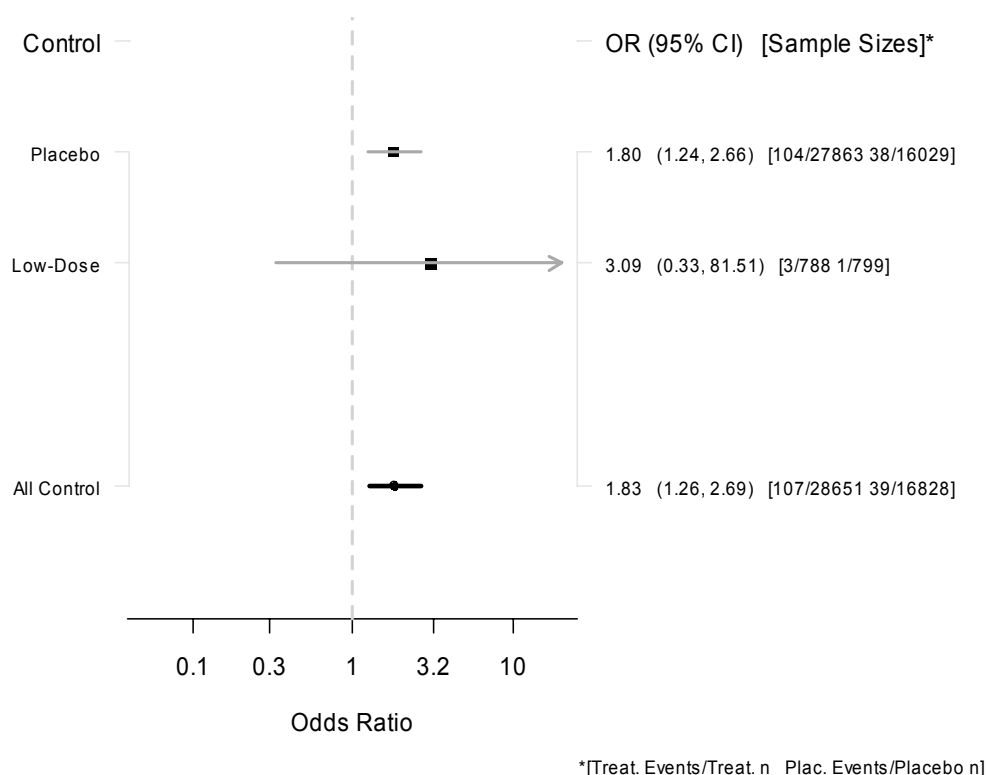


Figure 14: Suicidal Behavior or Ideation Odds Ratio Estimates, Placebo-Controlled and Low-Dose-Controlled Trials.

## 8 POST-HOC ANALYSES

In addition to the deviations and additions to the SAP noted above, there were analyses performed not specified in the SAP and performed after reviewing the initial analysis.

### 8.1 Lamotrigine Additional Data

On November 21, 2007, the sponsor of lamotrigine submitted additional data for the drug. The submission included (1) data from three trials that were ongoing at the time of the data requests to the sponsors and (2) 4 additional suicidality events from trials

previously submitted. As stated in Section 3.1.1, in the July 2005 letter to the sponsors, FDA stated that ongoing trials should not be submitted. FDA does not know if there are trials for other drugs that have been completed since July 2005. In the interests of adhering to FDA stated intentions, the additional lamotrigine data was not part of the primary analysis dataset. However, as a sensitivity analysis, the additional data was included.

The three additional lamotrigine trials were placebo-controlled trials and otherwise met the inclusion criteria for the analysis. These trials had a total of 9 Suicidal Behavior or Ideation events. Of these events, 1 was in a drug arm and 8 were in placebo arms.

Among the 4 additional events from trials previously submitted, 3 were in the drug arm and 1 was in the placebo arm.

Figure 15 gives the estimated odds ratio and 95% confidence intervals for Suicidal Behavior or Ideation by drug and overall with the additional lamotrigine data. The estimated overall rate ratio was 1.55 (95% CI: 1.09, 2.21). The estimate was lower than the estimate from the primary analysis, but statistically significant as well.

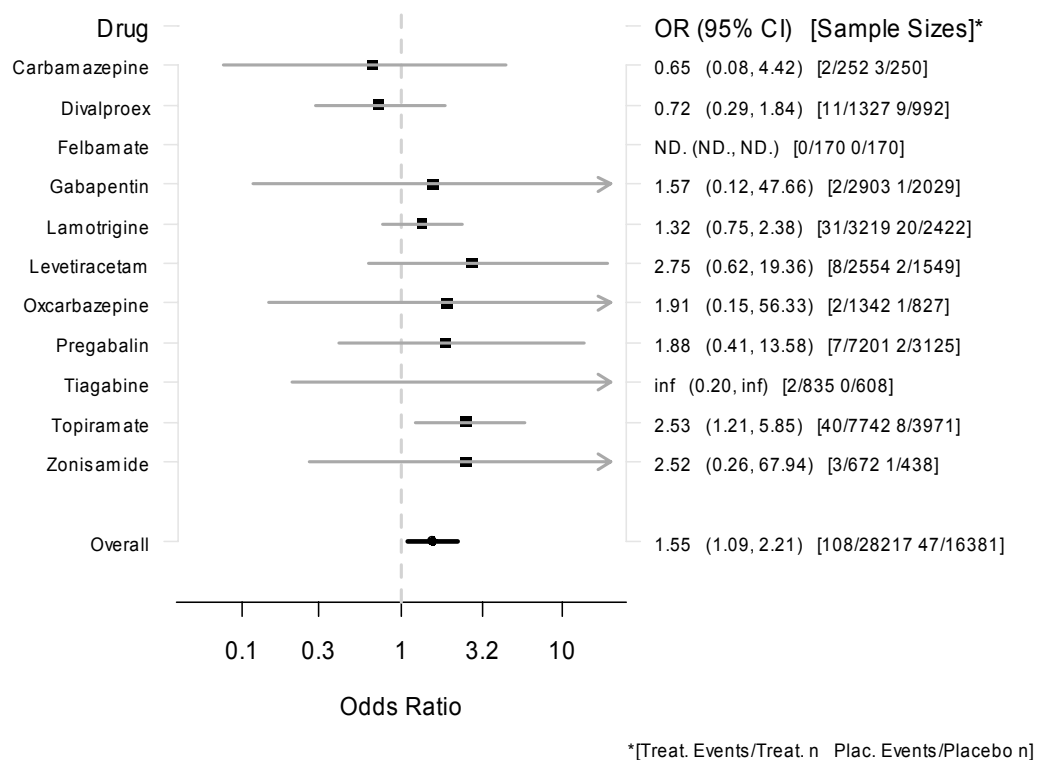


Figure 15: Suicidal Behavior or Ideation Odds Ratio Estimates with Additional Lamotrigine Data, Placebo-Controlled Trials.

## 8.2 Alternative Age Subgroups

In order to further explore the possibility of an interaction of age with the drug effect, a finer partition of the age subgroups was analyzed post-hoc. The 31 to 64 years age subgroup, which was part of the SAP, was partitioned into 4 age subgroups. Figure 16 gives the estimated odds ratios and 95% confidence intervals for Suicidal Behavior or Ideation by the post-hoc age groups. As was the case with the prospectively defined age subgroups, there was no clear pattern across age groups.

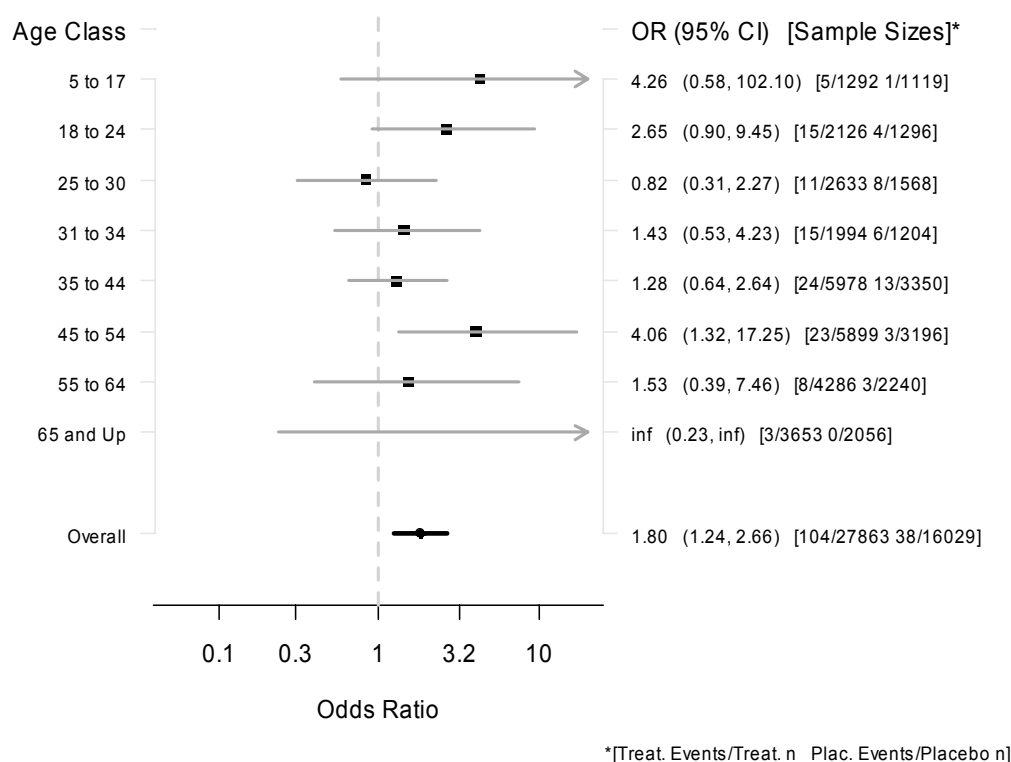


Figure 16: Suicidal Behavior or Ideation Odds Ratio Estimates by Post-Hoc Age Group, Placebo-Controlled Trials.

## 9 SUMMARY AND CONCLUSIONS

### 9.1 Review Summary

This reviewed analyzed data from 210 placebo-controlled and low-dose-controlled trials of antiepileptic drugs. The trials came from 11 different antiepileptic drugs. The indications for the trials included epilepsy, psychiatric disorders, and other indications. The primary focus of the review was on the 199 placebo-controlled trials. In these trials,



there were 27,863 patients in the drug arms and 16,029 patients in the placebo arms that met the analysis criteria of being at least 5 years of age.

There were no statistical differences among the baseline characteristics of the drug and placebo patients for age, gender, race, and location. The placebo patients had a statistically lower treatment discontinuation rate than the drug patients. Likewise, the placebo patients had statistically higher treatment duration (77 days for placebo versus 73 days for drug).

There were 4 completed suicides among drug patients and none among placebo patients. The majority of suicidality events for both drug and placebo patients were Suicidal Ideation. The second most frequent type of event was Suicide Attempt. Without adjusting for differences among trials, 0.37% of the drug patients had a Suicidal Behavior or Ideation event versus 0.24% of the placebo patients.

A meta-analysis was conducted to estimate an overall treatment effect for drug versus placebo patients and for various subgroups. The meta-analysis controlled for differences in background rates of events among the trials.

Overall, the drugs were associated with statistically significant increased the risk of Suicidal Behavior or Ideation relative to placebo. The estimated overall odds ratio was 1.80 (95% CI: 1.24, 2.66). There was consistency among the results for individual drugs. The estimated odds ratio was greater than 1 for 8 drugs and less than 1 for 2 drugs. The estimated odds ratio was greater for the Suicidal Behavior endpoint than the Suicidal Ideation endpoint.

Several sensitivity analyses were performed to examine the robustness of the result to the sparseness of the events, heterogeneity of the treatment effect, and differences in treatment duration between the placebo and drug arms. All the sensitivity analyses produced very similar results to the results of primary analysis for both the overall odds ratio and the individual drug odds ratios.

The higher risk of events for the drug-treated patients was observed as early as 1 week from initiating treatment until at least 24 weeks. After 24 weeks, it was not possible to draw conclusions due to the scarcity of data beyond 24 weeks.

Several subgroups were considered. Indication and location appeared to have the largest effects among the subgroups considered. The epilepsy indication subgroup had the largest estimated odds ratio compared to the psychiatric indication subgroup and the other indication subgroup. However, the psychiatric indication subgroup had the largest placebo risk of events. The result does not appear to be driven by particular drugs, since several drugs contributed comparable numbers of patients to the epilepsy subgroup. The estimated odds ratio for the Non-North American subgroup was notably larger than that of North American subgroup.

There was no obvious pattern in the risk with the age subgroups. For 4 of the 5 age subgroups, the estimated odds ratios were greater than 1. Likewise, there were no patterns in the risks for subgroups based on gender, race, setting, and prespecified drug groups.

## **9.2 Conclusions**

In conclusion, antiepileptic drugs are associated with increased risk of suicidality relative to placebo in randomized placebo-controlled trials. The effect appears consistent among the group of 11 drugs. There are 1.9 per 1000 (95% CI: 0.6, 3.9) more antiepileptic drug patients than placebo patients who experience Suicidal Behavior or Ideation. In terms of adjusted risk estimates for the treatment groups, 0.43% of the drug patients experience Suicidal Behavior or Ideation compared to 0.24% of the placebo patients.

There is no obvious subgroup of patients to which the increased risk is specifically attributed. The increased risk was seen in almost all subgroups, although epileptic and Non-North American patients may have higher relative risks.

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## **CLINICAL REVIEW: ANTIEPILEPTIC DRUGS AND SUICIDALITY**

Application Type	NDA
Submission Number	Carbamazepine (21-710) Divalproex sodium (18-723, 19-680, 21-168) Felbamate (20-189) Gabapentin (20-235, 20-882, 21-129, 21-216) Lamotrigine (20-241, 20-764) Levetiracetam (21-035, 21-505, 21-872) Oxcarbazepine (21-014, 21-285) Pregabalin (21-446) Tiagabine (20-646) Topiramate (20-505, 20-844) Zonisamide (20-789)
Reviewer Name	Evelyn Mentari, M.D., M.S.
Review Completion Date	June 12, 2008
Established Name	Multiple
(Proposed) Trade Name	Multiple
Therapeutic Class	Multiple Antiepileptic Drugs
Applicant	Multiple
Formulation	Multiple
Dosing Regimen	Multiple
Indication	Multiple
Intended Population	Users of Antiepileptic Products

<b>1. EXECUTIVE SUMMARY .....</b>	<b>5</b>
<b>1.1 OVERVIEW .....</b>	<b>5</b>
<b>1.2 FINDINGS .....</b>	<b>5</b>
<b>1.3 FDA ACTIONS .....</b>	<b>5</b>
<b>2. INTRODUCTION .....</b>	<b>6</b>
<b>2.1 BACKGROUND .....</b>	<b>6</b>
<b>2.2 MATERIALS REVIEWED .....</b>	<b>6</b>
2.2.1 Antiepileptic Drug Prescribing Information .....	6
2.2.2 FDA Documents .....	10
2.2.3 Sponsor Data Sets .....	11
2.2.4 Other Sponsor Communications .....	12
<b>2.3 REVIEW OBJECTIVES .....</b>	<b>12</b>
<b>3. METHODS.....</b>	<b>12</b>
<b>3.1 METHODS: DATA COLLECTION.....</b>	<b>12</b>
3.1.1 Data Requests.....	12
3.1.2 Trial Inclusion and Exclusion Criteria .....	12
3.1.3. Requests for Information about Trial Characteristics .....	13
3.1.4. Determination of Suicidal Behavior or Ideation Events .....	13
3.1.4.1. Identification of “Possibly Suicide-Related” Adverse Events (PSRAEs).....	13
3.1.4.2. Exposure Window for PSRAEs.....	14
3.1.4.3. “False Positive” Events .....	14
3.1.4.4. Adjudication of “Possibly Suicide-Related” Adverse Events (PSRAEs) .....	14
3.1.4.5. Data Processing and Verification .....	14
<b>3.2 METHODS: STATISTICAL ANALYSIS.....</b>	<b>15</b>
3.2.1 Consultation of the Division of Biometrics 6 .....	15
3.2.2 STATISTICAL ANALYSIS PLAN.....	16
3.2.2.1 Endpoints .....	16
3.2.2.2 Analysis Population.....	16
3.2.2.3 Subgroups and Special Populations .....	16
3.2.2.3.1. Individual Drugs .....	16
3.2.2.3.2. Drug Groups According to Main Mechanism of Action .....	16
3.2.2.3.3. Trial Indication.....	17
3.2.2.3.4. Demographics .....	17
3.2.2.3.5. Comparator Type .....	18
3.2.2.4. Statistical Methods .....	18
3.2.2.4.1. Primary Method .....	18
3.2.2.4.2. Sensitivity Methods.....	18
3.2.2.4.2.1. Zero-Event Trials .....	18
3.2.2.4.2.2. Trial Heterogeneity .....	19
3.2.2.4.2.3. Duration Differences.....	19
3.2.2.4.3. Exploratory Methods.....	19
3.2.2.4.3.1. Time Pattern .....	19
3.2.2.4.3.2. Demographics, Duration and Discontinuation .....	19
3.2.2.4.3.3. Multiple Events.....	19
3.2.2.4.4. Missing values .....	20
3.2.2.4.5. Statistical Significance.....	20
<b>4. TRIAL CHARACTERISTICS.....</b>	<b>20</b>
<b>4.1. TRIALS BY COMPARATOR AND DRUG.....</b>	<b>20</b>
<b>4.2. DURATION OF PLACEBO-CONTROLLED TRIAL DOUBLE-BLIND TREATMENT PHASES .....</b>	<b>21</b>
<b>4.3. MONOTHERAPY VERSUS ADJUNCTIVE THERAPY IN PLACEBO-CONTROLLED TRIALS .....</b>	<b>21</b>
<b>4.4. EXCLUSION OF SUBJECTS WITH RISK FACTORS FOR SUICIDAL BEHAVIOR OR IDEATION IN PLACEBO-CONTROLLED TRIALS ANALYZED.....</b>	<b>21</b>
<b>4.5. EPILEPSY TRIALS: SEIZURE TYPES STUDIED.....</b>	<b>23</b>

4.6. PSYCHIATRIC TRIALS: ACUTE VERSUS MAINTENANCE TREATMENT .....	23
<b>5. SUBJECT CHARACTERISTICS .....</b>	<b>23</b>
5.1. DRUGS AND DEMOGRAPHICS .....	23
5.2. DURATION OF TREATMENT AND DISCONTINUATION .....	26
<b>6. FINDINGS .....</b>	<b>27</b>
6.1. SUICIDAL BEHAVIOR OR IDEATION .....	27
6.3 SENSITIVITY ANALYSES .....	30
6.3.1. Sensitivity Analysis using Zero-Event Trials: Estimated Risk Differences .....	30
6.3.2. Trial Heterogeneity .....	31
6.3.3. Person-Time Analysis .....	32
6.4. EXPLORATORY ANALYSES .....	34
6.4.1. Time-to-Event Analysis .....	34
6.4.2. Multiple Events .....	36
<b>7. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS .....</b>	<b>36</b>
7.1. DRUG GROUPS ACCORDING TO MAIN MECHANISM(S) OF ACTION .....	36
7.2. TRIAL INDICATION .....	38
7.3.1. Age .....	40
7.3.2. Gender .....	41
7.3.4. Setting .....	43
7.3.5. Location .....	44
<b>8. POST-HOC ANALYSES .....</b>	<b>46</b>
8.1. LAMOTRIGINE ADDITIONAL DATA .....	46
8.2. ANALYSIS BY ALTERNATIVE AGE GROUPINGS .....	48
8.3. EVALUATION OF SUICIDAL BEHAVIOR NARRATIVES .....	48
8.3.1. Evaluation of Suicidal Behavior Narratives: Methods .....	48
8.3.2. Evaluation of Suicidal Behavior Narratives: Findings .....	49
8.3.2.1. Evaluation of Suicidal Behavior Narratives: Psychiatric Symptoms Associated with Suicidal Behavior Events .....	50
8.3.2.3. Evaluation of Suicidal Behavior Narratives: Factors Affecting the Likelihood of Ascertainment Bias .....	50
<b>9. DISCUSSION .....</b>	<b>50</b>
9.1. USE OF PLACEBO-CONTROLLED CLINICAL TRIAL DATA .....	50
9.2. RETROSPECTIVE ANALYSIS OF DATA .....	51
9.3. POSSIBILITY OF ASCERTAINMENT BIAS .....	51
9.4. CONSISTENCY OF RESULTS IN SUBGROUP ANALYSES .....	52
9.5. RISK OF SUICIDAL BEHAVIOR OR IDEATION IN INDIVIDUAL ANTIEPILEPTIC DRUGS .....	53
9.6. GENERALIZABILITY OF ANALYSIS RESULTS .....	53
9.7. MECHANISM OF INCREASED RISK OF SUICIDAL BEHAVIOR OR IDEATION IN ANTIEPILEPTIC DRUGS .....	53
OVERALL .....	53
<b>10. CONCLUSION .....</b>	<b>53</b>
<b>11. FDA ACTIONS .....</b>	<b>54</b>
11.1. PRESS RELEASE AND INFORMATION FOR HEALTHCARE PROFESSIONALS .....	54
11.2. ADVISORY COMMITTEE MEETING .....	54
<b>12. AREAS FOR FUTURE INVESTIGATION .....</b>	<b>54</b>
<b>REFERENCE LIST .....</b>	<b>54</b>
<b>APPENDICES .....</b>	<b>56</b>
APPENDIX 1: FDA DATA REQUEST LETTER TO SPONSORS (03/16/2005) .....	56
APPENDIX 2: FDA LETTER TO PROVIDING ADDITIONAL INFORMATION TO SPONSORS (07/11/2005) .....	63

<b>APPENDIX 3: ENCLOSURE FOR 07/11/2005 FDA LETTER TO PROVIDING ADDITIONAL INFORMATION TO SPONSORS</b>	67
<b>APPENDIX 4: E-MAIL REQUEST FOR ADDITIONAL INFORMATION ON MULTIPLE EVENTS IN INDIVIDUAL SUBJECTS (05/03/2006)</b>	69
<b>APPENDIX 5. FDA LETTER REQUESTING ADDITIONAL INFORMATION ON TRIALS INCLUDED IN THE ANALYSIS (01/31/2007)</b>	69
<b>APPENDIX 6: TRIAL LEVEL DATA SET DATA DEFINITION TABLE (01/31/2007)</b>	70
<b>APPENDIX 7. FDA PRESS RELEASE: FDA ALERTS HEALTH CARE PROVIDERS TO RISK OF SUICIDAL THOUGHTS AND BEHAVIOR WITH ANTIEPILEPTIC MEDICATIONS (01/31/2008)</b>	75
<b>APPENDIX 8. INFORMATION FOR HEALTHCARE PROFESSIONALS: SUICIDALITY AND ANTIEPILEPTIC DRUGS (01/31/2008)</b>	76
<b>APPENDIX 9. SUBJECT AND EVENT CHARACTERISTICS FROM SUICIDAL BEHAVIOR NARRATIVES</b>	81

## **1. EXECUTIVE SUMMARY**

### **1.1 Overview**

FDA analyzed suicidal behavior and ideation events for all FDA-approved antiepileptic drugs with controlled clinical trial data bases. Eleven sponsors of antiepileptic drugs had randomized controlled trials that met inclusion criteria for analysis. FDA used the Columbia Classification Algorithm of Suicide Assessment (C-CASA)<sup>1</sup> to identify and classify suicidal behavior or ideation events.

### **1.2 Findings**

FDA analyzed data for 43,892 drug and placebo arm subjects from 199 placebo-controlled trials. Of drug-treated subjects, 0.37% had a Suicidal Behavior or Ideation event, compared to 0.24% of placebo-treated subjects (incidences unadjusted for trial differences.) Drug-treated subjects had a statistically significant increase in risk of Suicidal Behavior or Ideation compared to placebo-treated subjects for all antiepileptic drugs combined [OR 1.80 (95% CI: 1.24, 2.66)]. Drug-treated subjects overall had 1.9 additional events of Suicidal Behavior or Ideation per 1000 subjects (95% CI: 0.6, 3.9) compared to placebo-treated subjects (approximately 1 additional event per 500 drug-treated subjects). The odds ratio for Suicidal Behavior (completed suicide, suicide attempt, and preparatory acts toward imminent suicidal behavior) was also statistically significant [OR 2.92 (95% CI: 1.44, 6.47)]. Results were generally consistent for individual drugs analyzed.

Increased risk of Suicidal Behavior or Ideation was observed in all categories of trial indications evaluated [Epilepsy (62 trials), Psychiatric Indications (56 trials), and Other Indications (81 trials).] Odds ratios calculated in trials for Epilepsy, Psychiatric Indications, and Other Indications were 3.53 (95% CI: 1.28, 12.10), 1.51 (95% CI: 0.95, 2.45), and 1.87 (95% CI: 0.81, 4.76), respectively.

No clear pattern of drug effect was seen among subgroups according to age, gender, race, setting, and drug groups according to main mechanism of action (sodium channel blockers, GABAergic and GABA-mimetic drugs, and carbonic anhydrase inhibitors). Increased risk of Suicidal Behavior or Ideation was seen in both trial location subgroups; the estimated odds ratio for the Non-North American subgroup [4.53 (95% CI: 1.86, 13.18)] was larger than that for the North American subgroup [1.38 (95% CI: 0.90, 2.13)].

Drug-treated subjects had a higher risk of Suicidal Behavior or Ideation Events in all time periods analyzed. Reliable assessments beyond 24 weeks of treatment could not be made, because limited data was available beyond 24 weeks.

### **1.3 FDA Actions**

On January 31, 2008 FDA issued a press release<sup>2</sup> and information for healthcare professionals,<sup>3</sup> which alerted the public and health care professionals to the results of this analysis. A joint meeting of the Peripheral and Central Nervous System Drugs and Psychopharmacologic Drugs



Advisory Committees is planned, where the results and implications of this analysis will be discussed. Members of the Drug Safety and Risk Management and Pediatric Advisory Committee members will also participate in this meeting.

## 2. INTRODUCTION

### 2.1 Background

FDA's analysis of suicidality (defined as suicidal behavior or ideation) and antiepileptic drugs was prompted by concerns of an individual antiepileptic drug sponsor about an increased risk of suicidal behavior or ideation in drug-treated subjects in its controlled clinical trial database. In response, FDA initiated an analysis of suicidal behavior or ideation events in controlled clinical trial databases of all antiepileptic drugs in March 2005. FDA instructed sponsors to use the Columbia Classification Algorithm of Suicide Assessment (C-CASA) <sup>4</sup> to classify suicidality events. This standardized approach was used in previous FDA analyses of suicidality in children, adolescents, and adults treated with antidepressants.

### 2.2 Materials Reviewed

#### 2.2.1 Antiepileptic Drug Prescribing Information

Antiepileptic Drug Prescribing Information related to suicidal behavior or ideation, or psychiatric symptoms potentially related to suicidal behavior or ideation, for drugs analyzed is summarized in Table 1 below. Information was obtained on February 8, 2008.

Table 1. Suicidal Behavior or Ideation and Related Psychiatric Symptom Labeling of Drugs Analyzed

Drug and Label Date	NDA #	Product Labeling
Equetro (carbamazepine) May 2007	021710	<i>Precautions Section:</i> "Suicide: The possibility of suicide attempt is inherent in Bipolar Disorder and close supervision of high risk patients should accompany drug therapy. Prescriptions for EQUETRO™ should be written for the smallest quantity consistent with good patient management in order to reduce the risk of overdose." <i>Adverse Reactions Section:</i> In a table summarizing adverse events in EQUETRO™ and placebo-treated patients from the two double-blind, placebo-controlled studies were enrolled in a 6-month open-label study depression (which included suicidal ideation) was listed as comprising 7% of adverse events. Suicide attempt was included in a list of significant adverse events seen in less than 5% of patients.
Carbatrol (carbamazepine) March 2007	021710	Label does not contain information related to suicidal behavior or ideation.
Felbatol (felbamate) November 2002	020189	Label does not contain information related to suicidal behavior or ideation.

Drug and Label Date	NDA #	Product Labeling
Neurontin (gabapentin) March 2007	020235, 020882, 021129, 021216	<i>Adverse Reactions Section under heading “Other Adverse Reactions Observed During All Clinical Trials”:</i> Suicide attempt is listed as an infrequent event for subjects in clinical trials in adults and adolescents (except clinical trials in neuropathic pain) and for subjects in clinical trials for adults with neuropathic pain of various etiologies.
Lamictal (lamotrigine) May 2007	020241, 020764	<p><i>Precaution Section under heading “Use in Patients with Bipolar Disorder”:</i></p> <p>Acute Treatment of Mood Episodes: Safety and effectiveness of LAMICTAL in the acute treatment of mood episodes has not been established.</p> <p>Children and Adolescents (less than 18 years of age): Treatment with antidepressants is associated with an increased risk of suicidal thinking and behavior in children and adolescents with major depressive disorder and other psychiatric disorders. It is not known whether LAMICTAL is associated with a similar risk in this population (see PRECAUTIONS: Clinical Worsening and Suicide Risk Associated With Bipolar Disorder).</p> <p>Safety and effectiveness of LAMICTAL in patients below the age of 18 years with mood disorders have not been established.</p> <p>Clinical Worsening and Suicide Risk Associated with Bipolar Disorder: Patients with bipolar disorder may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviors (suicidality) whether or not they are taking medications for bipolar disorder. Patients should be closely monitored for clinical worsening (including development of new symptoms) and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes.</p> <p>In addition, patients with a history of suicidal behavior or thoughts, those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults, are at an increased risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.</p> <p>Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition (including development of new symptoms) and /or the emergence of suicidal ideation/behavior or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who experience clinical worsening (including development of new symptoms) and/or the emergence of suicidal ideation/behavior especially if these symptoms are severe, abrupt in onset, or were not part of the patient’s presenting symptoms.</p> <p>Prescriptions for LAMICTAL should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Overdoses have been reported for LAMICTAL, some of which have been fatal (see OVERDOSAGE).</p> <p><i>Adverse Reactions Section:</i></p> <p>Suicidal ideation is listed under the heading “Adverse events that occurred with a frequency of less than 5% and greater than 2% of patients receiving LAMICTAL and numerically more frequent than placebo”</p> <p>Suicide/suicide attempt is listed as a rare event (defined as events occurring in less than 1/1000 patients) under the heading “Other Adverse Events Observed During All Clinical Trials For Pediatric and Adult Patients With Epilepsy or Bipolar Disorder and Other Mood Disorders.”</p> <p>Suicidal ideation is listed as an infrequent event (defined as events occurring in 1/100 to 1/1000 patients) under the heading “Other Adverse Events Observed During All Clinical Trials For Pediatric and Adult Patients With Epilepsy or</p>

Drug and Label Date	NDA #	Product Labeling
Lamictal (lamotrigine) May 2007	020241, 020764	<p>Bipolar Disorder and Other Mood Disorders.”</p> <p><i>Patient Information Leaflet, which is provided for distribution to patients, under the heading “The Purpose of Your Medicine” subheading “For Patients with Bipolar Disorder”:</i> “If you are taking LAMICTAL to help prevent extreme mood swings, you may not experience the full effect for several weeks. Occasionally, the symptoms of depression or bipolar disorder may include thoughts of harming yourself or committing suicide. Tell your doctor immediately or go to the nearest hospital if you have any distressing thoughts or experiences during this initial period or at any other time. Also contact your doctor if you experience any worsening of your condition or develop other new symptoms at any time during your treatment.</p> <p>Some medicines used to treat depression have been associated with suicidal thoughts and suicidal behavior in children or teenagers. LAMICTAL is not approved for treating children or teenagers with mood disorders such as bipolar disorder or depression.”</p>
Keppra (levetiracetam) November 2007	021035, 021505, 021872	<p><i>Warnings Section:</i></p> <p><b>Adults</b></p> <p>In addition, 4 (0.5%) of treated patients attempted suicide compared to 0% of placebo patients. One of these patients completed suicide. In the other 3 patients, the events did not lead to discontinuation or dose reduction. The events occurred after patients had been treated for between 4 weeks and 6 months.</p> <p><b>Pediatric Patients</b></p> <p>A total of 37.6% of the KEPPRA-treated patients experienced behavioral symptoms (reported as agitation, anxiety, apathy, depersonalization, depression, emotional lability, hostility, hyperkinesia, nervousness, neurosis, and personality disorder), compared to 18.6% of placebo patients. Hostility was reported in 11.9% of KEPPRA-treated patients, compared to 6.2% of placebo patients. Nervousness was reported in 9.9% of KEPPRA-treated patients, compared to 2.1% of placebo patients. Depression was reported in 3.0% of KEPPRA-treated patients, compared to 1.0% of placebo patients. One KEPPRA-treated patient experienced suicidal ideation.</p> <p><i>Primary Generalized Tonic-Clonic Seizures</i></p> <p>In patients 6 years of age and older experiencing primary generalized tonic-clonic seizures, KEPPRA is associated with behavioral abnormalities.</p> <p>In the double-blind, controlled trial in patients with idiopathic generalized epilepsy experiencing primary generalized tonic-clonic seizures, irritability was the most frequently reported psychiatric adverse event occurring in 6.3% of KEPPRA-treated patients compared to 2.4% of placebo patients. Additionally, non-psychotic behavioral disorders (reported as abnormal behavior, aggression, conduct disorder, and irritability) occurred in 11.4% of the KEPPRA-treated patients compared to 3.6% of placebo patients. Of the KEPPRA-treated patients experiencing non-psychotic behavioral disorders, one patient discontinued treatment due to aggression. Non-psychotic mood disorders (reported as anger, apathy, depression, mood altered, mood swings, negativism, suicidal ideation, and tearfulness) occurred in 12.7% of KEPPRA-treated patients compared to 8.3% of placebo patients. No KEPPRA-treated patients discontinued or had a dose reduction as a result of these events. One KEPPRA-treated patient experienced suicidal ideation. One patient experienced delusional behavior that required the lowering of the dose of KEPPRA.</p> <p>In a long-term open label study that examined patients with various forms of primary generalized epilepsy, along with the non-psychotic behavioral disorders, 2 of 192 patients studied exhibited psychotic-like behavior. Behavior in one case</p>

Drug and Label Date	NDA #	Product Labeling
Keppra (levetiracetam) November 2007	021035, 021505, 021872	<p>was characterized by auditory hallucinations and suicidal thoughts and led to KEPPRA discontinuation. The other case was described as worsening of pre-existent schizophrenia and did not lead to drug discontinuation.</p> <p><i>Precautions Section under heading “Information for Patients”:</i> Patients should be advised that Keppra may cause changes in behavior (e.g. aggression, agitation, anger, anxiety, apathy, depression, hostility, and irritability) and in rare cases patients may experience psychotic symptoms and/or suicidal ideation.</p> <p><i>Adverse Reactions under heading “Postmarketing Experience”:</i> There have been reports of suicidal behavior (including completed suicide) with marketed KEPPRA. These adverse experiences have not been listed above, and data are insufficient to support an estimate of their incidence or to establish causation.</p> <p><i>Patient Information Leaflet:</i> <b>What are the possible side effects of KEPPRA?</b> <b>Adults</b> KEPPRA may cause the following serious problems in adults. Call your healthcare provider right away if you get any of the following symptoms: extreme sleepiness, tiredness, and weakness problems with muscle coordination (problems walking and moving) mood and behavior changes such as aggression, agitation, anger, anxiety, apathy, mood swings, depression, hostility, and irritability. A few people may get psychotic symptoms such as hallucinations (seeing or hearing things that are really not there), delusions (false or strange thoughts or beliefs) and unusual behavior. A few people may get thoughts of suicide (thoughts of killing yourself).</p>
Trileptal (orcarbazepine) May 2007	021014, 021285	Label does not contain information related to suicidal behavior or ideation.
Lyrica (pregabalin) July 2007	021446	<i>Adverse Reactions Section under heading “Other Adverse Events Observed during the Clinical Studies of Lyrica (pregabalin):</i> Suicide attempt is listed as an infrequent event and suicide is listed as a rare event.
Gabitril (tiagabine) December 2006	020646	<i>Adverse Reactions Section under heading “Other Adverse Events Observed During All Clinical Trials”:</i> Suicide attempt is listed an infrequent event.
Topamax (topiramate) April 2007	020505, 020844	<p><i>Warnings Section under heading “Cognitive/Neuropsychiatric Adverse Events”:</i> <b>Psychiatric/Behavioral Disturbances</b> Psychiatric/behavioral disturbances (depression or mood problems) were dose-related for both the epilepsy and migraine populations. In the double blind phases of clinical trials with topiramate in approved and investigational indications, suicide attempts occurred at a rate of 3/1000 patient years (13 events/3999 patient years) on topiramate versus 0 (0 events/1430 patient years) on placebo. One completed suicide was reported in a bipolar disorder trial in a patient on topiramate.</p> <p><i>Adverse Reactions Section:</i> <b>Other Adverse Events Observed During All Epilepsy Clinical Trials:</b> Suicide attempt listed as a frequent adverse event. <b>Postmarketing Reports of Adverse Drug Reactions:</b> Suicidal attempts, ideation, and suicide listed as very rare events.</p> <p><i>Patient Information Section:</i> Patients are advised to tell their healthcare professional if they “suffer from depression, mood problems or suicidal thoughts or behavior.”</p>

Drug and Label Date	NDA #	Product Labeling
Depakoke Depakote ER (divalproex sodium) December 2006	018723, 019680, 021168	Label does not contain information related to suicidal behavior or ideation.
Zonegran (zonisamide) July 2007	020789	<i>Warnings Section:</i> Cognitive/Neuropsychiatric Adverse Events: In placebo-controlled trials, 2.2% of patients discontinued ZONEGRAN or were hospitalized for depression compared to 0.4% of placebo patients, while 1.1% of ZONEGRAN and 0.4% of placebo patients attempted suicide. Among all epilepsy patients treated with ZONEGRAN, 1.4% were discontinued and 1.0% were hospitalized because of reported depression or suicide attempts. In placebo-controlled trials, 2.2% of patients discontinued ZONEGRAN or were hospitalized due to psychosis or psychosis-related symptoms compared to none of the placebo patients. Among all epilepsy patients treated with ZONEGRAN, 0.9% were discontinued and 1.4% were hospitalized because of reported psychosis or related symptoms.

All of the drugs analyzed are approved for the treatment of epilepsy. Six of the drugs analyzed are approved for treatment indications other than epilepsy. Table 2 below lists the approved non-epilepsy treatment indications of drugs analyzed (collected February 8, 2008.)

Table 2. FDA-Approved Non-Epilepsy Treatment Indications of Drugs Analyzed

Drug	Treatment Indications
Carbamazepine	trigeminal neuralgia
Gabapentin	postherpetic neuralgia
Lamotrigine	bipolar disorder (maintenance)
Pregabalin	neuropathic pain from diabetic peripheral neuropathy, postherpetic neuralgia, fibromyalgia
Topiramate	migraine
Divalproex sodium	mania, migraine

## 2.2.2 FDA Documents

1. Statistical Review and Evaluation: Antiepileptic Drugs and Suicidality. Prepared by Mark Levenson, PhD. Dated May 23, 2008.
2. FDA Internet Publication: Background Information on the Suicidality Classification Project at <http://www.fda.gov/cder/drug/antidepressants/classificationProject.htm>.
3. Request for Information on Suicidal Behavior or Ideation to Sponsors of Antiepileptic Drugs. Dated May 16, 2005. (Appendix 1)
4. Clarification Regarding the May 16, 2005 Request for Information on Suicidal Behavior or Ideation to Sponsors of Antiepileptic Drugs. Dated July 11, 2005. (Appendices 2 and 3).

5. E-mail Communication Updating the May 16, 2005 Request for Information on Suicidal Behavior or Ideation to Sponsors of Antiepileptic Drugs. Dated May 3, 2006. (Appendix 4).
6. FDA Letter Requesting Additional Information on Trials in the Analysis of Antiepileptic Drugs and Suicidal Behavior or Ideation. Dated January 31, 2007. (Appendix 5)
7. Data Definition Table for Information on Trials in the Analysis of Antiepileptic Drugs and Suicidal Behavior or Ideation. Dated January 31, 2007. (Appendix 6)
8. FDA Press Release: FDA Alerts Health Care Providers to Risk of Suicidal Thoughts and Behavior with Antiepileptic Medications. Dated January 31, 2008. (Appendix 7)
9. Information for Healthcare Professionals: Suicidality and Antiepileptic Drugs. Dated January 31, 2008. (Appendix 8).

### 2.2.3 Sponsor Data Sets

1. NDA 21-710 (Carbamazepine/Carbatrol® Extended-Release Capsules), 21-712 (Carbamazepine/Equetro® Extended-Release Capsules): Suicidality Datasets. Prepared by Shire. Datasets submitted June 28, 2006, August 10, 2006, and September 6, 2006.
2. NDA 18-723 and 20-320 (Divalproex Sodium/Depakote® Tablets), 19-680 (Divalproex Sodium/Depakote® Sprinkle Capsules), 21-168 (Divalproex Sodium/Depakote® ER Tablets): Suicidality Datasets. Prepared by Abbott Laboratories. Datasets submitted July 21, 2006.
3. NDA 20-189 (Felbamate/Felbatol® Tablets and Oral Suspension): Suicidality Datasets. Prepared by Medpointe Pharmaceuticals. Datasets submitted May 31, 2007 and August 8, 2007.
4. NDA 20-235 (Gabapentin/Neurontin® Capsules), 20-882 (Gabapentin/Neurontin® Tablets), 21-129 (Gabapentin/Neurontin® Oral Solution): Suicidality Datasets. Prepared by Pfizer. Datasets submitted June 22, 2006 and July 24, 2006.
5. NDA 20-241 (Lamotrigine/Lamictal® Tablets), 20-764 (Lamotrigine/Lamictal® Chewable Dispersible Tablets): Suicidality Datasets. Prepared by GlaxoSmithKline. Datasets submitted June 27, 2006, September 22, 2006, October 11, 2007, and November 21, 2007.
6. NDA 21-035 (Levetiracetam/Keppra® Tablets), 21-505 (Levetiracetam/Keppra® Oral Solution): Suicidality Datasets. Prepared by UCB. Datasets submitted August 9, 2006.
7. NDA 21-014 (Oxcarbazepine/Trileptal® Tablets), 21-285 ((Oxcarbazepine/Trileptal® Oral Suspension): Suicidality Datasets. Prepared by Novartis. Datasets submitted June 21, 2006.
8. NDA 21-446 (Pregabalin/Lyrica® Capsules C-V): Suicidality Datasets. Prepared by Pfizer. Datasets submitted June 22, 2006 and July 24, 2006.
9. NDA 20-646 (Tiagabine/Gabitril® Tablets): Suicidality Datasets. Prepared by Cephalon. Datasets submitted June 7, 2006 and August 7, 2006.
10. NDA 20-505 (Topiramate/Topamax® Tablets), 20-844 (Topiramate/Topamax® Sprinkle Capsules): Suicidality Datasets. Prepared by Johnson and Johnson. Datasets submitted November 1, 2006.
11. NDA 20-789 (Zonisamide/Zonegran® Capsules): Suicidality Datasets. Prepared by Eisai Medical Research, Incorporated. Datasets submitted April 26, 2006.

## 2.2.4 Other Sponsor Communications

Electronic and written communication between FDA and sponsors occurred frequently in the process of verifying and revising data sets. Relevant communications between FDA and sponsors are referenced in the body of this review.

## 2.3 Review Objectives

1. Examine whether the class of antiepileptic drugs are associated with increased risk of suicidality relative to placebo in randomized placebo-controlled trials.
2. Examine whether the risk of suicidality varies by (a) individual drug, (b) drug subgroups, (c) indication subgroups, and (d) demographic subgroups.

## 3. METHODS

### 3.1 Methods: Data Collection

#### *3.1.1 Data Requests*

On March 16, 2005, FDA requested data sets from sponsors of antiepileptic drugs (see Appendix 1). Data sets provided detailed information about individual subjects. In response to sponsor questions about trial inclusion criteria, data collection, data classification, and data presentation, FDA sent a letter providing additional information and clarification on July 11, 2005 (see Appendices 2 and 3). FDA initially requested the most severe suicidality event for each subject. Due to a change in analysis plan, FDA sent an e-mail communication requesting information on less serious suicidality events in subjects with multiple events on May 3, 2006 (see Appendix 4).

#### *3.1.2 Trial Inclusion and Exclusion Criteria*

FDA instructed sponsors to submit data for all randomized, parallel-arm, placebo-controlled trials, with at least 30 patients total. Sponsors were also instructed to submit data from the first period of cross-over trials and trials with subtherapeutic comparator arms (“low dose-controlled studies”), if these trials otherwise met the trial inclusion criteria. (Note: Low-dose controlled studies were not included in the primary analysis.) Some trials had active-controlled arms in addition to placebo-controlled arms.

FDA excluded trials if the duration was less than 7 days or if there were fewer than 20 subjects in any trial arm. We excluded trials in which all subjects were less than 5 years old, because the study methods were not adapted to reliably assess suicidality in this age group. We excluded trials with a randomized withdrawal study design, in which all subjects initially receive the active drug and, subsequently, subjects are randomized to continue active treatment or to placebo. We excluded these trials because withdrawal of the drug in subjects randomized to placebo may complicate the interpretation of suicidality events. We also excluded these trials

because the double blind treatment phase of randomized withdrawal studies are often enriched with subjects who have adequate efficacy and are tolerant of adverse effects with drug treatment. The July 2005 FDA letter specified that studies with ongoing blinded treatment phases should not be included in data submissions. Trials for antiepileptic drugs not approved by the date of the initial information request, March 16, 2008, were not included.

According to the inclusion and exclusion criteria described above, data from some trials were not used in the FDA analysis, despite the fact that they were submitted to FDA. Table 3 describes trials with data submitted to FDA which were not used in this analysis.

### ***3.1.3. Requests for Information about Trial Characteristics***

In its July 2005 letter, FDA asked sponsors to summarize trial characteristics in two tables. One table provided the protocol dose, duration and number of subjects for each trial, and the other table provided the trial exclusion criteria (Appendix 3.)

FDA requested additional information about the analyzed trials on January 31, 2007. A copy of the request letter is located in Appendix 5, and the data definition table for the trial level data set is located in Appendix 6.

### ***3.1.4. Determination of Suicidal Behavior or Ideation Events***

#### **3.1.4.1. Identification of “Possibly Suicide-Related” Adverse Events (PSRAEs)**

FDA requested a search of adverse events that occurred during the double-blind phase of treatment, or within one day of stopping randomized treatment. Preferred terms, verbatim terms, and comments fields of trials included in the analysis were included in the search. We specified the search procedure which sponsors used to identify “possibly suicide-related” adverse events (PSRAEs).

The search for PSRAEs included the following criteria:

- Preferred terms with text strings “suic” or “overdos,” including all events coded as “accidental overdose”
- Verbatim terms with the text strings: “attempt”, “cut”, “gas”, “hang”, “hung”, “jump”, “mutilat-”, “overdos-”, “self damag-”, “self harm”, “self inflict”, “self injur-”, “shoot”, “slash”, “suic-”, “poison”, “asphyxiation”, “suffocation”, “firearm”; events were screened for false positives
- All deaths and other serious adverse events (SAEs)
- All adverse events coded as “accidental injury”

Sponsors prepared narratives for each PSRAE and were asked to remove information that may potentially cause bias.



#### 3.1.4.2. Exposure Window for PSRAEs

The search for PSRAEs was limited to events that occurred during the double-blind treatment phase, during the first period of a cross-over trial, or within one day of stopping randomized treatment. Sponsors were instructed to exclude PSRAEs that occurred during open label stabilization phases, run-in phases, open-label extension periods, or tapering periods. Events that occurred before randomization were also excluded.

#### 3.1.4.3. “False Positive” Events

“False positive” events, which met search criteria but were not suicide-related, were also identified. (For example, “epigastric pain” identified in the search for the key word “gas”). Sponsors submitted listings of events classified as “false positives,” which included the subject number, study number, treatment assignment, and the term in which the search text string was found.

#### 3.1.4.4. Adjudication of “Possibly Suicide-Related” Adverse Events (PSRAEs)

FDA asked sponsors to classify PSRAEs using the Columbia Classification Algorithm of Suicide Assessment (C-CASA) <sup>5</sup>. FDA’s data request letter specified that the persons who classify the PSRAE narratives must have the appropriate expertise and training to accomplish this task. Some, but not all, sponsors collaborated with Dr. Posner’s group (who developed this algorithm and classified all events in the pediatric data analysis of suicidality with antidepressants) in the classification of PSRAEs for this analysis. Table 1 lists the categories of suicidal behavior and ideation events used in the classification of PSRAEs.

Table 4: Suicidal Behavior and Ideation Events and Codes.

Event Code	Event
0	No Event
1	Completed suicide
2	Suicide attempt
3	Preparatory acts toward imminent suicidal behavior
4	Suicidal ideation
5	Self-injurious behavior, intent unknown
6	Not enough information, fatal
7	Not enough information, non-fatal

#### 3.1.4.5. Data Processing and Verification

After data sets were received from sponsors, the data was processed as follows:

- Data not eligible according to trial inclusion and exclusion criteria (see Section 3.1.2) was removed.

- Data was checked for plausibility and completeness.
- Data from all subjects less than 5 years old was removed.
- Multiple events in one subject in a single day were consolidated into one observation (see below.)
- Study indications were categorized (see below.)
- Data from 11 drug programs was concatenated into one data set.

Questions which arose during data processing were sent to the appropriate sponsor(s) for resolution.

Reporting on all events per subject was requested. If a subject had multiple events reported on the same day, only the most severe event was retained; this was done to standardize the distinction between a single event versus multiple events.

Sponsors were asked to confirm the numbers of each category of events for each treatment arm via e-mail communication on April 24, 2008. Data discrepancies were resolved; The March 5, 2008 Statistical Review on this topic was revised on May 23, 2008 to reflect these changes.

FDA categorized the numerous trial indications into 21 trial indication categories. These 21 indication categories were further categorized into three categories: (1) Epilepsy, (2) Psychiatric, and (3) Other. Table 2 gives the 21 trial indication categories and their further classification into three categories.

Table 5: Trial Indication Categories

<b>Epilepsy (62)</b>	<b>Psychiatric (56)</b>	<b>Other (81)</b>
Epilepsy (62)	Anxiety (13)	Agitation (2)
	Binge eating disorder (1)	Chronic pain (5)
	Bipolar disorder (28)	Fibromyalgia (2)
	Depression (3)	Impaired cognition (6)
	Panic disorder (4)	Insomnia (1)
	Post-Traumatic Stress Disorder (1)	Migraine (16)
	Schizophrenia (2)	Neuropathy (35)
	Social phobia (4)	Obesity (10)
		Radiculopathy (0)*
		Spasticity (1)
		Tremor (1)

The number of placebo-controlled trials in the primary analysis for each trial indication category is listed in parentheses.

\*One trial indicated for radiculopathy was submitted, but it was not eligible for analysis.

Note: The Other indication category also includes healthy volunteer studies (2).

### **3.2 METHODS: STATISTICAL ANALYSIS**

#### **3.2.1 Consultation of the Division of Biometrics 6**

The Division of Neurology consulted the Quantitative Safety and Pharmacoepidemiology Group in the Division of Biometrics 6 to assist with statistical analysis. Mark Levenson, PhD was the statistical reviewer, and C. George Rochester, PhD, RAC, was the statistical team leader.

### 3.2.2 STATISTICAL ANALYSIS PLAN

The statistical analysis plan (SAP), dated November 8, 2007, included definitions of the endpoints, study population, subgroups, and statistical methods, which were pre-specified prior to conducting the analyses. These definitions and specifications were chosen by medical reviewers in the Division of Neurology and statistical reviewers in the Quantitative Safety and Pharmacoepidemiology Group.

#### 3.2.2.1 Endpoints

The primary endpoint was Suicidal Behavior or Ideation, which was defined as the occurrence of any of the following events:

- Completed suicide
- Suicide attempt
- Preparatory acts toward imminent suicidal behavior
- Suicidal ideation

There were two secondary endpoints: a.) Suicidal Behavior and b.) Suicidal Ideation. The Suicidal Behavior endpoint was defined as the occurrence of any of the following events:

- Completed suicide
- Suicide attempt
- Preparatory acts toward imminent suicidal behavior

The Suicidal Ideation endpoint occurred if the patient had only a Suicidal Ideation event (because if the patient had a suicidal ideation event *and* a suicidal behavior event, only the more severe behavior event would be counted). Note that the endpoint Suicidal Ideation was not part of the pre-specified SAP.

#### 3.2.2.2 Analysis Population

The primary analysis population was all patients in test drug and placebo arms from placebo-controlled trials.

#### 3.2.2.3 Subgroups and Special Populations

##### 3.2.2.3.1. Individual Drugs

Each drug was evaluated separately.

##### 3.2.2.3.2. Drug Groups According to Main Mechanism of Action

To examine the effect of drug mechanism of action on the risk of suicidal behavior or ideation, three drug groups were evaluated: 1) Sodium Channel Blocking Drugs; 2) GABAergic drugs

and GABAergic drugs; and 3) Carbonic Anhydrase Inhibitors. These groupings were chosen by the medical officers from the Division of Neurology and were based on a drug's main mechanism(s) of action. Each group of drugs was compared to the complementary group of drugs. Note that the drug groups are neither mutually exclusive nor exhaustive.

#### Sodium Channel Blocking Drugs

- Carbamazepine
- Lamotrigine
- Oxcarbazepine
- Topiramate
- Zonisamide

#### GABAergic Drugs and GABAergic Drugs

- Divalproex
- Gabapentin
- Pregabalin
- Tiagabine
- Topiramate

#### Carbonic Anhydrase Inhibitors

- Topiramate
- Zonisamide

#### 3.2.2.3.3. Trial Indication

Three indication groups were considered as defined in Table 5:

1. Epilepsy
2. Psychiatric Indications
3. Other Indications

#### 3.2.2.3.4. Demographics

The following demographic subgroups were considered:

1. Age
  - 5-17
  - 18-24
  - 25-30
  - 31-64
  - $\geq 65$
2. Gender
  - Male
  - Female
3. Race
  - White Caucasian
  - Other
4. Setting

- Inpatient or Inpatient/Outpatient Combined
  - Outpatient
5. Location
- North America
  - Non-North America

The age subgroups were chosen to be the same as used in FDA analysis of the antidepressants and suicidal behavior or ideation. Only two race subgroups were used, because the overwhelming majority of patients were white. “Other” for race included African American, Hispanic, Asian, and other. For location, FDA did not specify the meaning of North America.

#### 3.2.2.3.5. Comparator Type

The group of patients from low-dose-controlled trials was considered. This group was compared to the primary analysis group of placebo-control trial patients and the group of patients from both placebo-controlled and low-dose-controlled trials. For the analysis of patients from both types of trials, the test drug patients were compared to the patients in the corresponding trial control arm patients (placebo or low-dose).

#### 3.2.2.4. *Statistical Methods*

The description of statistical methods below is excerpted from the statistical review by Mark Levenson, PhD.

##### 3.2.2.4.1. *Primary Method*

The primary analysis method was the exact method for a stratified odds ratio and associated 95% confidence interval.<sup>6</sup> The odds ratio was in terms of patient units. The stratification factor was the trial.

##### 3.2.2.4.2. *Sensitivity Methods*

Three sensitivity analyses were employed to examine the robustness of the primary method.

##### 3.2.2.4.2.1. Zero-Event Trials

The first sensitivity analysis examined the consequences of the fact that a large number of the trials were expected to have no events. The exact method for a stratified odds ratio does not make use of these trials. The Mantel-Haenszel risk difference and associated confidence interval,<sup>7</sup> which makes use of these trials, was used for this sensitivity analysis. However, if there are no events for any trials, for example in a subgroup, then the estimated variance will be zero. In this case, it is not appropriate to use the variance estimate, and no estimate and confidence intervals were presented.

#### 3.2.2.4.2.2. Trial Heterogeneity

The second sensitivity analysis examined between-trial heterogeneity of the effect measure. Zelen's test,<sup>6</sup> an exact test, was used to test the hypothesis of a common odds ratio. However, because of the small number of events, it was expected that there would be little power to detect heterogeneity of the odds ratio across trials. The result of the test was intended for qualitative purposes.

The trial weight of the Mantel-Haenszel odds ratio estimator was used to quantitatively identify trials with large influence. The weight was equal to  $(\text{control patients with events}) \times (\text{test patients without events}) / (\text{total patients})$ . Trials with no events had a weight of zero. For trials with events in one arm only, the weight was equal to  $(\text{control patients with events} + 0.5) \times (\text{test patients without events} + 0.5) / (\text{total patients} + 2)$ . Note that the SAP incorrectly specified "+1" rather than "+2" in the denominator.

A generalized linear mixed model (GLMM)<sup>8</sup> was used to estimate the overall odds ratio in the presence of trial heterogeneity of the odds ratio. The model used the binomial error distribution and logit link function. The model included fixed effects for the trial and treatment effects and a random effect on the trial-level for the treatment-trial interaction. The estimate and the 95% confidence interval of the treatment effect were qualitatively compared to those from the primary method to examine the effect of trial heterogeneity. The confidence interval of the variance component of the random effect was also examined to evaluate trial heterogeneity.

#### 3.2.2.4.2.3. Duration Differences

The third sensitivity method, which was not part of the SAP, examined the consequences of the observed difference in treatment duration between the treatment arms. The method was similar to the primary method, but used person-time rather than patients as the unit of analysis.<sup>6</sup> Because the duration difference was small, an assumption of constant hazards was not key.

#### 3.2.2.4.3. *Exploratory Methods*

##### 3.2.2.4.3.1. Time Pattern

Kaplan-Meier incidence curves were used to examine the time-pattern (hazard function) of the Suicidal Behavior or Ideation events. For patients with multiple events, only the most critical event was used. No stratification was employed in the analysis.

##### 3.2.2.4.3.2. Demographics, Duration and Discontinuation

Differences in treatment arms within trials of demographics, treatment duration, and premature discontinuation of patients were examined. For categorical variables, p-values for differences between treatment groups were based on the Cochran-Mantel-Haenszel test stratifying on trial. For continuous variables, p-values and least-squares means were based on a 2-way ANOVA controlling for trial.

##### 3.2.2.4.3.3. Multiple Events

For each patient that had multiple events, the events were summarized.

#### 3.2.2.4.4. Missing values

There were no missing values allowed for trial, treatment arm, and event codes. Therefore, the primary analysis was not affected by missing values. For each subgroup analysis, all patients with the necessary information to determine the subgroup membership were used.

#### 3.2.2.4.5. Statistical Significance

Statistical significance refers to a two-sided type 1 error of 0.05. Because the analysis was exploratory in nature, no adjustments for multiplicity were to be made.

### 4. TRIAL CHARACTERISTICS

#### 4.1. Trials by Comparator and Drug

Table 6 gives the number of trials by comparator type and drug. There were 210 trials. Of these, 199 were placebo-controlled and 11 were low-dose controlled. No study had both a placebo arm and a low-dose arm. There were 23 trials that also had an active control arm; events in active control treatment arms were not included in the analyses.

Table 6: Trials by Comparator Type and Drug.

Drug	Number of Trials		Total
	Placebo-Controlled	Low-Dose Controlled	
Carbamazepine	3	0	3
Divalproex	13	1	14
Felbamate	6	3	9
Gabapentin	28	0	28
Lamotrigine	27	2	29
Levetiracetam	21	0	21
Oxcarbazepine	10	1	11
Pregabalin	38	1	39
Tiagabine	6	0	6
Topiramate	42	3	45
Zonisamide	5	0	5
Total	199	11	210

Table excerpted from the statistical review by Mark Levenson, PhD.

#### 4.2. Duration of Placebo-controlled Trial Double-Blind Treatment Phases

The first quartile, median, and third quartile double-blind treatment phase durations of placebo-controlled trials were 8 weeks, 12 weeks, and 16 weeks, respectively. The minimum double-blind treatment phase duration was 1 week, because trials with shorter double-blind treatment phases were excluded. The longest double-blind treatment phase of a trial in this analysis was 112 weeks.

#### 4.3. Monotherapy versus Adjunctive Therapy in Placebo-Controlled Trials

Table 7 gives the number of placebo-controlled trials by indication group and therapy (monotherapy, adjunctive therapy, and other). In the majority of epilepsy trials (92%), the drug was used in combination with other therapies as adjunctive therapy. In contrast, in the majority of psychiatric trials (86%), the drug was used as monotherapy.

Table 7: Placebo-controlled Trials by Indication Group and Therapy (Monotherapy, Adjunctive Therapy, Other).

Therapy	Indication Group			Total N=199 n (%)
	Epilepsy N=62 n (%)	Psychiatric N=56 n (%)	Other N=81 n (%)	
Monotherapy	5 (8)	48 (86)	61 (75)	114 (57)
Adjunctive Therapy	57 (92)	8 (14)	12 (15)	77 (39)
Other	0 (0)	0 (0)	8 (10)	8 (4)

Note: Other therapy includes trials with optional adjunctive therapy and a trial in which one patient cohort received adjunctive therapy and one patient cohort did not receive adjunctive therapy. Table adapted from the statistical review by Mark Levenson, PhD.

#### 4.4. Exclusion of Subjects with Risk Factors for Suicidal Behavior or Ideation in Placebo-Controlled Trials Analyzed

The number of placebo-controlled trials in which sponsors reported that subjects with a history of suicide attempt were excluded, divided according to trial indication category, is listed in Table 8 below.

Table 8. Placebo-Controlled Trials Analyzed which Excluded Subjects with a History of Suicide Attempt by Trial Indication Category

Indication Category	n (%)
Epilepsy (N=62)	25 (40)
Psychiatric (N=56)	3 (5)
Other (N=81)	18 (22)
Total (N=199)	46 (23)



The number of trials in which sponsors reported that subjects with current suicide risk were excluded is reported below; this information is listed by trial indication category (Table 9) and by drug (Table 10).

Table 9. Placebo-Controlled Trials Analyzed which Excluded Subjects with Current Suicide Risk by Trial Indication Category

Indication Category	n (%)
Epilepsy (N=62)	20 (32)
Psychiatric (N=56)	39 (70)
Other (N=81)	12 (15)
Total (N=199)	71 (36)

Table 10. Placebo-Controlled Trials Analyzed which Excluded Subjects with Current Suicide Risk by Drug

Drug	n (%)
Carbamazepine (N=3)	3 (100)
Divalproex Sodium (N=13)	3 (23)
Felbamate (N=6)	3 (50)
Gabapentin (N=28)	1 (4)
Lamotrigine (N=27)	23 (85)
Levetiracetam (N=21)	11 (52)
Oxcarbazepine (N=10)	10 (100)
Pregabalin (N=38)	10 (26)
Tiagabine (N=6)	3 (50)
Topiramate (N=42)	4 (10)
Zonisamide (N=5)	0 (0)
Total (N=199)	71 (36)

The majority of placebo-controlled trials analyzed excluded subjects who abuse alcohol or other drugs (Table 11). Table 12 lists the number of placebo-controlled trials which excluded subjects diagnosed with a personality disorder by trial indication category.

Table 11. Placebo-Controlled Trials Analyzed which Excluded Subjects with a History of Substance Abuse by Trial Indication Category

Indication Category	n (%)
Epilepsy (N=62)	57 (92)
Psychiatric (N=56)	52 (93)
Other (N=81)	68 (84)
Total (N=199)	177 (89)

Table 12. Placebo-Controlled Trials Analyzed which Excluded Subjects Diagnosed with a Personality Disorder by Trial Indication Category

Indication Category	n (%)
Epilepsy (N=62)	8 (13)
Psychiatric (N=56)	34 (61)
Other (N=81)	6 (7)
Total (N=199)	48 (24)

#### 4.5. Epilepsy Trials: Seizure Types Studied

The majority of placebo-controlled trials indicated for epilepsy evaluated subjects with partial seizures [with or without secondary generalized seizures (Table 13)].

Table 13. Placebo-Controlled Epilepsy Trials: Seizure Types Evaluated

Seizure Type	N (%)
Partial seizures (with or without secondary generalized seizures)	52 (84)
Primary generalized seizures	4 (6)
Other	6 (10)
Total	62 (100)

#### 4.6. Psychiatric Trials: Acute versus Maintenance Treatment

Of 56 placebo-controlled trials indicated for psychiatric disorders, subjects were acutely symptomatic at randomization in 45 trials (80%); subjects were symptomatically stable and were receiving maintenance treatment in 8 trials (14%). Sponsors categorized treatment in 2 trials as being other than acute or maintenance treatment. In one trial indicated for binge eating disorder, the sponsor categorized the question of acute versus maintenance treatment as not applicable.

### 5. SUBJECT CHARACTERISTICS

#### 5.1. Drugs and Demographics

The number of subjects by treatment arm and comparator type is listed below (Table 14). There were 43,892 subjects in the placebo and the drug arms from placebo-controlled trials. More subjects were randomized to drug arms (27,863) than placebo arms (16,029) in these trials. Subjects from active-control arms (1,997) are not included in the table.

Table 14: Subjects by Treatment Arm and Comparator Type.

Comparator Type	Treatment Arm			Total
	Drug	Placebo	Low-Dose Placebo	
Placebo-Controlled	27863	16029	0	43892
Low-Dose Controlled	788	0	799	1587
Total	28651	16029	799	45479

Table excerpted from the statistical review by Mark Levenson, PhD.

Table 15 gives the number of patients by treatment arm and drug for placebo-controlled trials. The drugs topiramate and pregabalin provided over half of the total subjects (27% for topiramate and 24% for pregabalin).

Table 15: Patients by Treatment Arm and Drug, Placebo-Controlled Trials.

Drug	Treatment Group		
	Drug N = 27863 n (%)	Placebo N = 16029 n (%)	Total N = 43892 n (%)
Carbamazepine	252 (1)	250 (2)	502 (1)
Divalproex	1327 (5)	992 (6)	2319 (5)
Felbamate	170 (1)	170 (1)	340 (1)
Gabapentin	2903 (10)	2029 (13)	4932 (11)
Lamotrigine	2865 (10)	2070 (13)	4935 (11)
Levetiracetam	2554 (9)	1549 (10)	4103 (9)
Oxcarbazepine	1342 (5)	827 (5)	2169 (5)
Pregabalin	7201 (26)	3125 (19)	10326 (24)
Tiagabine	835 (3)	608 (4)	1443 (3)
Topiramate	7742 (28)	3971 (25)	11713 (27)
Zonisamide	672 (2)	438 (3)	1110 (3)

Table excerpted from the statistical review by Mark Levenson, PhD.

Table 16 gives the number of patients by indication group and drug. The Other Indication group had the most patients with 48% of the patients. The Epilepsy and Psychiatric Indication groups had 25% and 27% of subjects analyzed, respectively.

Table 16: Patients by Indication Group and Drug, Placebo-Controlled Trials.

Drug	Indication Group			Total N
	Epilepsy n (n/N%)	Psychiatric n (n/N%)	Other n (n/N%)	
Carbamazepine	0 (0)	502 (100)	0 (0)	502
Divalproex	147 (6)	1285 (55)	887 (38)	2319
Felbamate	340 (100)	0 (0)	0 (0)	340
Gabapentin	1485 (30)	331 (7)	3116 (63)	4932
Lamotrigine	1408 (29)	2313 (47)	1214 (25)	4935
Levetiracetam	1634 (40)	1609 (39)	860 (21)	4103
Oxcarbazepine	1110 (51)	115 (5)	944 (44)	2169
Pregabalin	1685 (16)	3204 (31)	5437 (53)	10326
Tiagabine	939 (65)	504 (35)	0 (0)	1443
Topiramate	1346 (11)	1933 (17)	8434 (72)	11713
Zonisamide	848 (76)	0 (0)	262 (24)	1110
Total	10942 (25)	11796 (27)	21154 (48)	43892

Table excerpted from the statistical review by Mark Levenson, PhD.

Table 17 gives the demographics of the patients by treatment arm. No statistically significant differences between the treatment arms existed for age, gender, race, and location. The P-value for setting could not be calculated due to the sparseness of the data; observed percentages were similar between the treatment arms.

The least-squares means for age was 42 for both treatment arms. The least-squares means control for differences among the trials and are more appropriate measures than the ordinary means in the context of the meta-analysis, which controls for differences among the trials. A majority of patients had outpatient treatment only (92%), and a majority of the patients were in North America (61%). Approximately five percent of the patients were under the age of 18, and 13% of the patients were age 65 or older. Most subjects were white Caucasian (79%).

Table 17: Demographics by Treatment Arm, Placebo-Controlled Trials.

Characteristic		Drug N=27863	Placebo N=16029	Total N=43892	P-Value
Age (Years)	5-17	1292 (5)	1119 (7)	2411 (5)	0.2745
	18-24	2126 (8)	1296 (8)	3422 (8)	
	25-30	2633 (9)	1568 (10)	4201 (10)	
	31-64	18157 (65)	9990 (62)	28147 (64)	
	≥ 65	3653 (13)	2056 (13)	5709 (13)	
	Missing	2 (0)	0 (0)	2 (0)	
	Mean (Std.)	45 (17)	43 (18)	44 (17)	0.2184
	Least-Squares Mean	42	42		
	Range (Min – Max)	(5 -100)	(5 – 99)	(5 – 100)	
Gender	Female	15586 (56)	8686 (54)	24272 (55)	0.6557
	Male	12276 (44)	7343 (46)	19619 (45)	
	Missing	1 (0)	0 (0)	1 (0)	
Race	White Caucasian	22302 (80)	12541 (78)	34843 (79)	0.1703
	Other	3588 (13)	2264 (14)	5852 (13)	
	Missing	1973 (7)	1224 (8)	3197 (7)	
Setting	Inpatient or Both	1893 (7)	1411 (9)	3304 (8)	NA
	Outpatient	25970 (93)	14618 (91)	40588 (92)	
	Missing	0 (0)	0 (0)	0 (0)	
Location	North America	16841 (60)	9941 (62)	26782 (61)	0.9523
	Non-North America	11022 (40)	6088 (38)	17110 (39)	
	Missing	0 (0)	0 (0)	0 (0)	

Notes: Results for categorical variables are expressed as counts and percentages of treatment arm. P-values for categorical variables are based on Cochran-Mantel-Haenszel test controlling for trial. P-values and least-squares means for continuous variables are based on 2-way ANOVA controlling for trial. P-value for setting could not be calculated due to the sparseness of the data. Table excerpted from the statistical review by Mark Levenson, PhD.

## 5.2. Duration of Treatment and Discontinuation

Table 18 gives the treatment discontinuation status and the duration by treatment arm. A statistically significant larger percentage of drug patients discontinued prematurely than placebo patients. The least-squares means show that the placebo patients had longer durations (77 days for placebo versus 73 days for drug). If events were related to duration, placebo patients may be expected to have more events independent of any treatment effect. Additional information on discontinuation and duration is available in Dr. Mark Levenson's statistical review. We

performed person-time analysis, described in Section 6.3.3., to account for the possibility of a duration effect.

Table 18: Patient Treatment Discontinuation and Duration by Treatment Arm, Placebo-Controlled Trials.

Characteristic		Drug N=27863	Placebo N=16029	Total N=43892	P-Value
Discontinue	No	17889 (64)	11118 (69)	29007 (66)	<.0001
	Yes	9974 (36)	4911 (31)	14885 (34)	
	Missing	0 (0)	0 (0)	0 (0)	
Duration (Days)	Least-Squares Mean	73	77		<.0001
	Range (Min – Max)	(0 – 575)	(1 – 582)	(0 – 582)	
	Missing	9	8	17	

Notes: Adapted from Statistical Review by Mark Levenson, Ph.D.. Results for categorical variables are expressed as counts and percentages of treatment arm. P-values for categorical variables are based on Cochran-Mantel-Haenszel test controlling for trial. P-values and least-squares means for continuous variables are based on 2-way ANOVA controlling for trial.

## 6. FINDINGS

### 6.1. Suicidal Behavior or Ideation

Table 19 lists the number of events by type and treatment arm in placebo-controlled trials. The table also lists the percentages of drug-treated and placebo-treated subjects who had each type of event. For all event categories, a higher percentage of drug-treated subjects had events compared to placebo-treated subjects. Suicidal ideation was the most common type of event in the data analyzed.

Table 19: Events by Type and Treatment Arm in Placebo-Controlled Trials

Event	Drug N=27863	Placebo N=16029	Total N=43892
Completed suicide	4 (0.01%)	0 (0%)	4
Suicide attempt	30 (0.11%)	8 (0.05%)	38
Preparatory acts	3 (0.01%)	1 (0.01%)	4
Suicidal ideation	67 (0.24%)	29 (0.18%)	96
Total	104 (0.37%)	38 (0.24%)	142

Notes: Events include only the most critical event for each patient.

Table displays the percentage of drug-treated and placebo-treated subjects who had each event type.

Adapted from the Statistical Review by Mark Levenson, Ph.D..

Table 20 gives the number of patients with a Suicidal Behavior or Ideation event, the number of patients, and the crude odds ratios by drug. Because the felbamate data had no events of suicidal behavior or ideation, its odds ratio is not defined. The drug tiagabine had events only in the drug arm; therefore, the odds ratio for tiagabine was infinity. No drug had events only in the placebo arm. The crude odds ratios ranged from 0.66 to 2.57.

Table 20: Suicidal Behavior or Ideation Events and Patients by Drug in Placebo-Controlled Trials

Drug	Drug Events/Patients	Placebo Events/Patients	Crude OR
Carbamazepine	2/252	3/250	0.66
Divalproex	11/1327	9/992	0.91
Felbamate	0/170	0/170	ND
Gabapentin	2/2903	1/2029	1.40
Lamotrigine	27/2865	11/2070	1.78
Levetiracetam	8/2554	2/1549	2.43
Oxcarbazepine	2/1342	1/827	1.23
Pregabalin	7/7201	2/3125	1.52
Tiagabine	2/835	0/608	Inf.
Topiramate	40/7742	8/3971	2.57
Zonisamide	3/672	1/438	1.96
Total	104/27863	38/16029	1.58

Notes: Events include only most critical event for each patient.

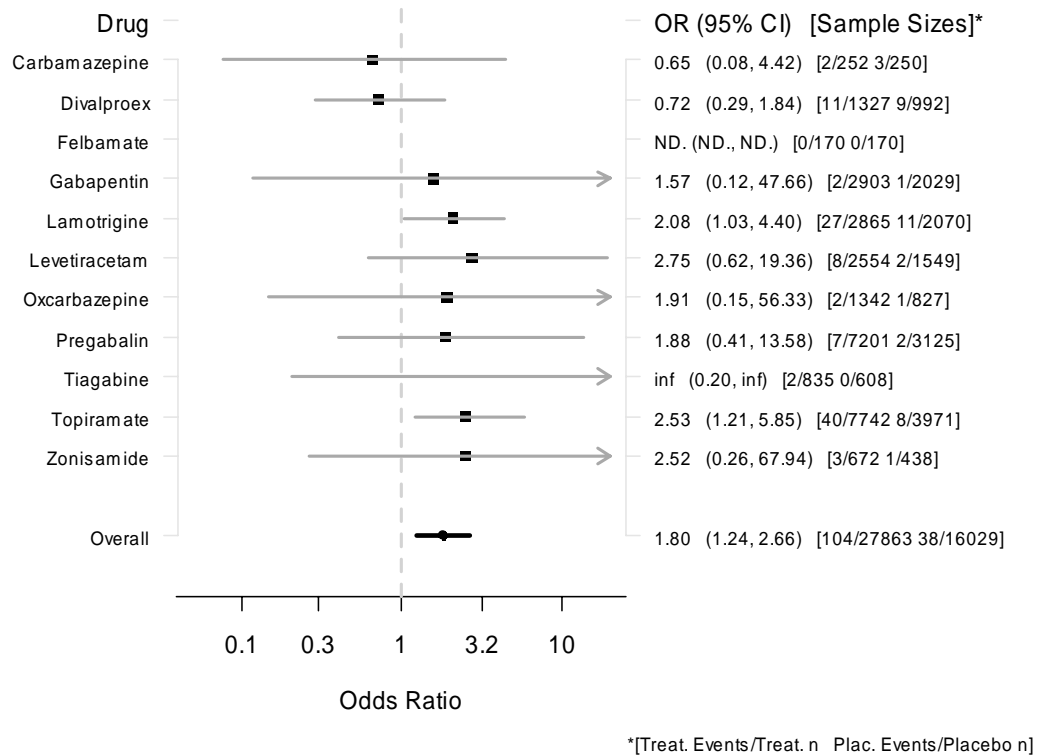
ND: Not defined. Inf.: Infinity.

Excerpted from the Statistical Review by Mark Levenson, Ph.D..

Figure 1 contains a forest plot of the estimated odds ratios and 95% confidence intervals for Suicidal Behavior and Ideation overall and by individual drug. For the drugs overall, the odds ratio was 1.80 (95% CI: 1.24, 2.66), consistent with a statistically significant increase in risk for Suicidal Behavior or Ideation in drug-treated subjects relative to placebo-treated subjects. Drug-treated subjects had 1.9 additional events of Suicidal Behavior or Ideation per 1000 subjects (95% CI: 0.6, 3.9) compared to placebo-treated subjects (approximately 1 additional event per 500 drug-treated subjects).

Figure 1 also contains the following results for individual drugs: of 11 drugs with data submitted, 10 drugs had Suicidal Behavior or Ideation events analyzed; estimated odds ratios were greater than one for 8 of these 10 drugs; 2 of these 8 drugs had statistically significant estimated odds ratios. Odds ratio point estimates for individual drugs ranged from 0.65 to 2.75.

Figure 1: Suicidal Behavior or Ideation Odds Ratio Estimates in Placebo-Controlled Trials



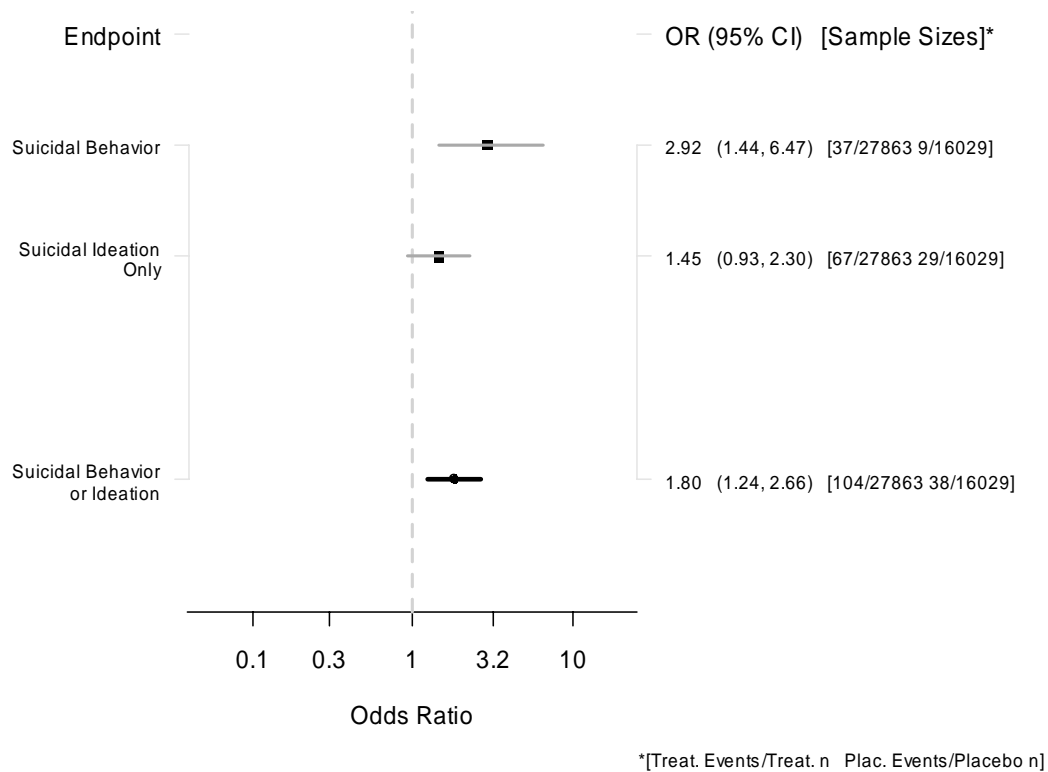
Excerpted from the Statistical Review by Mark Levenson, Ph.D..

## 6.2. Evaluations of Suicidal Behavior and Suicidal Ideation

Figure 2 displays the overall odds ratio estimates for the two endpoints: (1) Suicidal Behavior and (2) Suicidal Ideation. The Suicidal Behavior endpoint included events of completed suicide, suicide attempt, and preparatory acts toward imminent suicidal behavior. There was a statistically significant increase in risk of Suicidal Behavior for drug-treated subjects compared to placebo-treated subjects [OR 2.92 (95% CI: 1.44, 6.47)]. The odds ratio for Suicidal Ideation was 1.45 (95% CI: 0.93, 2.30).



Figure 2: Suicidal Behavior versus Suicidal Ideation Odds Ratio Estimates in Placebo-Controlled Trials.



Excerpted from the Statistical Review by Mark Levenson, Ph.D..

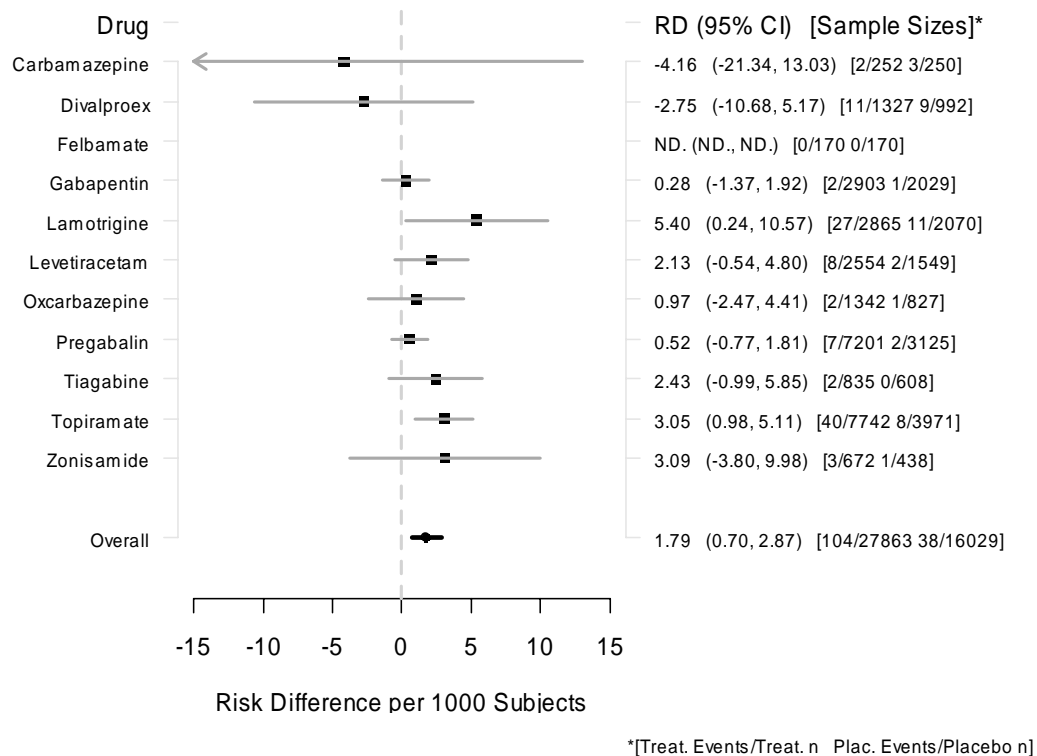
### 6.3 Sensitivity Analyses

#### 6.3.1. Sensitivity Analysis using Zero-Event Trials: Estimated Risk Differences

Figure 3 gives the estimated risk differences and 95% confidence intervals for Suicidal Behavior or Ideation by drug and overall. Unlike the odds ratio analysis, this risk difference analysis makes use of trials without any events.

The overall risk difference was 1.79 (95% CI: 0.70, 2.87) per 1000 patients, consistent with a statistically significant increase in risk of Suicidal Behavior or Ideation events compared to placebo. For each of the 11 drugs, the risk difference estimate had the same direction as the odds ratio estimate relative to the null value of no effect.

Figure 3: Suicidal Behavior or Ideation Risk Difference Estimates Placebo-Controlled Trials



Excerpted from the Statistical Review by Mark Levenson, Ph.D..

### 6.3.2. Trial Heterogeneity

The discussion of trial heterogeneity below was excerpted from the statistical review by Mark Levenson, Ph.D..

The primary analysis method was a fixed-effect method, which assumes that all the trials had a common treatment effect. The p-value based on Zelen's test for the null hypothesis that all trials had a common odds ratio test was 0.735. This value does not provide evidence for trial heterogeneity in the odds ratio. However, the lack evidence does not mean that there was no trial heterogeneity.

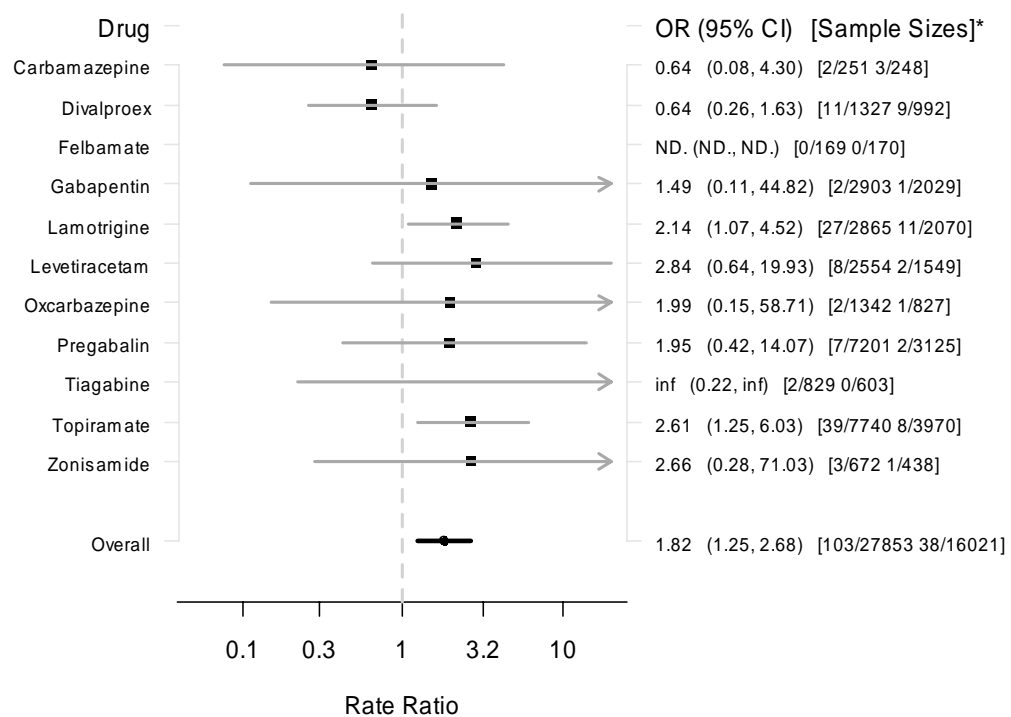
The general linear mixed model (GLMM) that allows for trial heterogeneity produced an overall odds ratio estimate of 1.86 (95% CI: 1.24, 2.78). Both the estimate and the confidence interval were very similar to those from the primary analysis method. The similarity implies that trial heterogeneity was not a major concern. The variance component estimate for the trial heterogeneity effect from the GLLM was 0.13 with a standard error of 0.26. The scale of the component is complex. However, the fact that the estimate was small relative to its standard error again does not provide evidence for trial heterogeneity.

The Mantel-Haenszel odds ratio weights were calculated to examine if there were trials with large influence on the overall odds ratio estimate. On a normalized scale such that the weights add to one, the largest five weights were 0.060, 0.020, 0.019, 0.017, and 0.016. The weight of 0.06 corresponded to the trial divalproex M92822. Except for this trial, no trial accounted for more than one fiftieth of the total weight. The overall odds ratio estimated using the exact method and excluding this trial was 2.12 (95% CI: 1.42, 3.25). This estimate was slightly larger than the estimate with all the trials; however, the two sets of estimates and confidence intervals were qualitatively similar.

### 6.3.3. Person-Time Analysis

Treatment duration was statistically significantly longer for placebo-treated subjects (least-squares means 77 days for placebo versus 73 days for drug). A person-time analysis was performed to adjust for differences in treatment duration. Figure 4 gives the estimated rate ratio and 95% confidence intervals from this analysis for Suicidal Behavior or Ideation by drug and overall. The overall rate ratio [1.82 (95% CI: 1.25, 2.68)] was very similar to the overall odds ratio [1.80 (95% CI: 1.24, 2.66)], which does not adjust for treatment duration. Rate estimates were similar to the odds ratio estimate for the 11 drugs individually.

Figure 4: Suicidal Behavior or Ideation Rate Ratio Estimates, Placebo-Controlled Trials



\*[Treat. Events/Treat. n Plac. Events/Placebo n]

Note: 18 Patients with missing or zero duration were not included in this analysis.  
Excerpted from the Statistical Review by Mark Levenson, Ph.D..

## 6.4. Exploratory Analyses

### 6.4.1. Time-to-Event Analysis

Table 21 shows the number of patients with a Suicidal Behavior or Ideation event and the estimated hazards by disjoint time intervals. Drug-treated subjects had a higher hazard of events compared to placebo-treated subjects in each of the time periods analyzed. Because there was limited data extending beyond 24 weeks of treatment, reliable assessments of risk beyond 24 weeks of treatment cannot be made.

Table 21: Suicidal Behavior or Ideation Hazard Estimates by Treatment Arm in Placebo-Controlled Trials

Week	Drug			Placebo		
	Events	Patients	Hazard	Events	Patients	Hazard
< 1	10	27337	0.37	5	15780	0.32
1 - 2	13	26077	0.50	4	15192	0.26
2 - 4	27	23979	0.56	11	14029	0.39
4 - 12	34	17591	0.24	14	10312	0.17
12 - 24	12	8139	0.12	3	4592	0.05
≥ 24	7	1862	0.05	1	886	0.02

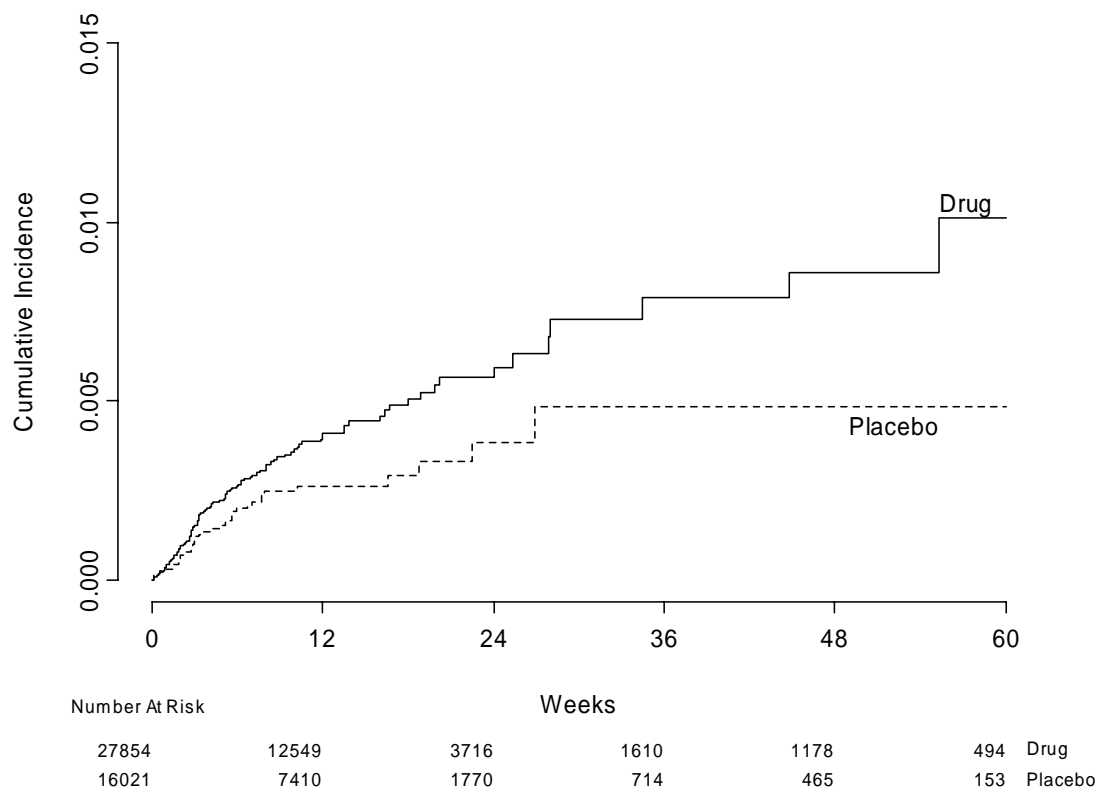
Notes: Events include only the most critical event for each patient. Patients are “effective sample size” which is the estimated number of patients at the midpoint of interval. Hazard is expressed as events per 1000 patient-weeks. For details see Klein and Moeschberger (2003, p. 152).<sup>9</sup>

Excerpted from the Statistical Review by Mark Levenson, Ph.D..

Figure 5 plots Kaplan-Meier incidence curves for the Suicidal Behavior or Ideation events by treatment arm. The Kaplan-Meier incidence curves for drug-treated and placebo-treated subjects diverge soon after the start of treatment and continue to diverge throughout the time period in which data was analyzed.

For the time-to-event analysis as in the other analyses, the most critical event was used. For all but one patient, this was the first event as well. One patient had a less critical event 2 days earlier than the most critical event.

Figure 5: Kaplan-Meier Suicidal Behavior or Ideation Incidence Curves by Treatment Arm in Placebo-Controlled Trials



Excerpted from the Statistical Review by Mark Levenson, Ph.D..

### 6.4.2. Multiple Events

Among the placebo-controlled trials, 9 patients in drug or placebo treatment arms had more than one Suicidal Behavior or Ideation event. Table 22 lists the events for these patients. One patient had two suicide attempts. Another patient had one suicide attempt. The events of the remaining 7 patients were all suicidal ideation.

Table 22: Events from Patients with Multiple Events in Placebo-Controlled Trials

Patient	Event	Event Day
Carbamazepine 105.301 004004	Ideation	11
	Ideation	12
Divalproex M92822 13709	Ideation	44
	Ideation	234
Divalproex M96493 20101	Ideation	17
	Suicide attempt	19
Lamotrigine P42040 37004	Ideation	5
	Ideation	75
	Ideation	83
	Ideation	88
Lamotrigine SCA3092/0946 63307	Ideation	56
	Ideation	78
Lamotrigine SCAA2010 03168	Suicide attempt	23
	Suicide attempt	30
Topiramate CAPSS168 00013403	Ideation	25
	Ideation	56
Topiramate OBES002 7123	Ideation	51
	Ideation	82
Topiramate PDMD005 10004	Ideation	1
	Ideation	11

Excerpted from the Statistical Review by Mark Levenson, Ph.D..

## 7. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

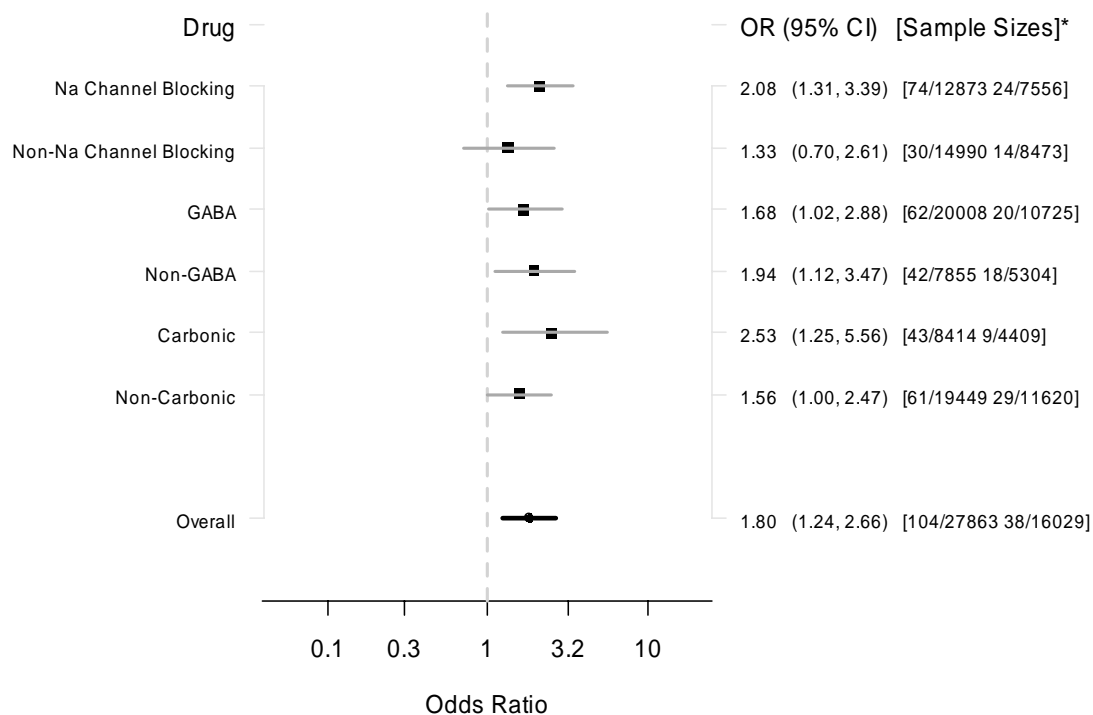
### 7.1. Drug Groups According to Main Mechanism(s) of Action

Figure 6 displays estimated odds ratios and 95% confidence intervals for Suicidal Behavior or Ideation according to drug group. The drug groups are based on a drug's main mechanism(s) of action. Each group of drugs was compared to the complementary group of drugs. The drug groups are neither mutually exclusive nor exhaustive.

The estimated odds ratio for each drug group and its complement were all greater than one. Except for the group of drugs not in the Sodium Channel Blocking group and the group of drugs not in the Carbonic Anhydrase Inhibiting group, the confidence intervals for all drug groups were statistically significant.

Topiramate is included in the groups of Sodium Channel Blocking Drugs, GABAergic and GABAmimetic Drugs, and Carbonic Anhydrase Inhibitors. The topiramate data contains a large number of subjects (7,742 drug-treated subjects and 3,971 placebo-treated subjects), so topiramate has a large influence on all 3 drug groups.

Figure 6: Suicidal Behavior or Ideation Odds Ratio Estimates by Drug Group in Placebo-Controlled Trials



\*[Treat. Events/Treat. n Plac. Events/Placebo n]

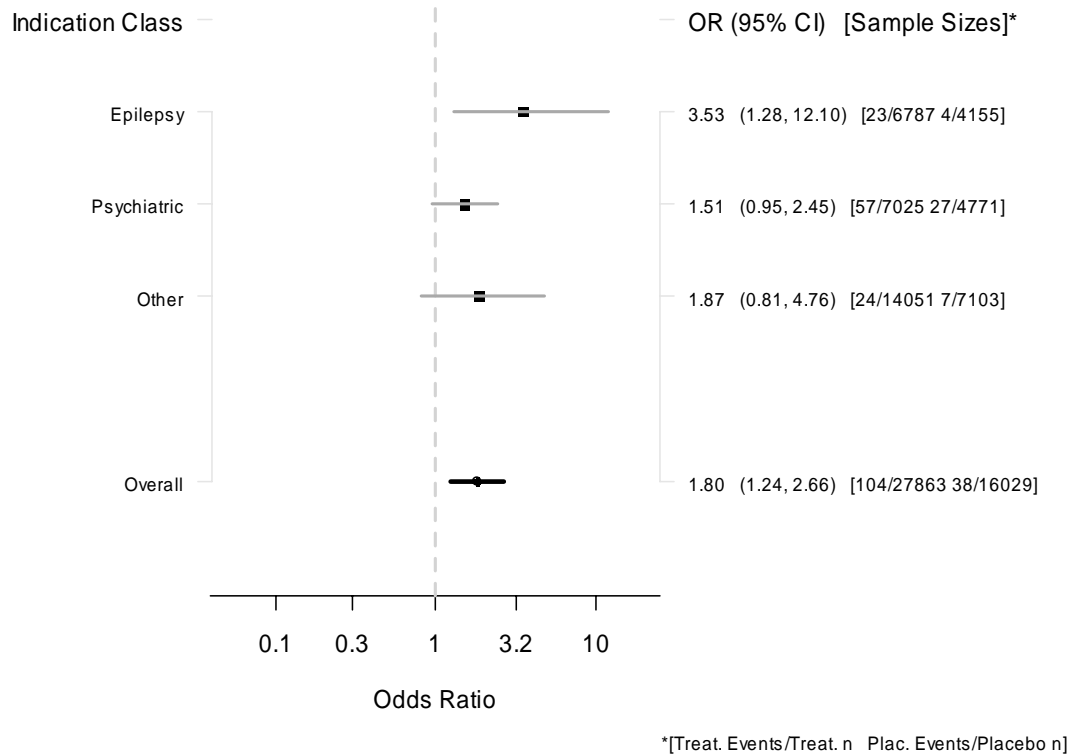
Excerpted from the Statistical Review by Mark Levenson, Ph.D..



## 7.2. Trial Indication

Figure 7 gives the estimated odds ratios and 95% confidence intervals for Suicidal Behavior or Ideation by indication group.

Figure 7: Suicidal Behavior or Ideation Odds Ratio Estimates by Indication Group in Placebo-Controlled Trials



Excerpted from the Statistical Review by Mark Levenson, Ph.D..

Table 23 gives estimates of the placebo and drug event rates and the risk difference risk by indication group. The psychiatric indication group had a notably higher placebo event rate than the other indication groups and had the highest risk difference, whereas the epilepsy indication group had the highest odds ratio.

Table 23: Placebo and Drug Suicidal Behavior or Ideation Event Rates and Risk Difference by Indication in Placebo-Controlled Trials

Indication	Odds Ratio	Drug Patients with Events Per 1000 Patients	Placebo Patients with Events Per 1000 Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients	Risk Ratio
Epilepsy	3.53	3.4	1.0	2.4	3.5
Psychiatric	1.51	8.5	5.7	2.9	1.5
Other	1.87	1.0	1.0	0.9	1.9
Total	1.80	4.3	2.4	1.9	1.8

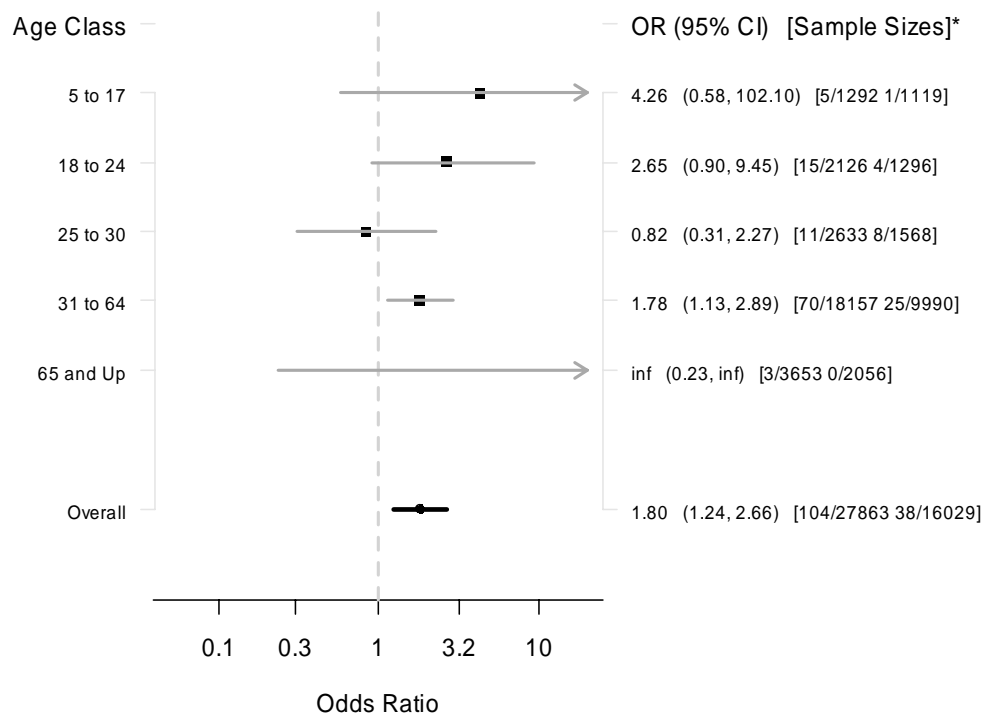
Notes: Drug event rate was calculated as the product of the placebo event rate and estimated odds ratio. Risk difference was calculated as the drug event rate minus the placebo event rate. Risk ratio was calculated as the ratio of the drug event rate to the placebo event rate. Adapted from the Statistical Review by Mark Levenson, Ph.D..

## 7.3. Demographics

### 7.3.1. Age

Figure 8 gives the estimated odds ratios and 95% confidence intervals for Suicidal Behavior or Ideation by age group. Estimated odds ratios were greater than 1 for all age groups, except for ages 25-30. No clear pattern of risk is seen across age groups.

Figure 8: Suicidal Behavior or Ideation Odds Ratio Estimates by Age Group, Placebo-Controlled Trials.



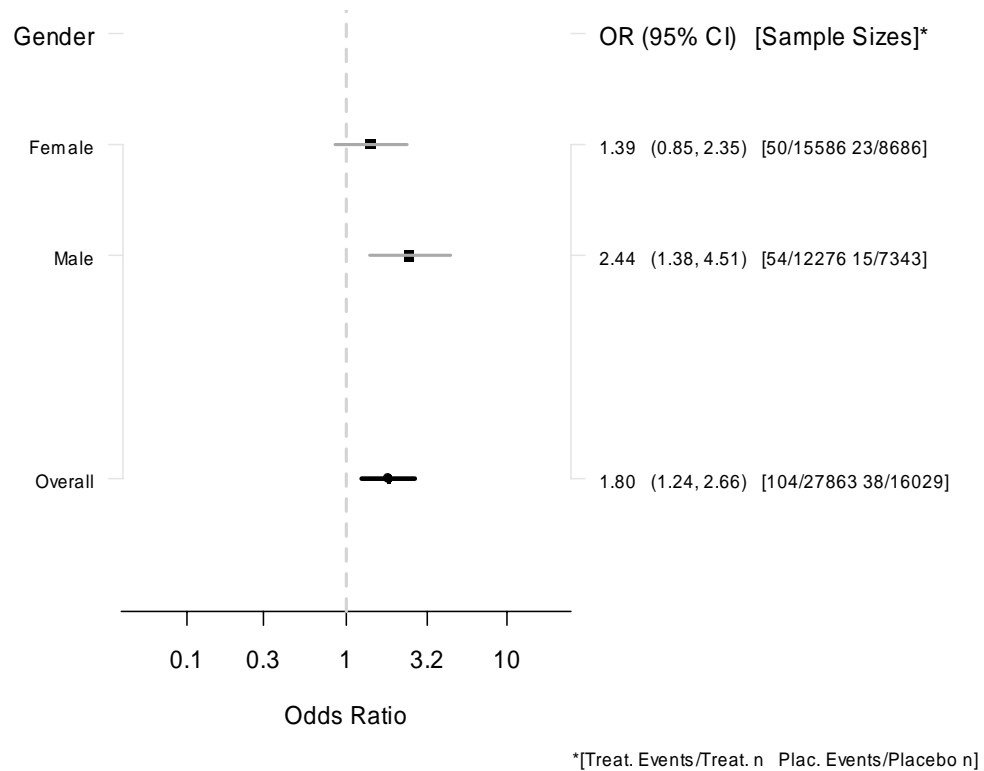
\*[Treat. Events/Treat. n Plac. Events/Placebo n]

Excerpted from the Statistical Review by Mark Levenson, Ph.D..

### 7.3.2. Gender

Figure 9 gives the estimated odds ratios and 95% confidence intervals for Suicidal Behavior or Ideation trials by gender. Estimated odds ratios were greater than 1 for both males and females.

Figure 9: Suicidal Behavior or Ideation Odds Ratio Estimates by Gender, Placebo-Controlled Trials.

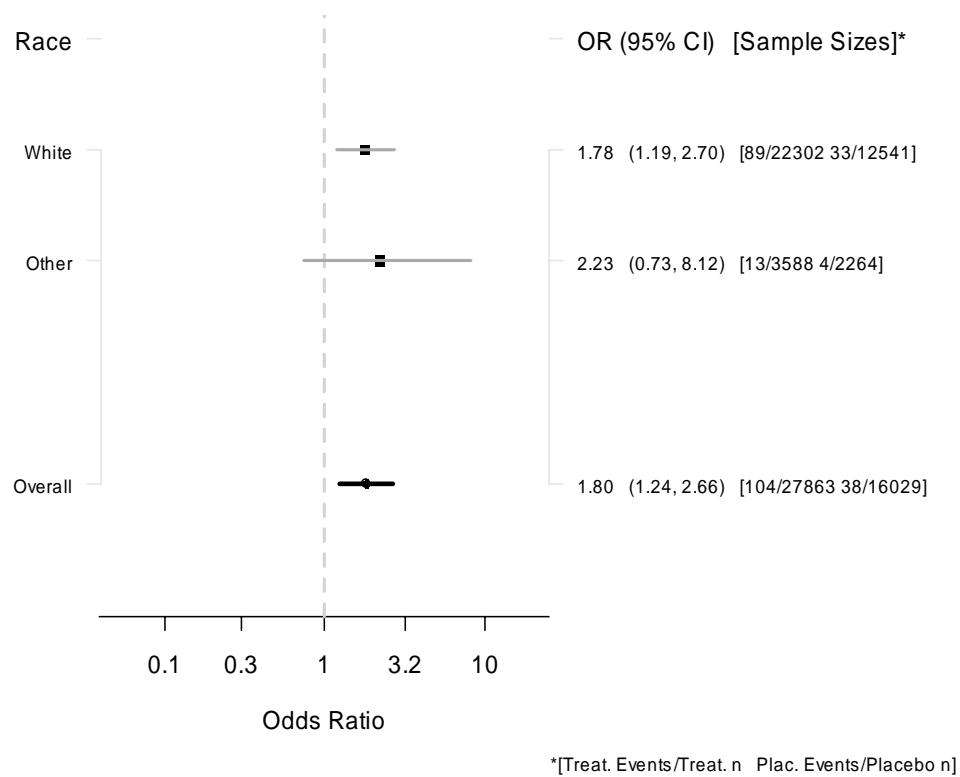


Excerpted from the Statistical Review by Mark Levenson, Ph.D..

### 7.3.3. Race

Figure 10 reports the estimated odds ratios and 95% confidence intervals for Suicidal Behavior or Ideation by race. For both the white and other (non-white) subgroups, the estimated odds ratios were greater than 1. The estimate for the other subgroup was higher than that for white subgroup, but the confidence interval was wide due to the small number of subjects in the other race group.

Figure 10: Suicidal Behavior or Ideation Odds Ratio Estimates by Race Group, Placebo-Controlled Trials.

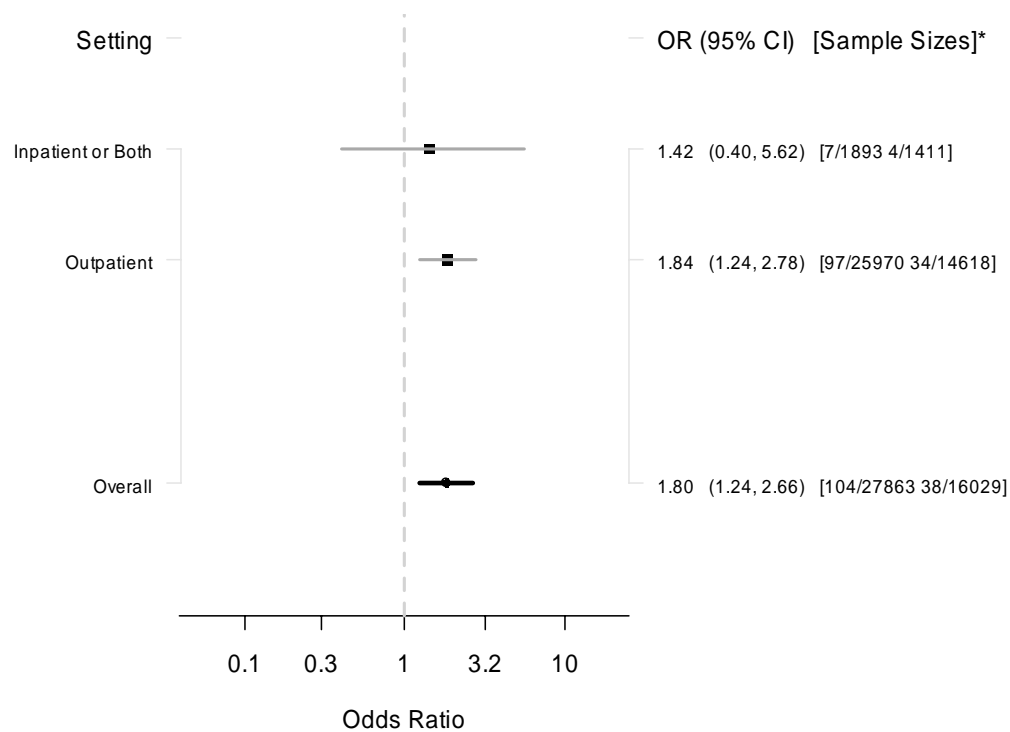


Excerpted from the Statistical Review by Mark Levenson, Ph.D..

#### 7.3.4. Setting

Figure 11 gives the estimated odds ratios and 95% confidence intervals for Suicidal Behavior or Ideation by trial setting. In settings categorized as inpatient or both outpatient and inpatient, the odds ratio was 1.42 (95% CI: 0.40, 5.62). In outpatient settings, the odds ratio was 1.84 (95% CI: 1.24, 2.78).

Figure 11: Suicidal Behavior or Ideation Odds Ratio Estimates by Setting, Placebo-Controlled Trials.



\*[Treat. Events/Treat. n Plac. Events/Placebo n]

Excerpted from the Statistical Review by Mark Levenson, Ph.D..

### 7.3.5. Location

We analyzed results according to North American versus Non-North American location. Table 23 displays the number and percentage of subjects reporting events according to treatment arm and location in placebo-controlled trials. Comparisons of the percentage of subjects with Suicidal Behavior events in drug-treated versus placebo-treated groups were qualitatively similar in the North American and Non-North American location subgroups.

However, comparisons of Suicidal Ideation in drug-treated versus placebo-treated subjects were not consistent between location subgroups. In the North American subgroup, the percentage of subjects with Suicidal Ideation events was nearly identical in drug-treated and placebo-treated groups; in Non-North American trials, there was a large difference in Suicidal Ideation between drug and placebo.

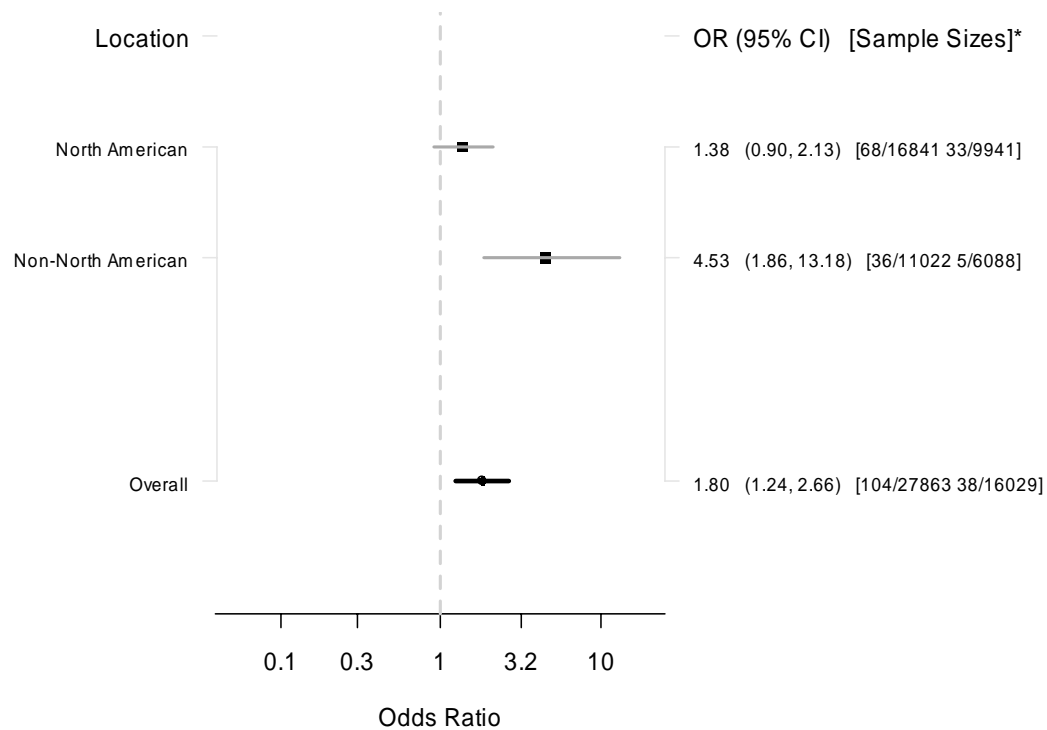
Table 23. Events According to Treatment Arm and Location in Placebo-Controlled Trials

Event	North America N=26782		Non-North America N=17110	
	Drug N=16,841	Placebo N=9941	Drug N=11022	Placebo N=6088
Completed suicide	2 (0.01%)	0 (0%)	2 (0.02%)	0 (0%)
Suicide attempt	16 (0.09%)	6 (0.06%)	14 (0.13%)	2 (0.03%)
Preparatory acts	3 (0.02%)	1 (0.01%)	0 (0%)	0 (0%)
Suicidal ideation	47 (0.28%)	26 (0.26%)	20 (0.19%)	3 (0.05%)
Total	68 (0.40%)	33 (0.33%)	36 (0.33%)	5 (0.08%)

Note: Events include only the most critical event for each patient.

Figure 12 gives the estimated odds ratios and 95% confidence intervals for Suicidal Behavior or Ideation by location. Both North America and Non-North America locations had estimated odds ratios greater than 1, but the odds ratio estimate for the Non-North America location was larger and statistically significant.

Figure 12: Suicidal Behavior or Ideation Odds Ratio Estimates by Location, Placebo-Controlled Trials.



\*[Treat. Events/Treat. n Plac. Events/Placebo n]

Excerpted from the Statistical Review by Mark Levenson, Ph.D..



Table 24 lists the odds ratios, event rates, and risk differences for Suicidal Behavior or Ideation by location subgroup. In both North American and Non-North American subgroups, drug-treated subjects have a higher event rate compared to placebo. The event rate in drug-treated subjects is similar in both location subgroups (4.0 events per 1000 patients for drug-treated North American subjects and 3.3 events per 1000 patients for Non-North American subjects.) However, the event rate in placebo-treated Non-North American subjects is much lower than other subgroups (0.8 events per 1000 patients), and this low placebo event rate leads to the elevated odds ratio and elevated risk difference in the Non-North American subgroup.

Table 24. Suicidal Behavior or Ideation Event Rates and Risk Differences by Treatment Arm and Location

Location	Odds Ratio	Drug Patients with Events Per 1000 Patients	Placebo Patients with Events Per 1000 Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
North America	1.38	4.0	3.3	0.7
Non-North America	4.53	3.3	0.8	2.5
Total	1.80	4.3	2.4	1.9

Notes: Risk difference was calculated as the drug event rate minus the placebo event rate.

Trial characteristics including proportions of trial indication groups, age, gender, race, and proportion with inpatient treatment were otherwise similar in North American and Non-North American Trials.

## 8. POST-HOC ANALYSES

Analyses planned and performed after reviewing analyses outlined in the statistical analysis plan are listed below.

### 8.1. Lamotrigine Additional Data

On November 21, 2007, the sponsor of lamotrigine (GlaxoSmithKline) submitted additional data for the drug. The submission included: 1) Data from three trials that were ongoing at the time of the data request to the sponsors; and 2) Four additional Suicidal Behavior or Ideation events from trials previously submitted. FDA's July 11, 2005 letter (Appendix 2) included a request that preferred terms, verbatim terms, and comments fields of trials included in the analysis be searched for "Possibly Suicide-Related Events (PSRAEs). The lamotrigine data base submitted prior to November 21, 2007 did not include a search of the comments fields. The four additional Suicidal Behavior or Ideation events from lamotrigine trials previously submitted came from a search of the comments fields.

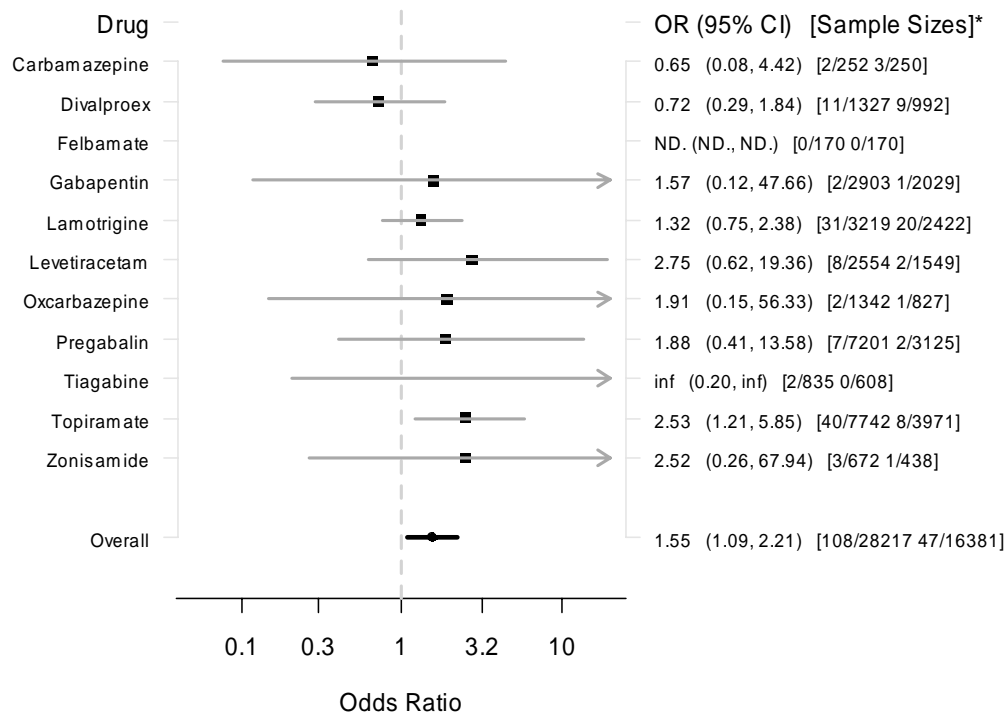
FDA instructions to sponsors in July 2005 (Appendix 2) stated that ongoing trials should not be submitted. The three additional lamotrigine trials otherwise met the inclusion criteria for the analysis. The three trials had a total of 9 Suicidal Behavior or Ideation events, 1 in a drug-treated subject and 8 in placebo-treated subjects. Because including trial data electively submitted by a

drug sponsor despite existing instructions may bias the results of the analysis, data from the three lamotrigine trials was not included in the main analysis.

Of the 4 additional events from trials previously submitted, 3 were in drug-treated subjects and 1 was in a placebo-treated subject.

Figure 13 gives the estimated odds ratio and 95% confidence intervals for Suicidal Behavior or Ideation overall and by individual drug with data from the three additional lamotrigine trials and data from the search of lamotrigine trial comments fields; the overall rate ratio estimate was lower than the primary analysis estimate, but it remained statistically significant [1.55 (95% CI: 1.09, 2.21)].

Figure 13: Suicidal Behavior or Ideation Odds Ratio Estimates with Additional Lamotrigine Data in Placebo-Controlled Trials



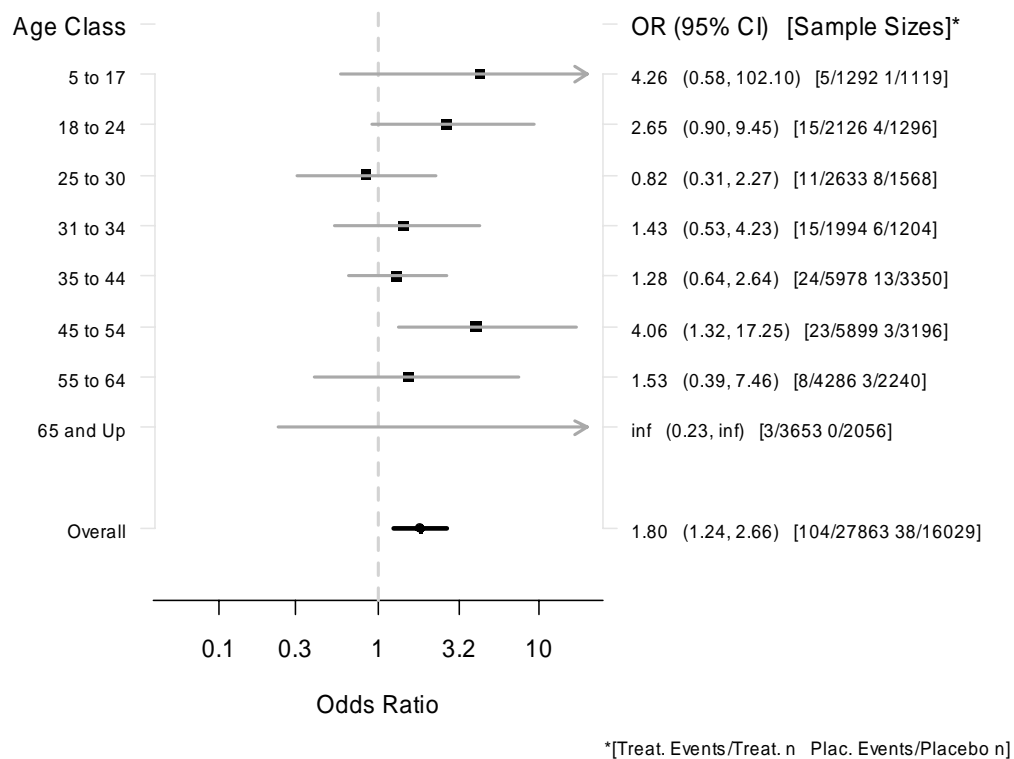
\*[Treat. Events/Treat. n Plac. Events/Placebo n]

Excerpted from the Statistical Review by Mark Levenson, Ph.D..

## 8.2. Analysis by Alternative Age Groupings

We performed an additional subgroup analysis using alternative age groupings, to evaluate the possibility of an interaction between age and drug effect. A finer grouping, in which the age group from 31 to 64 years was divided into 4 age groups, was used. Figure 14 displays the results of this analysis. Neither the prospectively-defined nor ad hoc-defined analyses by age group showed a clear pattern of risk according to age.

Figure 14: Suicidal Behavior or Ideation Odds Ratio Estimates by Post-Hoc Age Group in Placebo-Controlled Trials



Excerpted from the Statistical Review by Mark Levenson, Ph.D..

## 8.3. Evaluation of Suicidal Behavior Narratives

On May 7, 2008 FDA requested that sponsors submit narratives for Suicidal Behavior events in drug arm and placebo arm subjects from placebo-controlled trials.

### 8.3.1. Evaluation of Suicidal Behavior Narratives: Methods

Sponsors were provided specific instructions on preparing narratives in FDA's March 2005 information request (see excerpt below).

A complete set of narrative summaries should be prepared and collected for all

“possibly suicide-related” adverse events. In some cases, narratives will have already been prepared, e.g., deaths and SAEs. In other cases, however, you will need to prepare narrative summaries by searching CRFs for any information that might be considered possibly relevant to suicidality. You should also utilize other relevant sources of information, e.g., hospital records, results of consults, questionnaire responses, etc, in preparing these narrative summaries. Depending on how much information is available, narrative summaries may be longer than 1 page, however, in no case, should more than 1 narrative summary be included on a single page. Following is the type of information that should be included in the original narrative summaries:

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

We systematically abstracted data from narratives corresponding to Suicidal Behavior events in subjects from drug and placebo arms of placebo-controlled trials.

### 8.3.2. Evaluation of Suicidal Behavior Narratives: Findings

To better understand the nature of the increased risk of suicidality in antiepileptic drug-treated subjects in this analysis, we evaluated narratives for Suicidal Behavior events in drug and placebo arms of placebo-controlled trials (N=46). The narratives provide case descriptions of Suicidal Behavior events in this analysis. While specific information was requested for inclusion

in the narratives, it is important to note that pertinent negative findings, along with other information important for case interpretation, were frequently not documented. The narratives provide information on events detected by our methods, but events that were not detected may have different characteristics. Appendix 9 provides information on the 46 Suicidal Behavior narratives, including clinical trial source drug, treatment arm, trial indication, subject age, number of days from initiation of treatment to day of event, event description, noted associated psychiatric symptoms, and comorbid psychiatric diagnoses.

#### 8.3.2.1. Evaluation of Suicidal Behavior Narratives: Psychiatric Symptoms Associated with Suicidal Behavior Events

Table 23 describes psychiatric symptoms reported in Suicidal Behavior narratives. Depression was the most commonly reported psychiatric symptom associated with Suicidal Behavior events. Psychiatric symptoms including psychosis, anxiety, irritability, confusion, and impulsivity were also reported in drug-treated subjects with Suicidal Behavior events.

Table 23. Psychiatric Symptoms Reported in Drug-Treated Subjects with Suicidal Behavior Events

	Number of Subjects (%)
Depression	13 (35)
Psychosis	2 (5)
Anxiety	2 (5)
Irritability	4 (11)
Confusion	1 (3)
Impulsivity	1 (3)

#### 8.3.2.3. Evaluation of Suicidal Behavior Narratives: Factors Affecting the Likelihood of Ascertainment Bias

The majority of Suicidal Behavior events prompted notification of the study investigator by an outside party or prompted the subject's discontinuation from the trial. Of 46 narratives, 20 (43%) reported that the study investigator was notified of the Suicidal Behavior event by an outside party (e.g., notification during hospitalization, notification of death, notification by a family member); in 33 of 46 subjects (72%) the event prompted discontinuation from the trial. In these circumstances, reporting of Suicidal Behavior events is less likely to have been driven by a generally increased rate of adverse events or by additional contact with clinical trial staff.

## 9. DISCUSSION

### 9.1. Use of Placebo-Controlled Clinical Trial Data

A strength of this analysis is its use of placebo-controlled data. When evaluating the risk of suicidal behavior or ideation with antiepileptic drugs, comparison to placebo-treated subjects is necessary to understand the background rate of suicidality. Patients with epilepsy (and other illnesses for which AEDs are prescribed) are reported to have increased risk of suicidal behavior

or ideation, but estimates of suicidality rates vary widely;<sup>10</sup> without comparison to placebo-treated subjects, the background rate of suicidal behavior or ideation events is unclear.

When assessed over the lifetime of individuals in a population, suicidal behavior and ideation are frequent occurrences that amount to a major public health burden; in 2004 suicide was the eighth most common cause of death in the United States general population.<sup>11</sup> However, suicidal behavior and ideation are rare events within the limited time frame of clinical trials. This meta-analysis of existing clinical trial data provides a number of subjects that is larger than any group of subjects previously used to evaluate this question. Because data on suicidal behavior and ideation in clinical trials is typically sparse, large numbers of subjects are necessary to evaluate risk using clinical trial data.

## **9.2. Retrospective Analysis of Data**

Data was gathered retrospectively, since the majority of clinical trial data for currently marketed antiepileptic drugs was generated prior to the recognition of a possible suicidality signal for antiepileptic drugs. Because this was a post-hoc analysis with multiple outcomes and subanalyses, results should be interpreted with caution. No adjustments for multiplicity were made, because of the exploratory nature of this analysis. Trials included in this meta-analysis were not specifically designed to evaluate risk of suicidal behavior or ideation. Differences between clinical trials analyzed for individual drugs limit the possibility of making reliable comparisons between individual drugs.

## **9.3. Possibility of Ascertainment Bias**

To generate suicidality event data for this analysis, sponsors performed searches of their clinical trial adverse event data bases using search terms and instructions for processing the data specified by FDA; with these methods, ascertainment bias may occur. A drug-treated subject may have a higher rate of adverse events in general; drug-treated subjects may have additional contact with clinical staff, and this may cause drug-treated subjects to be more likely to generate an adverse event report with information on suicidal behavior or thinking. Prospective methods of assessing suicidality in randomized trials are not subject to ascertainment bias and will be useful in future studies.

Compared to placebo-treated subjects, drug-treated subjects had had higher incidence rates for all categories of suicidal behavior or ideation events (Table 19). The odds ratio estimate for Suicidal Behavior alone (completed suicide, suicide attempt, and preparatory acts toward imminent suicidal behavior) was statistically significant [2.92 (95% CI 1.44, 6.47)].

Ascertainment bias likely has less influence on the reporting of suicidal behavior than on the reporting of suicidal ideation. The majority of Suicidal Behavior events prompted notification of the study investigator by an outside party (e.g., notification during hospitalization, notification of death, notification by a family member) or prompted the subject's discontinuation from the trial. In these circumstances, reporting of Suicidal Behavior events is less likely to have been driven by a generally increased rate of adverse events or by additional contact with clinical trial staff.

#### 9.4. Consistency of Results in Subgroup Analyses

With meta-analyses, consistency of results in subgroups of the data analyzed is important in confirming that overall conclusions are valid. No clear pattern of drug effect was seen among subgroups according to age, gender, race, setting. No clear pattern of drug effect was seen among drug groups pre-specified according to main mechanism of action (sodium channel blocking, GABAergic and GABA-mimetic, and carbonic anhydrase inhibitors).

While estimates of drug effect varied among categories of trial indications, increased risk of suicidal behavior or ideation was observed in all categories of trial indications evaluated (Epilepsy, Psychiatric Indications, and Other Indications.) The majority of epilepsy trials involved adjunctive therapy, while the majority of trials for psychiatric indications or other indications involved monotherapy. Because increased risk in drug-treated subjects was seen in all trial indication categories, it may be expected that the increased risk exists, whether the antiepileptic drug is used in monotherapy or adjunctive therapy.

Increased risk of suicidal behavior or ideation was seen in both trial location subgroups; the estimated odds ratio for the Non-North American subgroup [4.53 (95% CI: 1.86, 13.18)] was larger than that for the North American subgroup [1.38 (95% CI: 0.90, 2.13)]. The Suicidal Behavior or Ideation event rate in placebo-treated Non-North American subjects was much lower than other subgroups (0.8 events per 1000 patients), mostly due to a low rate of Suicidal Ideation events; this low placebo event rate in the Non-North American subgroup leads to the elevated odds ratio and elevated risk difference in the Non-North American subgroup.

In analyses of Suicidal Behavior according to location subgroups, comparisons between drug-treated and placebo-treated subjects were similar in North American and Non-North American trials. However, comparisons of Suicidal Ideation in drug-treated versus placebo-treated subjects were not consistent between location subgroups. In the North American subgroup, the percentage of subjects with Suicidal Ideation events was nearly identical in the drug-treated and placebo-treated groups; in Non-North American trials, there was a large difference in the percentage of subjects with Suicidal Ideation events in drug and placebo groups.

In efforts to explain differences in location subgroup findings, there are several potential considerations. Of primary concern, the lack of consistency in results among Suicidal Ideation event rates between location subgroups may support that the analysis methods do not optimally capture Suicidal Ideation events. (In comparison, evaluations of Suicidal Behavior risk are more consistent.) Also, several differences between North American and Non-North American locations may contribute, including differences in clinical standards and the practice of medicine, differences in use of rating instruments (language differences, cultural differences), patient population differences (differences in dosing requirements, differences in treatment response, differences in placebo response), and investigator differences.

## **9.5. Risk of Suicidal Behavior or Ideation in Individual Antiepileptic Drugs**

Odds ratio point estimates for individual drugs ranged from 0.65 to 2.75 (Figure 1). For many individual antiepileptic drugs, 95% confidence intervals for odds ratio estimates included 1. Non-statistically significant odds ratio estimates and differences between clinical trials analyzed for individual drugs limit the possibility of making reliable comparisons between individual drugs.

## **9.6. Generalizability of Analysis Results**

A limitation of this analysis is that subjects with risk factors for suicidal behavior or ideation were commonly excluded from trials (e.g., history of suicide attempt, current suicide risk, substance abuse, personality disorders). Subjects with these risk factors may be underrepresented in clinical trials. Exclusion of subjects with risk factors for suicidal behavior or ideation varied between development programs of individual drugs, but we did not note a difference in suicidality event rates for drugs with more extensive trial exclusion criteria related to suicidality or psychiatric history.

Results of our analysis may not be generalizable to subjects who are treated with antiepileptic drugs in the setting of long term maintenance therapy. Because data beyond 24 weeks of treatment was limited, reliable assessments beyond 24 weeks of treatment could not be made. Also, in placebo-controlled trials indicated for psychiatric disorders, 80% evaluated subjects who were acutely symptomatic at randomization, and 14% evaluated subjects who were symptomatically stable and receiving maintenance treatment.

## **9.7. Mechanism of Increased Risk of Suicidal Behavior or Ideation in Antiepileptic Drugs Overall**

The mechanism of action of the increased risk of suicidal behavior or ideation with antiepileptic drugs is unclear. We considered the possible connection between improved seizure control and the appearance of psychiatric symptoms in patients with epilepsy. However, this explanation does not account for the increase in risk seen in trials for psychiatric indications and in trials for other indications, which included trials for migraine, fibromyalgia, neuropathic pain, and other chronic pain syndromes.

## **10. CONCLUSION**

FDA analyzed data for 43,892 drug and placebo arm subjects from 199 placebo-controlled trials. Drug-treated subjects had a statistically significant increase in risk of Suicidal Behavior or Ideation compared to placebo-treated subjects for all antiepileptic drugs combined [OR 1.80 (95% CI: 1.24, 2.66)]. Drug-treated subjects overall had 1.9 additional events of Suicidal Behavior or Ideation per 1000 subjects (95% CI: 0.6, 3.9) compared to placebo-treated subjects (approximately 1 additional event per 500 drug-treated subjects). All of the sensitivity analyses produced results similar to the primary analysis for overall and individual odds ratios. The odds ratio for Suicidal Behavior (completed suicide, suicide attempt, and preparatory acts toward imminent suicidal behavior) was also statistically significant [OR 2.92 (95% CI: 1.44, 6.47)].



Results were generally consistent for individual drugs analyzed. Increased risk of Suicidal Behavior or Ideation was observed in all categories of trial indications evaluated.

## **11. FDA ACTIONS**

### **11.1. Press Release and Information for Healthcare Professionals**

On January 31, 2008 FDA issued a press release (Appendix 7) and information for healthcare professionals (Appendix 8), which alerted the public and health care professionals to the results of this analysis.

### **11.2. Advisory Committee Meeting**

A joint meeting of the Peripheral and Central Nervous System Drugs and Psychopharmacologic Drugs Advisory Committees is planned, where the results and implications of this analysis will be discussed. Members of the Drug Safety and Risk Management and Pediatric Advisory Committee members will also participate in this meeting.

## **12. AREAS FOR FUTURE INVESTIGATION**

Future research using prospective data is necessary to evaluate the risk of antiepileptic drugs and suicidal behavior or ideation without the limitations of adverse event data. Also, further development of validated methods to assess suicidality, including suicidality rating scales, are necessary for more consistent and systematic assessments of suicidality. Other areas for additional research include characterizing potential underlying mechanisms of increased risk of suicidal behavior or ideation with antiepileptic drugs, and also research on whether certain patient subgroups are at particular risk.

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## APPENDICES

### **Appendix 1: FDA Data Request Letter to Sponsors (03/16/2005)**

Dear Sponsor:

There is evidence that patients with epilepsy are at an elevated risk for suicidality (suicidal thinking and behavior) and completed suicide. Despite this elevated population risk, the concern has been raised that some anti-epileptic drugs (AEDs) may be associated with an increased risk of suicidality. Given the recent observation of suicidality as a drug-induced adverse effect in pediatric patients exposed to various antidepressants in placebo-controlled trials, there is interest in examining data from placebo-controlled trials of AEDs to assess for a similar effect. Based on our experience with the pediatric antidepressant trials, the Division of Neuropharmacological Drug Products (DNPD) has developed a standard approach for evaluating drug-induced suicidality. Thus, we ask that you utilize the approach we have outlined in this letter for evaluating “possibly suicide related” adverse events occurring in placebo-controlled trials for divalproex sodium.

We request that you identify the trials from your development program (regardless of whether the indication is approved or not) that meet the following criteria: placebo-controlled; parallel arm; short-term (up to six months); at least 30 patients total. Some trials in epilepsy may have utilized a subtherapeutic dose of a standard AED as a comparator arm. Those trials should be included (if they meet the other criteria described above) and the subtherapeutic comparator arm should be coded as a “low dose-placebo” (see variable list below).

Once we have agreed upon the list of trials upon which to focus this exploration, we ask that you utilize the following approach to identifying and further evaluating “possibly suicide related” adverse events occurring in these trials.

#### **Search for “Possibly Suicide-Related” Adverse Events and Preparation of Narrative Summaries**

##### Time Frame for “Possibly Suicide-Related” Adverse Events

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

## Search Strategies for “Possibly Suicide-Related” Adverse Events

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

- Any events coded to preferred terms that include the text strings “suic” or “overdos,” including all events coded as “accidental overdose” should be included.
- 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-”, “poison”, “asphyxiation”, “suffocation”, “firearm” should be included.

Note: Any terms identified by this search because the text string was a substring of an unrelated word should be excluded (for example, the text string “cut” might identify the word “acute”). These terms might be characterized as “false positives” in the sense that the verbatim term was selected because one of the text strings occurred within that term but the term had no relevance to suicidality. Although we request that such terms be excluded, we ask that you prepare a table listing all such false positives, as follows:

<u>Study # Patient # Treatment Assignment</u>	<u>Term in Which</u> <u>Text String</u> <u>Occurred</u>
---	---

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

- All deaths and other serious adverse events (SAEs) should be included.
- All adverse events coded as “accidental injury” should be included.

## Preparation of Narrative Summaries for “Possibly Suicide-Related” Adverse Events

A complete set of narrative summaries should be prepared and collected for all “possibly suicide-related” adverse events. In some cases, narratives will have already been prepared, e.g., deaths and SAEs. In other cases, however, you will need to prepare narrative summaries by searching CRFs for any information that might be considered possibly relevant to suicidality. You should also utilize other relevant sources of information, e.g., hospital records, results of consults, questionnaire responses, etc, in preparing these narrative summaries. Depending on how much information is available, narrative summaries may be longer than 1 page, however, in no case, should more than 1 narrative summary be included on a single page. Following is the type of information that should be included in the original narrative summaries:

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

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

Other relevant information for preparing narrative summaries:

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

-Only events occurring during the “exposure window” defined as during the double-blind phase (including the first day after abrupt discontinuation or the first day of taper, if tapering is utilized) should be included in the narrative summary, i.e., do not include any pre-randomization events or events occurring more than 1 day after stopping randomized treatment or during the tapering period. -Do not exclude events of interest on the basis of your judgment that they might not represent “treatment-emergent” events; we feel this judgment is too difficult to make and we prefer to simply include all potentially relevant events, regardless of whether or not similar thoughts or behaviors may have occurred prior to treatment.

### **Classification of “Possibly Suicide-Related” Adverse Events**

Once the narrative summaries for “possibly suicide-related” adverse events are prepared and collected, we ask that you accomplish a rational classification of these events using the approach that was well-characterized by the Columbia group for the pediatric suicidality narratives. This approach was described in detail by Dr. Kelly Posner at the September 13 and 14, 2004 advisory committee meeting. The details are provided in her slides for that meeting (available on FDA’s website), in the transcript for that meeting, and in other reviews, etc. pertinent to pediatric suicidality and available on FDA’s website at the following URLs:

- Slides [http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4065S1\\_06\\_FDA-Posner.ppt](http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4065S1_06_FDA-Posner.ppt)
- Briefing Document, transcripts, etc.  
<http://www.fda.gov/ohrms/dockets/ac/cder04.html#PsychopharmacologicDrugs>

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

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

Those individuals who classify the narratives must have the appropriate expertise and training to accomplish this task.

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

- Identifying patient information, identity of study drug, and patient's randomized drug assignment Page 5
- All identifying information regarding the sponsor, the clinical trial number, and the location of the trial
- All years with the exception of years in remote history
- Study drug start and stop dates (month, day, and year)
- All medications, both prescription and non-prescription, whether taken before, during, or after the study; non-pharmaceutical substances (e.g., alcohol, tobacco) should not be blocked out
- Names of medications involved in overdoses; the number of pills consumed should not be blocked out
- Indications for medications started during or after the study
- Indications for study drug

Once you have decided on an approach to accomplishing the task of blinding and classifying the narratives, we would be happy to review and comment on your plan.

## Data Submission to DNDP

In order to perform additional analyses investigating the relationship between exposure to AEDs and “suicide-related” adverse events in adults and the pediatric population, we would appreciate your submitting the following variables as outlined in the next table. Note that we are requesting information from placebo (and “low dose-placebo”) controlled trials only. We would expect that you will provide us with a completed JMP dataset within 6 months from the date of this letter.

Variable name	Type	Description	Coding notes
SOURCE	Character	First few letters of your drug name	
INDICATION	Character	Disease being studied in trial	E.g., epilepsy- adjunctive, epilepsy- monotherapy, bipolar disorder, migraine, etc.
TRIAL	Character	Trial ID	
CTPID	Character	Patient ID within each trial	
UNIQUEID	Character	A unique ID for every patient	Composed of “TRIAL” and “CTPID” joined in that order with no intervening punctuation or dashes
AGE	Numeric	Patient age	In years
AGECAT	Numeric	Age category	1=5-11 2=12-17 3=18-24 y 4=25-64 y 5=65 y or more
GENDER	Numeric	Patient gender	1=female 2=male

Variable name	Type	Description	Coding notes
RACE	Numeric	Patient race	1=White Caucasian 2=African-American 3=Hispanic 4=Asian 5=Other . = Missing
SETTING	Numeric	Setting of trial	1=inpatient 2=outpatient 3=both
LOCATION	Numeric	Location of trial	1=North America 2=Non-North America

TXARM	Numeric	Randomized treatment	1=drug 2=placebo 3=active control 4=low dose-placebo No missing values are allowed in this variable.
TXLOW	Character	Name of drug used as low dose-placebo	Leave patients in other treatment arms blank
TXACTIVE	Character	Name of drug used as active control	Leave patients in other treatment arms blank
EVENT	Numeric	This variable contains the code for the first suicidality event. If a patient had more than one event in the desired “exposure window”, then the most severe event should be listed. Severity is decided based on the following order of codes 1>2>4>3>5	0=no event 1=suicide attempt 2=preparatory acts toward imminent suicidal behavior 3=self-injurious behavior, intent unknown 4=suicidal ideation 5=not enough information No missing values are allowed in this variable.
EVENTDAY	Numeric	The number of days to the first suicidal event counting from the day of the first dose.	for patients without events, this variable should contain days until end of trial or until premature discontinuation for patients with more than one event, this variable should contain days until the most severe event that is listed under the variable “EVENT”

Variable name	Type	Description	Coding notes
			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

If you have any questions, call Jacqueline H. Ware, Pharm.D., Senior Regulatory Health Project



Manager, at (301) 594-5533.

Sincerely,

Russell Katz, M.D.

Director

Division of Neuropharmacological Drug Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

## **Appendix 2: FDA Letter to Providing Additional Information to Sponsors (07/11/2005)**

Dear Sponsor:

We additionally refer to an Agency letter dated March 16, 2005, requesting you to evaluate “possibly suicide related” adverse events occurring in placebo-controlled trials.

In response to our March 16, 2005 letter, we have received a number of questions about which studies were suitable for inclusion in the proposed analyses. Other questions have been about the data collection, classification, and presentation. Because many sponsors had similar questions, we are providing the following general clarifications of our requests. In some instances, we have modified our previous requests.

### **Trials**

1. In our March 16, 2005 letter, we asked that only parallel-arm studies be included. We have reconsidered this request and now ask that crossover studies be included if they otherwise meet the stated requirements. Only the first period data from crossover studies (including within 1 day of stopping the first period of randomized treatment) should be included.
2. Also in our March 16, 2005 letter, we asked that short-term studies up to six months duration be included. We also have reconsidered this request and now ask that studies be included without an upper limit on duration.
3. Ongoing studies that are still blinded should not be included.
4. We reiterate that we want you to identify all trials that meet the described criteria (now modified) regardless of indication or approval status for any particular indication.
5. Our previous letter indicated that only trials with 30 “patients” should be included. We are now asking that volunteer studies be included as well, if they otherwise meet the criteria.
6. Studies using novel formulations, such as extended-release formulations, of approved anti-epileptic drugs (AEDs) [even if the novel formulation is not approved] should be included.
7. In order to comment on the list of studies included for purposes of these analyses, we ask that you submit a complete list of all clinical trials, indicating those that you believe should be included and excluded.
8. We request that, when you submit your completed dataset, you also submit two tables which will describe the features of the clinical trials. See the enclosed attachment for examples from other similar data requests. Note that for this request, the 4 variables, Extensive Diagnostic Screening, Exclude Treatment Resistant, Exclude Bipolar Disorder, and Exclude Family History of Bipolar are applicable to trials in psychiatric indications.

### **Miscellaneous**

1. We had previously asked for the completed JMP dataset within 6 month from the date of our previous letter. However, recognizing the difficulties in creating and classifying narratives, we are now asking that the dataset be submitted within 6

months from agreement on which of your studies should be included.

The policy of our electronic document room is that any electronic data files that are submitted to an NDA must be submitted as a SAS transport file. Therefore, please submit the data in this format.

2. Please do not submit narratives when you submit your completed SAS transport file. You should instead have the narratives ready to submit if specifically requested. We may ask to audit some subset of your narratives. Any narratives submitted should be in their blinded format.
3. We are revising the search strategy for “Possibly Suicide-Related” Adverse Events to simplify it. The following description replaces the strategy described in our original March 16, 2005 letter.

Please search preferred terms, verbatim terms, and comment fields for the following text strings:

- “suic”, “overdos”, “accident-“, “injur-“, “attempt”, “cut”, “gas”, “hang”, “hung”, “jump”, “mutilat-”, “self damag-”, “self harm”, “self inflict”, “self injur-”, “shoot”, “slash”, “poison”, “asphyxiation”, “suffocation”, “firearm”, “burn”, “drown”, “gun”, “immolate”, “monoxide” should be included.

Note: Any terms identified by this search because the text string was a substring of an unrelated word should be excluded (for example, the text string “cut” might identify the word “acute”). These terms might be characterized as “false positives” in the sense that the verbatim term was selected because one of the text strings occurred within that term but the term had no relevance to suicidality. Although we request that such terms be excluded, we ask that you prepare a table listing all such false positives, as follows:

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

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

[Some sponsors have specifically asked if all adverse events coded as “accidental injury” should be included. The answer is yes.]

4. Narratives should be prepared for all events identified by the search described in Item 3 above, and for all deaths and serious adverse events (SAEs), even for those that do not otherwise meet the above search criteria for possibly suicide-related AEs.

This latter requirement would apply, for example, to SAEs coded as seizures. For example, a patient might, as a suicide attempt, take an overdose of some drug that causes a seizure. The event might thus be classified as a seizure, when in fact it also represents a suicide attempt. Narratives should be prepared for ALL deaths and SAEs identified in a given trial.

5. Generally, events that are preexisting at baseline are not usually counted as treatment emergent if they recur during the course of a trial. However, in the requested analysis, suicidality-related events that occur during the course of the double-blind phase or within 1 day of beginning taper, switching or stopping treatment should be counted, even if they occur in a patient who had the condition at baseline.
6. In the March 16, 2005 letter, we stated that we would be available to review and comment on your specific plan for blinding and classifying the narratives. On further consideration, we believe there is adequate information available about the requested method. Therefore, we do not expect you to clear your plan through the Division; we expect that you will follow the standard outlines available. If, for any reason, you deviate from the established plan, the Division must review that proposal.
7. If previously prepared narratives do not include all of the identified elements from our request, the narratives should be rewritten to include this information. If some elements are not available, please note their absence in the narrative.
8. We have added a new code for the EVENT variable to denote completed suicides (the new “code 1”) and would like to clarify that corresponding changes should be made to the code numbers presented under the section entitled Classification of "Possibly Suicide-Related" Adverse Events in our last letter. Note the new addition of subcategories 6a and 6b. The categories should now be numbered as follows:

Completed suicide (code 1)

Suicide attempt (code 2)

Preparatory acts toward imminent suicidal behavior (code 3)

Self-injurious behavior, intent unknown (code 4)

Suicidal ideation (code 5)

Not enough information (code 6)

Fatal (code 6a)

Non-fatal (code 6b)

Self-injurious behavior, no suicidal intent (code 7)

Other: accident; psychiatric; medical (code 8)

The description of the variable “EVENT” in the table should now read:

This variable contains the code for the first suicidality event. If a patient had more than one event in the desired “exposure window”, then the most severe event should be listed. Severity is decided based on the following order of codes: 1>2>3>5>4>6. Every patient in every trial will be classified on this variable. For the majority of patients who are not identified as having a “possibly suicide-related adverse event”, the classification will be 0 (no event). Similarly, those patients who have “possibly suicide-related adverse events” that are coded as 7 or 8 will also be classified for this variable as 0 (no event), because we will not be using codes 7 or 8 in our analyses.

Patients with event codes 1 through 6 for suicide-related adverse events will be classified with their most severe event code.

9. In the proposed analysis, the final denominator is intended to be all patients studied. Therefore, the expectation is that the majority of patients will be coded as “no event.” “No event” means that there was no suicide-related adverse event or, if there was, it was coded to 7 or 8.
10. The available materials on the classification system make it clear what training is necessary for individuals who will perform the classification. No further expertise is being required by the Division at this time. There is no expectation that external experts must be used as long as the individuals involved have undergone the appropriate training. A minimum of 4 “experts” in classification will be needed. Three will serve as primary raters and the fourth will function as a facilitator, if needed.
11. In the variable table for the SAS transport file, some sponsors have asked how to code the “LOCATION” variable when the trial was conducted in both North American and Non-North American sites. This variable should be coded to reflect the study site location where the individual patient was treated.

If you have questions, call Jacqueline H. Ware, Pharm.D., Senior Regulatory Project Manager, at (301) 594-5533.

Sincerely,

Russell Katz, M.D.

Director

Division of Neuropharmacological Drug Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

### Appendix 3: Enclosure for 07/11/2005 FDA Letter to Providing Additional Information to Sponsors

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

- **Number of Patients:** number of patients randomized to the drug and placebo treatment groups.
- **DB TX Duration:** the nominal duration of the analyzed double-blind treatment phase.
- **Protocol Dose:** the protocol-specified daily target dose expressed as a range for flexible dose studies and as individual doses for fixed dose trials.
- **Extensive DX Screening:** indicate yes if the study required confirmation of the diagnostic entry criteria by two or more independent raters. Otherwise, indicate no.
- **Exclude TX Resistant:** indicate yes if a study exclusion criterion was a history of treatment resistance or poor response of the index illness to previous treatment. Otherwise, indicate no.
- **Exclude Bipolar D/O:** indicate yes if a study exclusion criterion was a history or presence of bipolar disorder or mania in the patient. Otherwise, indicate no.
- **Exclude Family H/O Bipolar Disorder:** indicate yes if a study exclusion criterion was any family history of bipolar disorder or mania. Otherwise, indicate no.

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

TABLE 2: SCREENING AND KEY EXCLUSIONARY CRITERIA									
Drug	Study	Indication	Extensive DX Screen	Placebo Lead-In	Exclude TX Resistant	Excl. Current Suicide Risk	Excl. H/O Suicide Attempt	Excl. Bipolar D/O	Excl. Family H/O Bipolar Disorder
XYZ	123	Epilepsy	No	Yes	No	Yes	No	Yes	No
	456	Migraine	Yes	Yes	No	No	No	Yes	Yes
	789	Bipolar	Yes	Yes	Yes	Yes	No	Yes	Yes
	1111	Epilepsy	No	No	No	Yes	No	Yes	Yes

#### **Appendix 4: E-mail Request for Additional Information on Multiple Events in Individual Subjects (05/03/2006)**

Dear Sponsor:

In the request letter [dated 07/11/2005], we provided guidance that for the dataset, patients with more than one suicidality event should have only the most serious event listed for the variable "EVENT". After further consideration of our analysis plan, we have determined that in order to interpret most accurately the meaning of the most serious event that occurred in a subject, it is necessary to have information on all suicidality events that may have occurred in a subject. We are therefore making an additional request for data on the other less serious suicidality events that occurred in the patients with more than one event. The format for datasets is exactly the same as our previous request; the only difference is that there should be one row for each event rather than one row for each subject. Subjects without any suicidality events would, as before, have a single row describing no event.

To facilitate your compliance with this request, we are offering you the option of submitting this dataset instead of the dataset we originally requested. If, on the other hand, you have already prepared a dataset based on our previous instructions, you may initially submit that dataset to us with the understanding that a dataset containing all suicidality events will follow (within 45 days).

Please let me know if you have any questions.

*Courtney R. Calder, Pharm.D., LT USPHS  
Regulatory Project Manager  
Division of Neurology Products, HFD-120  
Center For Drug Evaluation and Research, FDA  
Office of Drug Evaluation I  
Ph: (301) 796-1050  
Fax: (301) 796-9842  
Email: [courtney.calder@fda.hhs.gov](mailto:courtney.calder@fda.hhs.gov)*

#### **Appendix 5. FDA Letter Requesting Additional Information on Trials Included in the Analysis (01/31/2007)**

We are requesting additional trial-level information pertaining to our analysis of suicidal thoughts and behavior in anti-epileptic drugs. There are three parts to this request for additional information.

First, we request a narrative description of each trial submitted that describes the trial design and dosing. The description should include, but not be limited to, the following information:

- What were the study inclusion criteria?
- What were the study exclusion criteria?
- Was there was any placebo run-in period?
- Was there was any open-label extension?
- Was there was any tapering period?
- Was there was any adjunct therapy and if so what was it?
- Was the design a cross-over design?
- Was the time on therapy fixed or event dependent?
- Was there any withdrawal from therapy either of the test drug or adjunct therapy?
- What was the dosing protocol, including use of any flexible dosing and titration?



Second, we request a data set which summarizes characteristics of each trial. The data definitions are contained in the attached table. Each line in the data set will represent a trial. Please ensure that the entries for the source drug and entries for the trial names are identical to those used in the subject-level dataset. If the categories provided in the variable definition table are not sufficient to describe key trial characteristics, please enter “other” and provide a description.

Third, we would like to confirm the following information:

- (1) The duration of the trial as specified in the basic design table (Table 1) includes only the double-blind phase of the trial (or first period of cross-over trial) and does not include any open label stabilization phases, run-in phases, open-label extension periods, or tapering periods.
- (2) Only “Possibly Suicide-Related” adverse events that occurred during the double-blind phase (and within one day of stopping treatment) were considered. Events beyond 1 day of stopping randomized treatment and events in the tapering period were not considered. For cross-over trials, only the first period of the design was considered.

Please note that events should not have been reported from run-in, open label extension, or tapering periods; please let us know if previously reported events are from these trial periods. Revised data sets may need to be submitted if events occurring in these periods have been included.

- (3) For each subject that has a value for the variable EVENTDAY that exceeds the duration of the trial (as listed in Table 1) by more than 14 days, please provide an explanation on the discrepancy; if the cause of the discrepancy affects other subjects in the trial, please correct the entries for those subjects as well. We have attached a data set which lists subjects from your submission that have a value for the variable EVENTDAY that exceeds the duration of the trial (as given in Table 1) by more than 14 days.
- (4) The variable EVENTDAY should also not be negative or equal to zero. Please provide an explanation for EVENTDAY entries listed below:

Please respond to this request by April 30, 2007.

If you have any additional questions, please contact us.

#### **Appendix 6: Trial Level Data Set Data Definition Table (01/31/2007)**

**Data Definitions: Anti-Epileptic Drug Suicidality Trial Level Dataset**  
 \* Denotes information previously requested as part of Table 1 or Table 2.

	Variable Name	Type	Description	Coding Notes
*	SOURCE DRUG	Character	First few letters of the source drug name	*Please use same coding as was used in the subject-level dataset

	Variable Name	Type	Description	Coding Notes
*	TRIAL	Character	Trial ID	*Please use same coding as was used in the subject-level dataset
*	INDICAT	Character	Trial Indication	
	SZTYPE	Numeric	If the trial indication is epilepsy, did the trial include subjects with partial seizures or primary generalized seizures? If the trial indication is not epilepsy, enter 4.	1=partial seizures (with or without secondary generalized seizures) 2=primary generalized seizures 3=other 4=not applicable
	PSYACUTE	Numeric	If trial indication is a psychiatric or behavioral disorder, were subjects acutely symptomatic at randomization (as opposed to stable and receiving maintenance treatment)? If the trial did not have a psychiatric or behavioral indication, enter 4.	1=acute treatment 2=maintenance treatment 3=other 4=not applicable
	BITYPE	Numeric	If the trial indication is bipolar disorder, did subjects have bipolar mania, mixed state, or bipolar depression? If the trial indication is not bipolar disorder, enter 6.	1=bipolar mania 2=bipolar mixed 3=bipolar mania <u>or</u> mixed 4=bipolar depression 5=other 6=not applicable
	MONOAJD	Numeric	Is trial source drug used as monotherapy or adjunctive therapy?	1=monotherapy 2=adjunctive therapy 3=withdrawal to monotherapy 4=other
	TXDC	Numeric	Was the primary outcome of the trial the time to a clinical event (failure), and did the trial protocol specify stopping	0=no 1=yes

	Variable Name	Type	Description	Coding Notes
			treatment based on the occurrence of this clinical event [e.g., seizures(s) or status epilepticus]?	
*	RUNIN	Numeric	Was a placebo lead-in period part of the trial protocol?	0=no 1=yes
	OPENEXT	Numeric	Was an open-label extension period part of the trial protocol?	0=no 1=yes
	FIXDOSE	Numeric	Did the trial use a fixed dosing protocol?	0=no 1=yes
	CROSS	Numeric	Was this a crossover study?	0=no 1=yes
	RWITHDR	Numeric	Were subjects randomized to withdrawal of the source drug?	0=no 1=yes
	TAPER	Numeric	Was there a tapering period?	0=no 1=yes
	TXDOSE	Numeric	Mean modal dose for the source drug in mg/day	
*	MINDOSE	Numeric	Minimum target dose of source drug per the study protocol in mg/day. Do not list low dose placebo dosages.	
*	MAXDOSE	Numeric	Maximum target dose of the source drug per the study protocol in mg/day	
	CMP1	Character	Name of active drug in first active comparator arm. (If none, leave column blank.)	*Please use the same coding as was used in the subject-level dataset
	CMPDOSE1	Numeric	Mean of the modal doses received by each patient for the active drug in first active comparator arm in mg/day. (If none, leave column blank.)	

# Data Definitions: Anti-Epileptic Drug Suicidality Trial Level Dataset

\* Denotes information previously requested as part of Table 1 or Table 2.

	Variable Name	Type	Description	Coding Notes
	CMP2	Character	Name of active drug in second active comparator arm. (If none, leave column blank.)	*Please use the same coding as was used in the subject-level dataset
	CMPDOSE2	Numeric	Mean of the modal doses received by each patient for the active drug in second active comparator arm in mg/day. (If none, leave column blank.)	
	DBTX	Numeric	Duration of the double-blind treatment period in days	Exclude placebo run-in, open label extension, and tapering periods. For cross-over designs, provide the duration of the first period.
*	MINAGE	Numeric	Minimum age for study inclusion (years)	
*	MAXAGE	Numeric	Maximum age for study inclusion (years)	
*	NTX	Numeric	Number of subjects in the index drug treatment arm	In fixed dose studies, list the sum of patients in active drug treatment arms.
*	NPBO	Numeric	Number of subjects in placebo arm	
*	NACT	Numeric	Number of subjects in the active control arm(s)	
*	NLDPBO	Numeric	Number of subjects in the low dose placebo arm	
	LDPBO	Character	Name of low dose placebo drug	*Please use the same coding as was used in the subject-level dataset
*	DXSCRN	Numeric	Did the trial require confirmation of the diagnostic entry criteria by two or more independent	0=no 1=yes

	Variable Name	Type	Description	Coding Notes
			ratars?	
*	RESIST	Numeric	Did the trial exclude subjects with a history of treatment resistance or poor response of the index illness to previous treatment?	0=no 1=yes
*	SURISK	Numeric	Did the trial exclude subjects with current suicide risk?	0=no 1=yes
*	SUHX	Numeric	Did the trial exclude subjects with a history of suicide attempt?	0=no 1=yes
*	EXCLBI	Numeric	Did the trial exclude subjects with a diagnosis of bipolar disorder?	0=no 1=yes
*	FHBI	Numeric	Did the trial exclude subjects with a family history of bipolar disorder?	0=no 1=yes
	PSYCHOT	Numeric	Did the trial exclude patients with psychotic symptoms (e.g., hallucinations, paranoia, delusions)?	0=no 1=yes
	RAPID	Numeric	Did the trial exclude subjects with rapid cycling bipolar disorder?	0=no 1=yes
	FIRSTM	Numeric	Did the trial exclude subjects experiencing their first manic episode?	0=no 1=yes
	PERDO	Numeric	Did the trial exclude subjects diagnosed with a personality disorder?	0=no 1=yes
	SUBSTAB	Numeric	Did the trial exclude subjects who abuse alcohol or other drugs?	0=no 1=yes

**Appendix 7. FDA Press Release: *FDA Alerts Health Care Providers to Risk of Suicidal Thoughts and Behavior with Antiepileptic Medications* (01/31/2008)**

FDA News

**FOR IMMEDIATE RELEASE**

January 31, 2008

**Media Inquiries:**

Sandy Walsh, 301-827-6242

**Consumer Inquiries:**

888-INFO-FDA

FDA Alerts Health Care Providers to Risk of Suicidal Thoughts and Behavior with Antiepileptic Medications

The U.S. Food and Drug Administration today issued new information to health care professionals to alert them about an increased risk of suicidal thoughts and behaviors (suicidality) in patients who take drugs called antiepileptics to treat epilepsy, bipolar disorder, migraine headaches, and other conditions.

An FDA analysis of suicidality reports from placebo-controlled studies of 11 antiepileptic drugs shows that patients taking these drugs have about twice the risk of suicidal thoughts and behaviors (0.43 percent), compared with patients receiving placebo (0.22 percent). This risk corresponds to an estimated 2.1 per 1,000 more patients in the drug treatment groups who experienced suicidality than in the placebo groups.

"We want health care professionals to have the most up to date drug safety information," said Russell Katz, M.D., director of the Division of Neurology Products in FDA's Center for Drug Evaluation and Research. "This is an example of FDA working with drug manufacturers throughout products' lifecycles to keep health care professionals informed of new safety data."

Patients who are currently taking antiepileptic medicines should not make any changes without first talking to their health care provider. Health care providers should notify patients, their families, and caregivers of the potential for an increase in the risk of suicidal thoughts or behaviors so that patients may be closely observed for notable changes in behavior.

Following a preliminary analysis of data from several antiepileptic drugs that suggested an increased risk of suicidality, in March 2005 FDA requested this type of data from manufacturers of marketed antiepileptic drugs for which there were adequately designed controlled clinical trials. FDA received and reviewed data from 199 placebo-controlled studies of 11 drugs.

The analysis included 27,863 patients in drug treatment groups and 16,029 patients in placebo groups. There were four suicides among patients in the drug treatment groups and none among patients in placebo groups. There were 105 reports of suicidal thoughts or behaviors in the drug-treated patients and 35 reports in placebo-treated patients.

The higher risk of suicidal thoughts and behaviors was observed at one week after starting a drug and continued to at least 24 weeks. The results were generally consistent among all the different drug products studied and were seen in all demographic subgroups. There was no clear pattern of risk across age groups. Antiepileptic drugs in the analyses included the following:

Carbamazepine (marketed as Carbatrol, Equetro, Tegretol, Tegretol XR)  
Felbamate (marketed as Felbatol)  
Gabapentin (marketed as Neurontin)  
Lamotrigine (marketed as Lamictal)  
Levetiracetam (marketed as Keppra)  
Oxcarbazepine (marketed as Trileptal)  
Pregabalin (marketed as Lyrica)  
Tiagabine (marketed as Gabitril)  
Topiramate (marketed as Topamax)  
Valproate (marketed as Depakote, Depakote ER, Depakene, Depacon)  
Zonisamide (marketed as Zonegran)

Some of these drugs are also available in generic form.

Although only the drugs listed above were part of the analysis, the FDA expects that all medications in the antiepileptic class share the increased risk of suicidality.

FDA will be working with manufacturers of marketed antiepileptic drugs to include this new information in the labeling for these products. The agency anticipates that labeling changes will be applied broadly to the entire class of drugs. FDA is also planning to discuss these data at an upcoming advisory committee meeting.

For more information

FDA Information for Healthcare Professionals: Suicidality and Antiepileptic Drugs

[www.fda.gov/cder/drug/InfoSheets/HCP/antiepilepticsHCP.htm](http://www.fda.gov/cder/drug/InfoSheets/HCP/antiepilepticsHCP.htm).

## **Appendix 8. Information for Healthcare Professionals: Suicidality and Antiepileptic Drugs (01/31/2008)**

### **Information for Healthcare Professionals Suicidality and Antiepileptic Drugs**

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**FDA ALERT [1/31/2008]:** The FDA has analyzed reports of suicidality (suicidal behavior or ideation) from placebo-controlled clinical studies of eleven drugs used to treat epilepsy as well as psychiatric disorders, and other conditions. These drugs are commonly referred to as antiepileptic drugs (see the list below). In the FDA's analysis, patients receiving antiepileptic drugs had approximately twice the risk of suicidal behavior or ideation (0.43%) compared to patients receiving placebo (0.22%). The increased risk of suicidal behavior and suicidal ideation was observed as early as one week after starting the antiepileptic drug and continued through 24 weeks. The results were generally consistent among the eleven drugs. Patients who were treated for epilepsy, psychiatric disorders, and other conditions were all at increased risk for suicidality when compared to placebo, and there did not appear to be a specific demographic subgroup of patients to which the increased risk could be attributed. The relative risk for suicidality was higher in the patients with epilepsy compared to patients who were given one of the drugs in the class for psychiatric or other conditions.

All patients who are currently taking or starting on any antiepileptic drug should be closely monitored for notable changes in behavior that could indicate the emergence or worsening of suicidal thoughts or behavior or depression.

*This information reflects FDA's current analysis of available data concerning these drugs. Posting this information does not mean that FDA has concluded there is a causal relationship between the drug products and the emerging safety issue. Nor does it mean that FDA is advising health care professionals to discontinue prescribing these products. FDA intends to update this document when additional information or analyses become available.*

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*Adverse reactions or quality problems experienced with the use of this product may be reported to the FDA's MedWatch Adverse Event Reporting program; see addresses below.*

## **Considerations for Physicians and Other Health Care Professionals**

Data from 199 placebo-controlled clinical studies covering eleven different antiepileptic drugs were reviewed and analyzed for reports of suicidal behavior (completed suicides, suicide attempts and preparatory acts) and suicidal ideation. The studies examined the effectiveness of the drugs in epilepsy, psychiatric disorders (e.g., bipolar disorder, depression and anxiety) and other conditions (e.g., migraine and neuropathic pain syndromes). The analysis included a total of 43,892 patients ages five and older (27,863 in drug treatment groups and 16,029 in placebo groups).

There was a statistically significant increased risk of suicidal behavior and suicidal ideation in the patients randomized to receive an antiepileptic drug compared to patients who received a placebo. The estimated overall risk was about twice that of the placebo group. There were an estimated 2.1 per 1000 (95% CI: 0.7, 4.2) more patients in the drug treatment groups who experienced suicidal behavior or ideation than in the placebo groups.

Four of the patients who were taking one of the antiepileptic drugs committed suicide, whereas none of the patients in the placebo group did. The increased risk of suicidal behavior and suicidal ideation was observed at one week after starting the drug and continued to at least 24 weeks. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be reliably assessed.

FDA will be working with manufacturers of marketed antiepileptic drugs to include this new information in the labeling for these products. FDA is also planning to discuss these data at an upcoming advisory committee meeting.

All patients treated with antiepileptic drugs should be monitored for suicidality and other unusual changes in behavior. Symptoms such as anxiety, agitation, hostility, mania and hypomania may be precursors to emerging suicidality.

### **Healthcare professionals who prescribe antiepileptic drugs should:**

- Balance the risk for suicidality with the clinical need for the drug
- Be aware of the possibility of the emergence or worsening of depression, suicidality, or any unusual changes in behavior;
- Inform patients, their families, and caregivers of the potential for an increase in the risk of suicidality so they are aware and able to notify their healthcare provider of any unusual behavioral changes.

### **Information for patients, family members, and caregivers:**



- Taking antiepileptic medicines may increase the risk of having suicidal thoughts or actions;
- Do not make any changes to the medication regimen without first talking with the responsible healthcare professional;
- Pay close attention to any day-to-day changes in mood, behavior and actions. These changes can happen very quickly so it is important to be mindful of any sudden differences.
- Be aware of common warning signs that might be a signal for risk of suicide. Some of these are:
  - Talking or thinking about wanting to hurt yourself or end your life
  - Withdrawing from friends and family
  - Becoming depressed or having your depression get worse
  - Becoming preoccupied with death and dying
  - Giving away prized possessions

**If these or any new and worrisome behaviors occur, contact the responsible healthcare professional immediately.**

### **Background and Data Summary**

After preliminary analyses of data from several drugs in this class suggested an increased risk of suicidality, in March 2005, FDA requested data from manufacturers of marketed antiepileptic drugs for which there were adequately designed controlled clinical trials in order to review the possible association between these drugs and suicidality events. In an effort to obtain the most complete and accurate data for this review, requests for additional information and clarification were sent to the manufacturers in 2006 and 2007. The analyses performed were similar to those performed by FDA for antidepressant drugs in the last several years.

One-hundred ninety nine placebo-controlled clinical studies covering eleven different drugs were included in the primary analysis. The conditions studied in these clinical trials included epilepsy, selected psychiatric illnesses, and other indications, including migraine and neuropathic pain syndromes. The analysis included 27,863 patients in drug treatment groups and 16,029 patients in placebo groups. Patients included in the analysis were five years of age or older. The individual sponsors of the drugs were responsible for identifying suicidal behavior and suicidal ideation events in their databases based on the instructions provided by FDA.

There were 4 completed suicides among patients in drug treatment groups and none among the patients in placebo groups. Overall, 0.43% of the patients in drug treatment groups experienced suicidal behavior or ideation versus 0.22% of the patients in placebo groups, corresponding to an estimated 2.1 per 1000 (95% CI: 0.7, 4.2) more patients in the drug treatment groups who experienced suicidal behavior or ideation than in the placebo treatment groups (See Table). In this analysis, the relative risk for suicidal thoughts or behavior was higher for patients with epilepsy compared to those patients with psychiatric or other disorders (See Table). The higher risk for suicidal behavior or suicidal ideation was observed at one week after starting a drug and continued to at least 24 weeks. The results were generally consistent among the drugs and were seen in all demographic subgroups. Specifically, there was no clear pattern of risk across age groups.

## Relative Risk and Risk Difference for Suicidality According to Trial

### Indication

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.5	3.6	2.5
Psychiatric	5.2	8.3	1.6	3.1
Other	0.8	2.0	2.3	1.1
Total	2.2	4.3	2.0	2.1

**The following is a list of antiepileptic drugs\* included in the analyses:**

- [Carbamazepine](#) (marketed as Carbatrol, Equetro, Tegretol, Tegretol XR)
- Felbamate (marketed as Felbatol)
- [Gabapentin](#) (marketed as Neurontin)
- [Lamotrigine](#) (marketed as Lamictal)
- [Levetiracetam](#) (marketed as Keppra)
  - [Patient Information Sheet](#)
- [Oxcarbazepine](#) (marketed as Trileptal)
- [Pregabalin](#) (marketed as Lyrica)
- [Tiagabine](#) (marketed as Gabitril)
- [Topiramate](#) (marketed as Topamax)
- [Valproate](#) (marketed as Depakote, Depakote ER, Depakene, Depacon)
- [Zonisamide](#) (marketed as Zonegran)

\* Some of these drugs are also available in generic form.

Although the drugs listed above were the ones included in the analysis, FDA expects that the increased risk of suicidality is shared by all AEDs and anticipates that the class labeling changes will be applied broadly.

Adverse reactions or quality problems experienced with the use of this Product may be reported to the FDA's MedWatch Adverse Event Reporting program either online, by regular mail or by fax.

- **Online:** [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)
- **Regular Mail:** use postage-paid FDA form 3500 available at: [www.fda.gov/MedWatch/getforms.htm](http://www.fda.gov/MedWatch/getforms.htm).
- Mail to MedWatch 5600 Fishers Lane, Rockville, MD 20852-9787

- **Fax:** 1-800-FDA-0178

## APPENDIX 9. SUBJECT AND EVENT CHARACTERISTICS FROM SUICIDAL BEHAVIOR NARRATIVES

Drug	Trial Indication	Age	Event Day	Event Description	Noted Associated Psychiatric Symptoms and Comorbid Psychiatric Diagnoses
EVENTS IN DRUG-TREATED SUBJECTS					
Lam	Bipolar Disorder	38	17	Completed suicide by shooting himself.	"His level of depression was worse during the study compared to the time of study entry"
Lev	Epilepsy	43	129	Completed suicide. Cut both forearm veins.	"No signs of depression were observed during the...study"
Lev	Anxiety Disorder	44	6	Completed suicide by hanging.	"patient experienced depression that the Investigator described as suicidal tendency induced by bad tolerance (i.e. nausea and vomiting)." History of Depression.
Pre	Epilepsy	44	74	Completed suicide. "helium anoxia/plastic bag suffocation"	"The subject's depression was considered stable at the time of death" History of "mild depression"
Oxc	Bipolar Disorder	9	6	Suicide attempt. "Took 10 acetaminophen pills"	
Oxc	Epilepsy	17	72	Suicide attempt. "'overdose... took remaining study medication... and carbamazepine 5400 mg"	
Pre	Social Anxiety Disorder	19	29	Suicide attempt. "His mother reported that the subject took 25 capsules (100 mg capsules" of the study medication at once on day 29.	"During a study visit, the subject was noted to be depressed."
Val	Mania Maintenance	21	241	Suicide attempt."overdose of Ativan, taking 20 to 30 1 mg tablets"	
Lam	Bipolar Disorder	21	7	Suicide attempt. "'threatening suicide with a dull knife...superficial cuts"	"subject's mother phoned the study team...the subject appeared 'manic'"
Lam	Bipolar Disorder	23	15	Suicide attempt. Overdose of chloral hydrate with 7-10 alcoholic drinks.	On day of event, pt seen at study visit and complained of depression and insomnia.

Drug	Trial Indication	Age	Event Day	Event Description	Noted Associated Psychiatric Symptoms and Comorbid Psychiatric Diagnoses
Top	Bipolar Disorder	23	23	Suicide attempt. Overdose of topiramate, total 7425 mg.	subject stated that "this was an impulsive act because his mother was not home when he came from the hospital and he felt he had no place to live"
Lam	Bipolar Disorder	24	11	Suicide attempt. Ingested excess alcohol an an unspecified over the counter drug	"The patient had started taking alprazolam, viloxazine, and zopiclone for anxiety, depression, and insomnia the day before the suicide attempt." History of Depression.
Lev	Anxiety Disorder	24	36	Suicide attempt. Details not available.	
Pre	Social Anxiety Disorder	26	16	Suicide attempt. "drug overdose with 45 Sominex"	History of "Depressive Disorder."
Lam	Schizophrenia	27	36	Suicide attempt. "took all of his medication", which included lamotrigine, risperidone, benztropine, and zolpidem	
Pre	Epilepsy	29	19	Suicide attempt. "hospitalized for a life-threatening suicide attempt." Details not available.	Hospitalized for depression. Noted to be irritable while hospitalized.
Lam	Depression	33	4	Suicide attempt. Overdose with 10 tablets hydrocodone+acetaminophen.	
Zon	Epilepsy	33	20	Suicide attempt. No other details provided.	
Top	Diabetic Per. Neuropathy	34	114	Suicide attempt. "On day 104-113 she took no study medication (reason unknown). On Day 114, patient attempted suicide after taking an overdose of the study drug (a dosage equivalent to 800 mg.)"	
Top	Bipolar Disorder	34	14	Suicide attempt. Diphenhydramine overdose.	

Drug	Trial Indication	Age	Event Day	Event Description	Noted Associated Psychiatric Symptoms and Comorbid Psychiatric Diagnoses
Top	Obesity	39	132	"attempted suicide by taking an overdose of 100 tablets of Fegenen"	"severe paranoid schizophrenic reaction" History of paranoid schizophrenia, depression, personality disorder
Top	Bipolar Disorder	41	8	Suicide attempt. "swallowed 38 lorazepam tablets"	Subject reported confusion, ataxia, myalgia, disturbed dreaming.
Top	Obesity	42	387	Attempted suicide twice using a gas stove on days 387 and 389	
Val	Mania Maintenance	43	313	Suicide attempt. Overdosed on 5-7 Ativan tablets.	
Lam	Bipolar Disorder	43	12	"attempted suicide by ingesting 2 dL of alcohol and 3 dL of industrial glycol."	History of Depression.
Lev	Epilepsy	44	83	" attempted suicide with one of her concomitant medications, Dipiperon"	
Lam	Bipolar Disorder	46	23	Suicide attempt. No other description	
Top	Obesity	48	195	Suicide attempt. "'subject was hospitalized for psychosis after attempting suicide by taking 200 tablets of study medication."	"One week before the suicide attempt she expressed anxiety, stopped eating, and was only drinking. " Hisotry of panic attacks.
Zon	Epilepsy	48	23	Suicide attempt. Took Antabuse, alcohol, Tegretol	History of Depression.
Lam	Bipolar Disorder	50	53	Suicide attempt. Overdose with lithium and carbamazepine.	"becoming gradually depressed over the previous week [prior to the suicide attempt]. "
Lam	Epilepsy	52	58	Suicide attempt. Carbamazepine overdose (80 tablets).	"The overdose attempt occurred at the same time as the subject experienced depression.""History of sertraline therapy."
Lam	Epilepsy	52	141	Suicide attempt. Overdose lanoxin, nifedipine, procainamide, ASA, metoprolol	"'down' after death of mother." "'Depressed at baseline"

Drug	Trial Indication	Age	Event Day	Event Description	Noted Associated Psychiatric Symptoms and Comorbid Psychiatric Diagnoses
Top	Bipolar Disorder	57	37	Suicide attempt. Jumped from 3rd floor window. Broke pelvis.	Said she jumped because she heard voices telling her to jump." History of anxiety
Lev	Cognition	75	3	Suicide attempt. "overdosed using a benzodiazepine"	"patient experienced depression"
Lev	Migraine	33	30	Prep. Act. "father had to interverene to prevent her from stabbing herself"	"admitted to the hospital with a major depressive episode...screaming, yelling, crying" Received tx for cocaine and benzodiazepine dependence. History of bipolar disorder and anxiety disorder.
Lam	Bipolar Disorder	36	5	Prep. Act. Suicidal ideation with a plan to overdose. Required hospitalization.	"became severely depressed" History of alcohol abuse.
Car	Bipolar Disorder	55	18	Prep Act. "subject reported that she had experienced suicidal ideation the previous night to the point of holding a loaded gun for half an hour."	
EVENTS IN PLACEBO-TREATED SUBJECTS					
Val	Bipolar Depression	18	19	Suicide attempt. " subject reported taking 7-8 "reds" [amphetamines]"	"[2 days prior to the event], the subject began to have suicidal ideations following the first snowfall of the season. This event precipitated the recollection of his mother's death 1 year ago."
Lev	Migraine	25	4	Suicide attempt. "admitted to hospital or ingestion of approximately 15-20...Phrenilin Forte (butalbital 50 mg and acetaminophen 325 mg)"	"worsening of pre-existing depression"
Val	Mania Maintenance	29	71	Suicide attempt. "subject took 5 mg of Ativan in combination with alcohol that resulted in hospitalization. ...the subject's boyfriend added that the subject had later stated that she wished she had taken the whole bottle."	"discontinued from the study due to a non-treated aspect of bipolar illness (depression)."

Drug	Trial Indication	Age	Event Day	Event Description	Noted Associated Psychiatric Symptoms and Comorbid Psychiatric Diagnoses
Lam	Bipolar Disorder	30	41	Suicide attempt. Overdose of unspecified medications.	"two days after the event while she was hospitalized, and she was de-pressed, hopeless and crying, but she denied...suicidal ideation at that time."
Lam	Bipolar Disorder	30	21	Suicide attempt. Jumped from a window.	History of Depression.
Lev	Cognition	30	40	Suicide attempt. "patient intentionally overdosed by taking 60 tablets of the pain medication solpadeine and 2 tablets of the study medication."	
Zon	Epilepsy	34	21	Suicide attempt by overdose of prescription medication	"He reported onset of depressive symptoms, including depressed mood, frequent crying, decreased energy, decreased appetite," anhedonia, poor concentration, decreased self-esteem, and difficulty sleeping, all beginning approximately two weeks prior to his suicide attempt. History of cocaine abuse and depression.
Lam	Neuropathic Pain	39	49	Suicide attempt. Took large amount of crack cocaine.	
Val	Mainia Maintenance	26	29	Prep. Act. "the subject developed a plan for suicide and established a will."	History of alcohol abuse.

Drug abbreviations: Lam = Lamotrigine; Lev = Levetiracetam; Pre = Pregabalin; Oxc = Oxcarbazepine; Val = Divalproex Sodium; Car = Carbamazepine; Top = Topiramate; Zon = Zonisamide.

Other Abbreviations: Diabetic P. Neuropathy = Diabetic Peripheral Neuropathy



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MEDICAL OFFICER

## **Suicidality Class Labeling (certain sections only) and MedGuide Language**

[Begin Package Insert Language]

### **Boxed Warning**

#### **Suicidal Behavior and Ideation and Antiepileptic Drugs**

Antiepileptic drugs increase the risk of suicidal thoughts and behavior in patients taking the drugs for any indication. In a meta-analysis of placebo-controlled studies, antiepileptic drugs approximately doubled the risk of suicidal behavior and ideation compared to placebo. Anyone considering the use of [antiepileptic drug name] or any other antiepileptic drug must balance this risk with the clinical need. Patients who take antiepileptic drugs should be monitored closely for suicidal thinking or actions, thoughts about self-harm, or any notable changes in behavior that could indicate the emergence or worsening of depression or suicidal thoughts or behavior.

Families and caregivers should be advised that close observation and communication with the prescriber are important.

### **WARNINGS**

#### **Suicidal Behavior and Ideation**

Antiepileptic drugs increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Pooled analyses of 199 placebo-controlled clinical trials of 11 different antiepileptic drugs showed that patients receiving one of the antiepileptic drugs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.6) of suicidal thinking or behavior compared to patients receiving placebo. The estimated incidence of suicidal behavior or ideation among 27,863 antiepileptic drug-treated patients was 0.43% compared to 0.24% among 16,029 placebo-treated patients. There were suicides in the trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior was observed as early as one week after starting drug treatment and continued to at least 24 weeks. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be reliably assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs and did not vary substantially by age in the clinical trials analyzed.

The relative risk for suicidal thoughts or behavior was higher in patients in clinical trials for epilepsy compared to those in clinical trials for psychiatric or other conditions. The absolute risk differences, however, were comparable in patients with epilepsy and psychiatric conditions.

The following table shows absolute and relative risk by indication.

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

Anyone considering prescribing [antiepileptic drug name] or any other antiepileptic drug must balance this risk with the clinical need. Patients treated with any antiepileptic drug for any indication should be monitored appropriately and observed closely for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior.

Patients, their caregivers, and families should be informed that antiepileptic drugs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

## PRECAUTIONS - Information for Patients

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

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

**Suicidal Thinking and Behavior** - Patients, their caregivers, and families should be informed that antiepileptic drugs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

[Begin MedGuide language]

## **Medication Guide**

### **Your Medicine and Suicidal Thoughts or Actions**

Read the Medication Guide that comes with your or your family member's medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with your medicine.

#### **Talk to your, or your family member's, healthcare provider about:**

- all risks and benefits of treatment with this medicine
- all treatment choices for the illness for which this medicine has been prescribed

#### **What should I know about this medicine and suicidal thoughts or actions?**

1. **This medicine may cause suicidal thoughts or actions in a very small number of people.**
2. **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**
  - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
  - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
  - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

#### **Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:**

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability

- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

**What else do I need to know about this medicine?**

- **Never stop this medicine without first talking to a healthcare provider.** Stopping this medicine suddenly can cause other symptoms.
- **This medicine has other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Your medicine can interact with other medicines.** Know all of the medicines that you take or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.

**Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.**

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**U.S. Food and Drug Administration**  
Department of Health and Human Services

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*This information reflects FDA's current analysis of available data concerning these drugs. Posting this information does not mean that FDA has concluded there is a causal relationship between the drug products and the emerging safety issue. Nor does it mean that FDA is advising health care professionals to discontinue prescribing these products. FDA intends to update this document when additional information or analyses become available.*

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- Be aware of common warning signs that might be a signal for risk of suicide. Some of these are:
  - Talking or thinking about wanting to hurt yourself or end your life
  - Withdrawing from friends and family
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- [Tiagabine](#) (marketed as Gabitril)
- [Topiramate](#) (marketed as Topamax)
- [Valproate](#) (marketed as Depakote, Depakote ER, Depakene, Depacon)
- [Zonisamide](#) (marketed as Zonegran)



\* Some of these drugs are also available in generic form.

Although the drugs listed above were the ones included in the analysis, FDA expects that the increased risk of suicidality is shared by all AEDs and anticipates that the class labeling changes will be applied broadly.

Adverse reactions or quality problems experienced with the use of this Product may be reported to the FDA's MedWatch Adverse Event Reporting program either online, by regular mail or by fax.

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FDA/Center for Drug Evaluation and Research

# Columbia Classification Algorithm of Suicide Assessment (C-CASA): Classification of Suicidal Events in the FDA's Pediatric Suicidal Risk Analysis of Antidepressants

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**Objective:** To evaluate the link between antidepressants and suicidal behavior and ideation (suicidality) in youth, adverse events from pediatric clinical trials were classified in order to identify suicidal events. The authors describe the Columbia Classification Algorithm for Suicide Assessment (C-CASA), a standardized suicidal rating system that provided data for the pediatric suicidal risk analysis of antidepressants conducted by the Food and Drug Administration (FDA).

**Method:** Adverse events (N=427) from 25 pediatric antidepressant clinical trials were systematically identified by pharmaceutical companies. Randomly assigned adverse events were evaluated by three of nine independent expert suicidologists using the Columbia classification algorithm. Reliability of the C-CASA ratings and agreement with pharmaceutical company classification were estimated.

**Results:** Twenty-six new, possibly suicidal events (behavior and ideation) that were not originally identified by pharmaceutical companies were identified in the C-CASA, and 12 events originally labeled as

suicidal by pharmaceutical companies were eliminated, which resulted in a total of 38 discrepant ratings. For the specific label of "suicide attempt," a relatively low level of agreement was observed between the C-CASA and pharmaceutical company ratings, with the C-CASA reporting a 50% reduction in ratings. Thus, although the C-CASA resulted in the identification of more suicidal events overall, fewer events were classified as suicide attempts. Additionally, the C-CASA ratings were highly reliable (intraclass correlation coefficient [ICC]=0.89).

**Conclusions:** Utilizing a methodical, anchored approach to categorizing suicidality provides an accurate and comprehensive identification of suicidal events. The FDA's audit of the C-CASA demonstrated excellent transportability of this approach. The Columbia algorithm was used to classify suicidal adverse events in the recent FDA adult antidepressant safety analyses and has also been mandated to be applied to all anticonvulsant trials and other centrally acting agents and nonpsychotropic drugs.

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Antidepressant use by children and adolescents dramatically increased in recent decades (1, 2), with up to 8 million prescriptions written annually in the United States (3). However, the use of antidepressant drug treatment has been fraught with controversy because of questions regarding both efficacy and safety. Efficacy results from pediatric trials are mixed and difficult to interpret, largely because of methodological limitations and regulatory idiosyncrasies in determining what is an "effective" study (4–6). Furthermore, regulatory agencies in the United States and the United Kingdom raised concerns in 2003 about the emergence of suicidal thoughts or behaviors during antidepressant treatment in pediatric populations, which may have led to a recent decline in prescription rates (7, 8), rendering risk-benefit analyses even more challenging.

To evaluate the potential association between suicidality and antidepressants, the Food and Drug Administration (FDA) decided to undertake a meta-analysis to examine suicidal events from 24 randomized placebo-controlled pediatric trials of selective serotonin reuptake inhibitors (SSRIs) and other newer generation antidepressants. However, inconsistent labeling of potentially suicidal events was identified as a significant threat to accurate risk-assessment analyses. This concern first arose during an FDA review of one pediatric SSRI study, in which events suggestive of suicidality were labeled "emotional lability." Subsequent examination of suicidality data from the other eight pediatric antidepressant studies underscored the problem, with a notable example being a subject who slapped herself in the face and was deemed as having made a suicide attempt (Table 1). The FDA deter-

This article is featured in this month's *AJP Audio*, is the subject of a *CME* course, and is discussed in an editorial by Dr. Brent on p. 989.

TABLE 1. Examples of Difficulties in Adverse Event Labeling<sup>a</sup>

Original Label	Original Investigator Text From Adverse Event Report
Personality disorder	[A] 10-year-old male exhibited symptoms of personality disorder of moderate severity and was discontinued. One day later, [the patient] attempted to hang himself with a rope after [a] dispute with his father. [The] investigator did not consider this a serious adverse event but rather part of the personality disorder.
Accidental overdose and neurosis	The overdose of six capsules of study medication was in fact intentional and in response to an argument with the subject's mother.
Medication error	Age 14: The patient took 11 tablets impulsively and then went to school...the patient denied that it was a suicide attempt.
Suicide attempt	[The patient] had thoughts of killing self but had no intention of acting on them.
Hostility	Age 10: Before his mother's call to the site and again after arguing with his stepfather, he wrapped a cord from the miniblinds around his neck, threatening to kill himself.
Emotional lability/suicide attempt	Age 14: The patient is reported to have engaged in an episode of "automutilation," where she slapped herself in the face.

<sup>a</sup> These labels were given by the study clinicians in the pharmaceutical company trials. They were given prior to the implementation of C-CASA and reflect why reclassification was necessary. Some labels are more severe than they should be, and other labels are less severe than warranted.

mined that conclusions based on these data would be unreliable and might produce either a false signal that would result in unwarranted restriction of useful medications or an underestimation of risk and subsequent danger to the general public.

The problem of inconsistent nomenclature of suicidal ideation and behavior (suicidality) encountered in this data set is not unique. Indeed, the ongoing debate concerning nomenclature has perpetuated the use of multiple terms to refer to the same behavior, frequently with pejorative connotations (e.g., threat, gesture) and descriptors (e.g., "manipulative," "hostile," "nonserious") (9–12). Such variability in terminology has consequences that extend beyond imprecise communication, limiting comparison of epidemiological prevalence rates and hampering prevention efforts (13). Additionally, it undermines the validity of risk-benefit analyses.

To enhance interpretability of pediatric antidepressant trial data to be used in their risk analysis, the FDA commissioned a study by Columbia University/New York State Psychiatric Institute investigators to classify all events that could represent suicidality. The investigators developed a systematic approach to the categorization of potential suicidal adverse events covering the full spectrum of suicidality, rooted in consensus recommendations and empirical findings regarding suicide-related definitions (10, 12, 14–16).

The whole continuum of suicidality was included in the system, given evidence that manifestations along the spectrum are linked (17, 18). For example, evidence suggests that suicide attempts with intent to die are predictive of completed suicide (16, 18, 19), and individuals who engage in preparatory suicidal behaviors with intent to die are also at risk for future suicide attempts (20) and completion (21). Epidemiological and clinical studies of adolescents and adults have established that severe or pervasive suicidal ideation is a predictor of both future attempts (17, 22–25) and completed suicide (26). Moreover, Brown et al. identified passive thoughts about wanting to be dead as a risk factor for completed suicide (27). These studies provide

the links between manifestations of suicidal process despite well-documented differences between them (28).

In the present article, we describe the structure and reliability of the Columbia Classification Algorithm of Suicide Assessment (C-CASA), the classification system of suicidal adverse events that produced the data used by the FDA in their critical assessment of pharmacologic risk.

## Method

### C-CASA

The C-CASA is a classification system that utilizes definitions of suicidality derived from empirical findings on the phenomenology of suicidality and identified predictive and risk factors. The criteria for a suicide attempt include both self-injurious behavior and suicidal intent (at least some intention to commit suicide). Intent to die portends a risk for future suicide and repeated attempts (15, 18, 29, 30) and can be reliably obtained (27). Inclusion of intent in the definition of suicide allows a distinction between those who self-injure in an attempt to die and those who self-injure for purely other nonsuicidal reasons (e.g., to manage affect) (31). The C-CASA has eight categories that distinguish suicidal events from nonsuicidal events and indeterminate or potentially suicidal events (Table 2). C-CASA definitions and training examples are presented in Table 2. Figure 1 illustrates the boundaries between categories.

### C-CASA Rating Guidelines

The C-CASA includes operationalized guidelines for inference of suicidal intent. "Clinically impressive" behavior or circumstances are used to infer suicidal intent when the stated intent is missing, unclear, or denied. For example, a highly lethal act that is clearly not an accident might mean that no other intent except suicide can be inferred (e.g., a gunshot to the head, jumping from a high-story building). An illustrative example was a case of self-immolation, which was a circumstance allowing inference of intent to classify the event a suicide attempt. Alternatively, inference of suicidal intent could also be based on two other pieces of data, including clinical circumstances such as the method used, number of pills ingested, and location of injury on the body. For example, cuts on the legs typically represent nonsuicidal self-injurious behavior. According to C-CASA guidelines, other relevant data that could be used included past history of suicide attempt, past history of self-injurious behavior/self-mutilation, and family history of suicide/suicide attempts.

TABLE 2. C-CASA Definitions and Training Examples

Classification/ Category	Definition	Training Examples
<b>Suicidal events</b>		
Completed suicide	A self-injurious behavior that resulted in fatality and was associated with at least some intent to die as a result of the act.	1) After a long argument with his girlfriend, which resulted in the end of their relationship, the patient collected a rope and rode his bike to an isolated area where he fatally hanged himself. A suicide note was later found. 2) After four documented attempts at suicide, the patient stole his uncle's gun and shot himself and was fatally injured.
Suicide attempt	A potentially self-injurious behavior, associated with at least some intent to die, as a result of the act. Evidence that the individual intended to kill him/herself, at least to some degree, can be explicit or inferred from the behavior or circumstance. A suicide attempt may or may not result in actual injury.	1) After a fight with her friends at school, in which they discontinued speaking with her, the patient ingested approximately 16 aspirin and eight other pills of different types on the school grounds. She said that she deserved to die, which was why she swallowed the pills. 2) The patient used a razor blade to lacerate his wrists, his antecubital fossae, and his back bilaterally. He told his therapist that the "the main objective was to stop feeling like that," and he knew that he could die but didn't care. According to the patient, he also ingested a bottle of rubbing alcohol because in his health class he heard "that the medulla will get more suppressed that way," thereby increasing the chances that he would be "successful" and die.
Preparatory acts toward imminent suicidal behavior	The individual takes steps to injure him- or herself, but is stopped by self or others from starting the self-injurious act before the potential for harm has begun.	1) The patient had run away from home overnight because his father had gone to school and retrieved a recent "bad" report card. He was fearful of his father's reaction. Upon his return home, a 5- to 6-hour argument with his parents ensued, and he took a vegetable (broad, sharp) knife and went to his room. He reported putting the knife to his wrist but never puncturing the skin. 2) The patient stated that he "couldn't stand being depressed anymore" and "wanted to die." He decided to hang himself. He tied a telephone cord to the door knob and placed the cord loosely around his neck. Then, he stopped himself and did not follow through with the attempt.
Suicidal ideation	Passive thoughts about wanting to be dead or active thoughts about killing oneself, not accompanied by preparatory behavior. <sup>a</sup>	1) Active: The patient reported to the doctor that he was thinking about hanging himself in the closet. He was taken to the hospital and admitted. 2) Passive: The patient reported ideas about wanting to be dead but denied acting on these feelings.
<b>Nonsuicidal events</b>		
Self-injurious behavior, no suicidal intent	Self-injurious behavior associated with no intent to die. The behavior is intended purely for other reasons, either to relieve distress (often referred to as "self-mutilation," e.g., superficial cuts or scratches, hitting/banging, or burns) or to effect change in others or the environment.	1) The patient was feeling ignored. She went into the family kitchen where her mother and sister were talking. She took a knife out of the drawer and made a cut on her arm. She denied that she wanted to die at all ("not even a little"), but she just wanted them to pay attention to her. 2) The patient reported feeling agitated and anxious after a fight with her parents. She went into her room, locked the door, and made several superficial cuts on the inside of her arms. She stated that she felt relieved after cutting herself and that she did not want to die. She reported that she had done this before at times of distress and that it usually helped her feel better. 3) The patient was in class, where a test was about to begin, and stabbed himself with a pencil in order to be taken to the nurse's office. 4) A 14-year-old girl wrote her name on her arm with a penknife and said that she often does so in order to reduce her anxiety. 5) The patient was noted to have multiple superficial burns on his arms. Upon questioning, he denied trying to kill himself.
Other, no deliberate self-harm	No evidence of any suicidality or deliberate self-injurious behavior associated with the event. The event is characterized as an accidental injury, psychiatric or behavioral symptoms only, or medical symptoms or procedure only.	1) The patient had a cut on the neck from shaving. 2) The patient was hospitalized for worsening of OCD or depressive symptoms with no suicidal thoughts or actions or 3) aggressive behavior. 4) Hospitalization was because of an infection, rhinoplasty, or pregnancy.
<b>Indeterminate or potentially suicidal events</b>		
Self-injurious behavior, suicidal intent unknown	Self-injurious behavior where associated intent to die is unknown and cannot be inferred. The injury or potential for injury is clear, but why the individual engaged in that behavior is unclear.	1) The patient cut her wrists after an argument with her boyfriend. 2) The patient was angry at her husband. She took 10 to 15 diazepam tablets and flushed the rest down the toilet. Her husband called the police for help, and she was taken to the hospital. She was groggy and stayed overnight in the hospital. 3) A 9-year-old patient had spoken about suicide frequently. After learning that his baseball coach was retiring, he began scratching his arm with a pencil.

(continued)

TABLE 2. C-CASA Definitions and Training Examples (*continued*)

Classification/ Category	Definition	Training Examples
Not enough information	Insufficient information to determine whether the event involved deliberate suicidal behavior or ideation. There is reason to suspect the possibility of suicidality but not enough to be confident that the event was not something other, such as an accident or psychiatric symptom. An injury sustained on a place on the body consistent with deliberate self-harm or suicidal behavior (e.g., wrists), without any information as to how the injury was received, would warrant placement in this category.	1) A child who “stabbed himself in [the] neck with a pencil.” The event may have been deliberate as opposed to accidental, as suggested by “stabbed,” but not enough information was provided to determine whether the event was deliberate. 2) A cut on the neck.

<sup>a</sup> If ideation is deemed inherently related to a behavioral act, a separate rating is not given. However, if there is no clear relationship to a behavioral event, a separate classification of ideation is warranted.

## Data

Adverse event reports from 25 trials of antidepressant medications with a combined sample of 4,562 pediatric patients were included. Reports were provided by the FDA. Twenty-four trials were sponsored by pharmaceutical companies, and one was funded by the National Institute of Mental Health (NIMH) (32); however, data from that particular trial was subsequently utilized for a pediatric indication by a pharmaceutical company. Twenty-three trials were randomized controlled trials, and two were nonrandomized controlled trials. Participants were pediatric patients, ages 6 to 17 years, and clinical trials were conducted between 1983 and 2004. The treatment duration, across nine medications, ranged between 4 and 16 weeks. Among SSRI-medication trials, two were on citalopram, three on fluoxetine, one on fluvoxamine, six on paroxetine, and three on sertraline. Other newer generation antidepressants studies were three bupropion trials, one mirtazapine study, two nefazodone trials, and four venlafaxine trials. Psychiatric diagnoses treated were major depressive disorder (15 trials), obsessive-compulsive disorder (OCD) five trials), generalized anxiety disorder (two trials), social phobia (one trial), and attention deficit hyperactivity disorder (ADHD) two trials). Fifteen of the trials were conducted exclusively in the United States. The two nonrandomized controlled trials were 1) an open-label trial of bupropion for ADHD (N=17) and 2) a randomized withdrawal study of paroxetine for OCD (N=194). The FDA analysis (33) used a subset of events, classified by the C-CASA, from the 23 randomized controlled trials described previously and events from an additional federally funded trial (Treatment for Adolescent Depression Study). Events from the Treatment for Adolescent Depression Study were classified using the C-CASA but were not included in the present reliability study, since a different pool of raters was used and it was sponsored by NIMH.

## Adverse Events

**Pharmaceutical company identification of “possibly suicidal” events.** The FDA requested that manufacturers of all nine antidepressants identify adverse events that could represent “possibly suicidal” events. Events were identified using an electronic text-string search of trial databases of patient data recorded by local study clinicians. Pharmaceutical companies were asked to search for any adverse events report that included the terms “suic overdos attempt,” “cut,” “gas,” “hang,” “hung,” “jump,” “mutilate,” “overdos,” “self-damage,” “self-harm,” “self-inflict,” “self-injur,” “shoot,” “slash” in the labeling of an event. The FDA permitted exclusion of obvious false positives (e.g., “gas” in “gastrointestinal”). The pharmaceutical companies were also asked to select a subset of events that were considered suicide attempts. No definitional criteria were given to categorize possibly

suicidal events and suicide attempts. The string search identified 114 possibly suicidal events; of these, 87 (76.3%) were considered suicide attempts by pharmaceutical companies.

**Broadening of event search.** To insure that all potentially suicidal events were identified, the scope of the search was broadened beyond those events originally identified by pharmaceutical companies to include all accidental injuries, overdoses, and serious adverse events, such as life-threatening events and hospitalizations. Inclusion of these additional events enabled a blinded review, since both suicidal and other adverse events were included. For classification, 427 potentially suicidal adverse events were included. Among these events, 114 were originally rated by pharmaceutical companies as possibly suicidal.

**Adverse event narrative construction.** Once adverse events were flagged by the string search, pharmaceutical companies composed narratives for each adverse event using data from case report forms, recorded by local study investigators during the course of the trials, and other sources, such as hospital records. When available, narratives included age, sex, history of suicidality, hospitalization status, current psychosocial stressors, and family history of suicide.

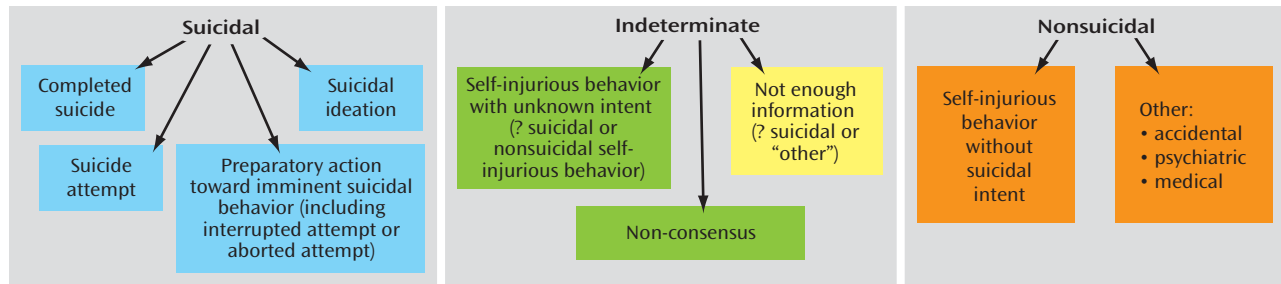
## Blinding

Columbia University investigators developed comprehensive blinding procedures that removed information from all narratives that might have biased a classification decision. The FDA then implemented these procedures, removing all potential drug-identifying information, including the drug name, company/sponsor name, patient identification numbers, primary diagnosis, active or placebo arm, and all medication names and types, since treatment with other medications may be associated with a particular antidepressant side-effect profile. Case numbers that had no link to patient identifying information were randomly assigned to narratives by the FDA. Columbia University investigators further removed all original labels given by the pharmaceutical companies to categorize events (“preferred terms”) as well as adverse event labels given by participating investigators, including “serious” and “nonserious” determinations.

## Expert Raters

Nine internationally recognized experts in suicide and suicide assessment were recruited as “raters.” Expert review of cases was needed for inference of suicidal intent based on the details of behaviors and related clinical data, since many narratives lacked stated suicidal intent. Expertise in suicidality was determined by relevant experience and publications. Panel members neither were involved in these industry trials nor were employed by Columbia University.



FIGURE 1. Suicidality Classification Scheme<sup>a</sup>

<sup>a</sup> Blue boxes=FDA “primary analysis” (includes events deemed suicidal). Blue+green boxes=FDA “sensitivity analysis” (includes any event that could possibly be suicidal).

### Randomization and Expert Review Procedures

Event narratives were randomly distributed among raters using a balanced incomplete block design. Each event was classified by three raters; each triad of raters shared five cases. This randomization approach reduces rater burden without sacrificing precision in variance estimates (34).

Raters participated in a training teleconference to review classification parameters (categories, associated definitions, and case examples), followed by training reliability exercises prior to receiving narratives. Training exercises of each rater were reviewed for agreement with C-CASA definitions, and disagreements were discussed with the individual rater.

Each rater classified approximately 125 events. Raters could consult with a Columbia University trainer regarding the application of classification processes but were restricted from discussing specific events. Cases with discordant ratings were identified, and corresponding narratives were resent to raters. If ratings did not result in a unanimous agreement, a consensus discussion including the three raters assigned to assess the event was held and was led by another rater. The goal was to reach 100% agreement; otherwise, the event was classified as “indeterminate.” Final consensus classification determinations were provided to the FDA.

### FDA Independent Audit of the C-CASA

To assess the reproducibility and reliability of the C-CASA methodology, four independent, nonsuicidologist FDA clinical reviewers were selected, including two pediatricians, one pharmacist, and one psychiatrist. Fifteen percent of the 427 event narratives were selected for review, with oversampling of “difficult-to-classify” cases. Raters received the same training and procedures as the expert panel. Audit results showed 89% agreement ( $\kappa=0.84$ ) between audit ratings and expert ratings (35).

### Statistical Analysis

Reliability coefficients were estimated with a random-effects linear model using the restricted maximum likelihood algorithm in SPSS 12.0 for Windows. Random effects modeled event-to-event, rater-to-rater, and error variation. Intraclass correlation coefficients (ICC) were estimated by the ratio of the variance because of the event divided by the total variance (sum of event-to-event, rater-to-rater, and error variation) (34). ICCs were estimated for each category.

Cohen's kappa was used to evaluate the agreement between pharmaceutical companies and C-CASA classifications. These analyses were conducted with only one event per subject. For subjects with multiple events, statistical calculations used the most severe event, which was chosen according to the severity hierarchy employed by the FDA for their unblinded analyses. This severity hierarchy was as follows: suicide attempt>preparatory behavior>suicidal ideation>self-injurious behavior intent un-

known>not enough information>self-injurious behavior, no suicidal intent. This approach identified 377 individual subjects, all of whom experienced one or more relevant adverse event. Only 50 individuals had more than one event, and most of those were accidental injuries.

Blinded examination of de-identified case records was considered exempt from review by the institutional review board of the New York State Psychiatric Institute and the Columbia University Department of Psychiatry.

## Results

Frequencies of the 427 events according to C-CASA classifications are presented in Table 3. Completed suicides are not included, since none occurred in the pediatric trials.

### Reliability of C-CASA

Excellent overall reliability (median ICC=0.89) was demonstrated among independent ratings of nine experts using the C-CASA. ICCs for the seven categories are presented in Table 3.

Of the 427 events, 366 (85.7%) had unanimous agreement among the three raters. Fifty-nine events (13.8%) had agreement between two of three raters, while two (0.47%) events had no agreement. Consensus discussions were held via teleconference whereby agreement was reached for all cases that were not unanimous.

### Comparison With Pharmaceutical Companies

**Discrepant cases.** Thirty-eight discrepant cases were identified when comparing C-CASA with pharmaceutical company ratings (Table 4). Of these, 26 were new, possibly suicidal cases that were originally labeled by pharmaceutical companies as something other than suicidal (e.g., accidental injury). These cases were as follows: one suicide attempt, one suicidal preparatory act, 13 suicidal ideation events, four self-injurious behaviors with unknown intent, and seven cases without enough information but reason to suspect suicidality. The following is an example of a newly identified suicidal event: “The patient, age 11, held a knife to his wrist and threatened to harm himself. The patient was hospitalized with an acute exacerbation of major depressive disorder.” The original adverse event label was “exacerbation of major depres-

TABLE 3. Frequency and Reliability Results

Classification/Category	Frequency (N=427)	Percent (N=427)	Reliability of C-CASA Ratings ICCs (Mean=0.89)
Suicide attempt	36	8.4	0.81
Preparatory acts toward imminent suicidal behavior	8	1.9	0.89
Suicidal ideation	62	14.5	0.97
Self-injurious behavior, suicidal intent unknown	35	8.2	0.67
Not enough information	9	2.1	0.47
Self-injurious behavior, no suicidal intent	17	4.0	0.59
Other, no deliberate self-harm	260	60.9	0.93

TABLE 4. Agreement Between C-CASA and Pharmaceutical Company Ratings of Possible Suicidal Events and Suicide Attempts

Pharmaceutical Company Ratings	C-CASA Ratings		
	Yes	No	Total
Possibly suicidal events			
Yes	102	12	114
No	26	237	263
Total	128	249	377
Suicide attempts			
Yes	33	45	78
No	1	298	299
Total	34	343	377

sive disorder,” without an indication of suicidality from either the site investigator or pharmaceutical company. The new label was preparatory suicidal behavior. This event was discovered only because it was within a serious adverse event report of a hospitalization.

Twelve cases that were originally identified as potentially suicidal by pharmaceutical companies were classified as *not* potentially suicidal by C-CASA raters. These events were reclassified as psychiatric, involving no suicidality (N=2), accidental injury (N=1), and self-injurious behavior without suicidal intent (N=9).

**Agreement on suicide attempts.** Modest agreement was found between pharmaceutical company and C-CASA raters' classification of suicide attempts ( $\kappa=0.53$  [SE=0.06]) (Table 4). Of their 114 possibly suicide-related events, pharmaceutical companies rated 78 (68.4%) as attempts, versus the C-CASA raters identifying 34 out of 128 (26.6%) as attempts. Forty-five of the 78 (57.7%) events classified as suicide attempts by the pharmaceutical company raters were not classified by C-CASA raters as suicide attempts. One suicide attempt was identified by C-CASA raters that had not been identified by pharmaceutical companies. Although the C-CASA identified more potentially suicidal cases overall, the rate of specific suicide attempts was lower.

**Agreement on definitely suicidal cases.** Agreement between C-CASA and pharmaceutical company ratings increased when comparing the broader C-CASA categorization of definitely suicidal events (attempts, preparatory acts, and suicidal ideation) with the pharmaceutical company rating of possibly suicidal cases ( $\kappa=0.69$  [SE=0.04]). Thirty-two events identified as possibly suicidal by pharmaceutical companies were not classified as definitely suicidal by the C-CASA. Conversely, 15 newly identified definitely suicidal cases were identified by the C-

CASA. This C-CASA grouping was used by the FDA in their primary analysis (33).

**Agreement on possibly suicidal cases.** When comparing the broad nonspecific pooling of all categories that could possibly represent suicidality, there was good agreement between C-CASA (suicide attempts, preparatory behaviors, suicidal ideation, self-injurious behavior with unknown intent, and not enough information) and pharmaceutical company identification of possibly suicidal events ( $\kappa=0.77$  [SE=0.04]) (Table 4). This C-CASA grouping was used in the FDA's "sensitivity analysis" to conservatively examine results that included anything that could have possibly represented suicidality (i.e., "worst case") (33). Thus, the C-CASA identified an increased number of possibly suicidal events in the data set overall.

## Discussion

Classification of suicidal adverse events in 25 pediatric antidepressant trials with the C-CASA resulted in reliable classification of suicidal events. The C-CASA classification identified 38 discrepant cases, including events not previously deemed potentially suicidal (N=26) and those changed from suicidal to nonsuicidal (N=12). Furthermore, while C-CASA classification found more suicidal events, estimates of suicide attempts were significantly reduced. The new potentially suicidal events identified involved both suicidal ideation and behavior, across a range of classifications. Thus, when we expanded the search, many new suicidal events were found that had been missed by the pharmaceutical companies. However, of the suicidal events that the pharmaceutical companies identified, C-CASA classification resulted in a 50% reduction in the rate of suicide attempts. This reflects a tendency of the pharmaceutical companies to label any potentially suicidal event or self-injurious behavior as a suicide attempt

(e.g., suicidal ideation or a “slap in the face” labeled suicide attempt). These findings underscore the need for a standardized assessment of suicidality. Additionally, the need to expand the search for suicidal events as evidenced by the 26 newly found cases suggests that approaches currently employed in clinical trials lack sensitivity.

When comparing the C-CASA ratings with pharmaceutical company ratings, a relatively low level of agreement was found with more specific identification of suicidal occurrences, namely suicide attempts. Only when identifying a “suicidal range” or a broad nonspecific category of “possibly suicidal” was there better agreement. Pharmaceutical companies rated 45 events as suicide attempts that C-CASA raters did not. Thus, with respect to suicide attempts, reclassification with C-CASA would yield less of a hazard from the medication than if the original pharmaceutical ratings were used. Indeed, the FDA safety analysis that used these C-CASA ratings (33) found reduced risk estimates of suicidality in a depressed pediatric sample when compared with earlier FDA estimates that relied on the pharmaceutical labels (36). Additionally, a more precise risk estimate resulted (i.e., tighter confidence interval) using the C-CASA. These findings support the notion that misclassification may lead to overestimation of true risk (37). Such a change in risk estimation has clinical implications and likely affects risk-benefit analyses. Furthermore, the final FDA data set with the C-CASA ratings (33) included one-third (38/114) of cases that were different compared with the original data set (36), a substantially different sample. The use of data sets with imprecisely classified suicidal events can result in misleading findings, such as inaccurate risk and protective factors for suicidality.

The reliability of this classification approach was confirmed by the FDA's independent audit, which concluded that the C-CASA was “robust and reproducible” (35). The reliable use of this classification schema by nonsuicidologists reflects the transportability of this methodology. Notably, the FDA has mandated application of C-CASA to classify suicidal adverse events in adult antidepressant trials, as well as nonpsychotropic drug classes, and other centrally acting agents, including all anticonvulsants, cannabinoid 1 receptor (CB1R) inverse agonists for the treatment of obesity and metabolic disease. C-CASA classified data were used in the recent FDA investigation of an association between antidepressants and suicidality in adults (38).

### **Limitations and Future Directions**

The study findings are limited by the quality of the available data describing adverse events. Descriptions of suicidal occurrences were variable and limited, particularly regarding intent. Furthermore, the expanded search for unidentified occurrences elucidated the inadequate quality of the elicitation and description of suicidal adverse events.

Although neither the C-CASA raters nor Columbia University investigators were responsible for subsequent

analysis using C-CASA ratings—by Hammad et al. (33) in the FDA's safety analysis, for example—some discussion of the limitations of these subsequent analyses is warranted. Suicidal adverse events were not systematically elicited but were revealed spontaneously, allowing the possibility of ascertainment bias. Subjects receiving active medication may be more likely to report suicidal occurrences than those on placebo because of increased contact with providers, consequent to other side effects. Such ascertainment bias is an alternate explanation for differential rates among subjects receiving drug treatment versus those receiving placebo found in the FDA safety analysis (33). In addition, improvement from active medication may lead subjects to discuss suicidal thoughts with their clinician for the first time, as opposed to such thoughts being caused by the medication.

Future intervention trials that prospectively and systematically monitor occurrence and emergence of suicidality with consistent methods of ascertainment would be informative. Such investigations would more optimally delineate the relationship between suicidal adverse events and antidepressant treatments as well as for any other treatment risk analysis. Improved assessment of suicidal events is necessary both to better inform research-derived risk-benefit analyses and to foster improved clinical management and identification. Accordingly, a prospective counterpart to this system, the Columbia Suicide Severity Rating Scale (39), is being widely used and frequently recommended by the FDA. The Columbia Suicide Severity Rating Scale is a tool designed to systematically assess and track suicidal adverse events (behavior and ideation) throughout any clinical trial as well as other settings.

The strength of this suicide classification system is, perhaps, in its ability to comprehensively identify suicidal events while limiting the overidentification of suicidal behavior. This classification system is research-based and can be applied in both clinical and research settings. Its use might result in more accurate identification of suicidality and more precise communication among researchers and clinicians, which would ultimately benefit treatment of suicidal individuals. The incorporation of research-supported, standardized suicidality terminology into psychiatric diagnostic manuals could also promote greater accuracy in communication between clinicians, allowing dissemination to a broad audience. Such a common language of suicide classification could be used in the same way that diagnostic criteria are currently used to provide a method for precise, widely understood communication.

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APA policy requires disclosure by CME authors of unapproved or investigational use of products discussed in CME programs. Off-label use of medications by individual physicians is permitted and common. Decisions about off-label use can be guided by scientific literature and clinical experience.

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