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

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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.

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

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