Suicidality and Antiepileptic Drugs

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Background

- The Division of Neurology Products has evaluated the potential association between anti-epileptic drugs (AEDs) and suicidal thinking and behavior in placebo-controlled trials
- Post-marketing cases of suicidal thinking and behavior are difficult to interpret
    - Known limitations of post-marketing data
    - Patients with epilepsy (and other illnesses for which AEDs are prescribed) have increased risk of suicide

Background

- An AED sponsor approached the Division with concern of a suicidality signal in their controlled clinical trial database
- In response, the Division initiated an analysis of suicidality events in controlled clinical trial databases of all AEDS
- Sponsors were asked (in March 2005) to provide data from their placebo-controlled trial experience

Background

- Standardized approach is based on previous FDA analyses of suicidality in children, adolescents, and adults treated with antidepressants
  - In these analyses, pediatric and young adult patients treated with antidepressants were found to have an increased risk of suicidality compared to those treated with placebo

Suicidality Events: Search Terms

- 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”

Suicidality Analysis

- Analysis includes parallel-arm, placebo-controlled trials with at least 20 subjects in each treatment arm
- Subjects under age 5 were excluded
- A search for events related to suicidal behavior or possibly related to suicidal behavior was performed by the sponsors, using search terms specified by FDA

Suicidality Analysis

- After events were found using this search strategy, structured narratives were prepared
- Based on these narratives, events were classified into 7 categories
  - Classification was done by raters blinded to treatment

Suicidality Event Classification

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

Suicidality Analyses

Results Overall

Antiepileptic Drugs Analyzed

- Carbamazepine (Carbatrol®, Equetro®)
- Divalproex sodium (Depakote®, Depakote ER®)
- Felbamate (Felbatol®)
- Gabapentin (Neurontin®)
- Lamotrigine (Lamictal®)
- Levetiracetam (Keppra®)
- Oxcarbazepine (Trileptal®)
- Pregabalin (Lyrica®)
- Tiagabine (Gabitril®)
- Topiramate (Topamax®)
- Zonisamide (Zonegran®)

Data Analyzed

- Data from 199 placebo-controlled trials
- 43,892 total patients
- 27,863 drug-treated patients
- 16,029 placebo-treated patients

Results

- Drug-treated subjects had approximately twice the risk of suicidal behavior or ideation (0.43%) compared with placebo-treated subjects (0.22%).
- Risk difference 2.1 per 1000 (95% CI: 0.7, 4.2)
- Increased risk observed throughout time periods for which data was obtained
- No clear pattern of risk across age groups
- Results generally consistent across all drugs

Events by Treatment Arm in Placebo-controlled Trials

Event	Drug (N=27,683)	Placebo (N=16,029)	Total (N=43,892)
Completed suicide	4	0	4
Suicide attempt	30	8	38
Preparatory acts	3	1	4
Suicidal ideation	68	26	94
Total	105	35	140

Events in table include only the most critical event for each patient.

Suicidality Analyses

Results by Indication

Trial Indication Distribution Placebo-controlled Trials

- Epilepsy: 62 trials (31%)
- Psychiatric Indications: 56 trials (28%)
- Other Indications: 81 trials (41%)

Psychiatric Trial Indications

- Bipolar Disorder
- Anxiety
- Post-traumatic Stress Disorder
- Depression
- Panic Disorder
- Schizophrenia
- Social Phobia
- Binge Eating Disorder

Other Trial Indications

- Agitation
- Chronic Pain
- Impaired Cognition
- Neuropathy
- Insomnia
- Migraine
- Spasticity
- Obesity
- Fibromyalgia
- Tremor

Drugs Analyzed: Approved Non-epilepsy Treatment Indications

- Carbamazepine: trigeminal neuralgia
- Gabapentin: postherpetic neuralgia
- Lamotrigine: bipolar disorder
- Pregabalin: neuropathic pain from diabetic peripheral neuropathy, postherpetic neuralgia, fibromyalgia
- Topiramate: migraine
- Divalproex sodium: mania, migraine

Relative Risk and Risk Difference According to Trial Indication

Indication	Drug Patient Events Per 1000	Placebo Patient Events Per 1000	Risk Difference	Relative Risk
Epilepsy	3.5	1.0	2.5	3.6
Psychiatric	8.3	5.2	3.1	1.6
Other	2.0	0.8	1.1	2.3
Total	4.3	2.2	2.1	2.0

Suicidality Analyses

Results by Subject Age Group

Antiepileptic Drugs with Pediatric Subject Data

- Divalproex sodium (Depakote®, Depakote ER®)
- Felbamate (Felbatol®)
- Gabapentin (Neurontin®)
- Lamotrigine (Lamictal®)
- Levetiracetam (Keppra®)
- Oxcarbazepine (Trileptal®)
- Pregabalin (Lyrica®)
- Tiagabine (Gabitril®)
- Topiramate (Topamax®)
- Zonisamide (Zonegran®)

Pediatric Data Analyzed

- Pediatric subgroup: subjects 5-17 years
- Data from 65 placebo-controlled trials
- 2411 total pediatric patients
- 1292 drug-treated pediatric patients
- 1119 placebo-treated pediatric patients

Pediatric Events by Treatment Arm in Placebo-controlled Trials

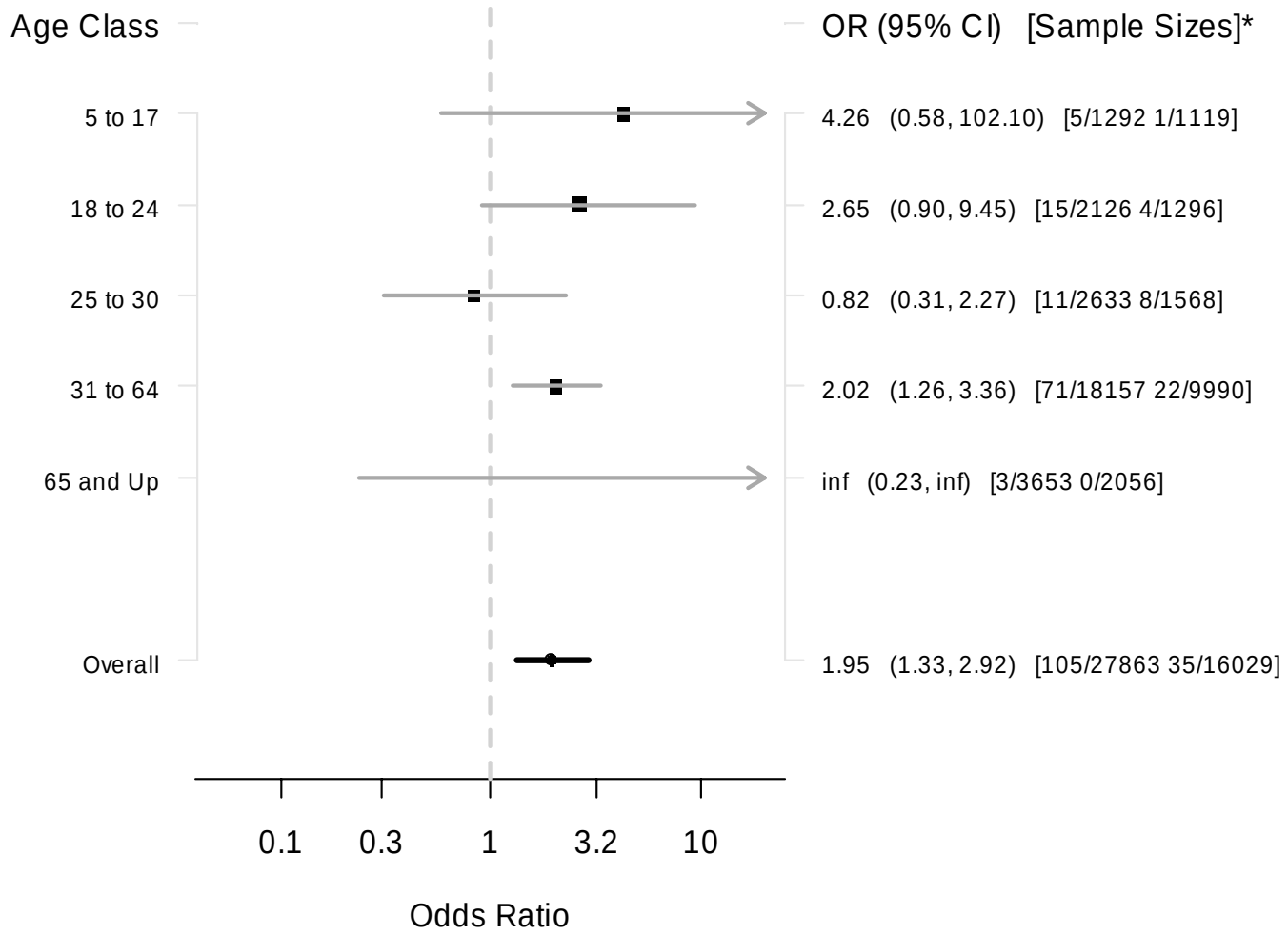
Event	Drug (N=1292)	Placebo (N=1119)	Total (N=2411)
Completed suicide	0	0	0
Suicide attempt	2	0	2
Preparatory acts	0	0	0
Suicidal ideation	3	1	4
Total	5	1	6

Events in table include only the most critical event for each patient.

Pediatric Data: Number of Subjects by Trial Indication

- Epilepsy: 2015 subjects (83%)
- Bipolar Disorder: 181 subjects (7%)
- Migraine: 222 subjects (9%)

Suicidal Behavior or Ideation
Odds Ratio Estimates by Age Group



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

Actions

- Press Release and Information for Healthcare Professionals have been issued
- Class labeling for antiepileptic drugs is in progress
- Joint Advisory Committee Meeting is planned

  -Peripheral and Central Nervous System Drugs

  -Psychopharmacologic Drugs

  - Drug Safety and Risk Management A.C. and Pediatric A.C. members will also participate

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