Suicidality and Antiepileptic Drugs

Evelyn Mentari, MD, MS
Medical Reviewer
Division of Neurology Products
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”
- 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

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

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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Drug Patient Events Per 1000</th>
<th>Placebo Patient Events Per 1000</th>
<th>Risk Difference</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>3.5</td>
<td>1.0</td>
<td>2.5</td>
<td>3.6</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>8.3</td>
<td>5.2</td>
<td>3.1</td>
<td>1.6</td>
</tr>
<tr>
<td>Other</td>
<td>2.0</td>
<td>0.8</td>
<td>1.1</td>
<td>2.3</td>
</tr>
<tr>
<td>Total</td>
<td>4.3</td>
<td>2.2</td>
<td>2.1</td>
<td>2.0</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Event</th>
<th>Drug (N=1292)</th>
<th>Placebo (N=1119)</th>
<th>Total (N=2411)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed suicide</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Preparatory acts</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Age Class</th>
<th>OR (95% CI)</th>
<th>Sample Sizes</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 to 17</td>
<td>4.26 (0.58, 102.10)</td>
<td>[5/1292 1/1119]</td>
</tr>
<tr>
<td>18 to 24</td>
<td>2.65 (0.90, 9.45)</td>
<td>[15/2126 4/1296]</td>
</tr>
<tr>
<td>25 to 30</td>
<td>0.82 (0.31, 2.27)</td>
<td>[11/2633 8/1568]</td>
</tr>
<tr>
<td>31 to 64</td>
<td>2.02 (1.26, 3.36)</td>
<td>[71/18157 22/9990]</td>
</tr>
<tr>
<td>65 and Up</td>
<td>inf (0.23, inf)</td>
<td>[3/3653 0/2056]</td>
</tr>
<tr>
<td>Overall</td>
<td>1.95 (1.33, 2.92)</td>
<td>[105/27863 35/16029]</td>
</tr>
</tbody>
</table>

*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
Acknowledgements

- Division of Biometrics 6
- Division of Psychiatry Products
- Office of Surveillance and Epidemiology
- Division of Neurology Products