Suicidal Behavior or Ideation in Pediatric Trials: Risk Ratios for Atomoxetine vs. Placebo Using FDA Methods

| Study | Risk Ratio (95% CI) | Weight (n) | Nohria-Harrell | TIEF | FDA
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<tbody>
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<td>Overall</td>
<td>1.29 (0.94, 1.79)</td>
<td>0.37</td>
<td>0.74</td>
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ADHD and Suicide Risk

- Children with ADHD have increased risk for comorbidities, including conduct disorders, depression, anxiety disorders, and tic disorders.

- Suicide, psychiatric conditions can affect the ADHD clinical presentation, diagnosis, prognosis, and overall treatment.

- Study of patients with ADHD with age, gender, and index-year-matched controls found increased risk compared with controls.
  - Intentional self-injury was 1.7 times more likely in patients with ADHD.
  - 0.7% of patients with ADHD (0.0%) vs. controls (7.4%) were found to have suicidal ideation at any trial time point.
  - Suicide attempts were 2.1 times more likely in patients with ADHD.
  - 0.4% of patients with ADHD (0.0%) vs. controls (0.0%) were found to have suicidal ideation at any trial time point.

- ADHD appears to increase the risk of suicide, especially in males, via increased severity of comorbid conditions, particularly conduct disorders and depression.

Other ADHD Medications

- It does not appear that a similar analysis of suicide ideation and behavior has been conducted with other ADHD medications. Even if such an analysis is done, it may be difficult/impossible to draw definitive conclusions from such a review because of:
  - Limited number of patients in placebo-controlled registration trials (underpowered to detect a signal).
  - Duration of parallel-arm trials only 2 to 4 weeks (less exposure).
  - Trials in databases using crossover design are problematic (very short arms, less exposure, possible discontinuation phenomena).
  - Evaluation criteria of previous studies cannot be applied to all patients included in clinical trials.

- FDA has stated it will review psychiatric adverse events associated with all ADHD drugs in 2006.

CONCLUSIONS

- Suicide-related events uncommon in atomoxetine-treated patients with most categorized as “suicidal ideation.”
  - Incidence of suicidal ideation was statistically greater in atomoxetine-treated pediatric patients compared with placebo.

- Suicide-related events in pediatric ADHD trials, all occurred in male patients 12 years or younger.

- More than 75% of pediatric patients with ADHD were 12 years or younger and male; thus, unclear whether this population is more at risk.

- Data does not demonstrate increased risk for suicide-related events in adults taking atomoxetine for ADHD.

- Benefit and risk as assessed by number needed to treat (NNT) for atomoxetine remains positive.
  - NNT for atomoxetine defined as 40% reduction in ADHD RS total score is 5, for atomoxetine (compared with 4 for MPH) and 272 for ideation.

- Changes to Stratification label are being made.

- Additional research regarding suicidal ideation and behavior in treated and untreated patients with ADHD is needed.

REFERENCES