Meta-analysis of Suicide-related Events in Atomoxetine-treated Patients

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ABSTRACT

Objective: Atomoxetine, a selective norepinephrine reuptake inhibitor, is approved in the US and Canada for the treatment of ADHD in children, adolescents, and adults. The purpose of these analyses was to examine suicidal ideation and behaviors in acute, double-blind, placebo-controlled trials with atomoxetine.

Methods: Pediatric trials included 11 ADHD trials (8 with ADHD alone and 1 each with comorbid tics, depression, and anxiety) and 1 enuresis trial. Adult trials included 6 major depression trials and 3 ADHD trials. Similar methods, the "FDA" and "Lilly", were applied to all trials. For both methods, a text string search was used to search adverse events and comment fields in the trials database to identify potential events. Events occurring prior to randomization or more than 1 day after last dose of study drug as well as "false positives" were excluded. Blinded summaries of the remaining potential events were categorized as to suicide-related event types by teams of clinicians, at least one a physician. Subjects were assigned to only one category (the most severe). A meta-analysis was conducted using the Maentel-Haenzel Risk Ratio (MHRR) and Maentel-Haenzel Incidence Difference (MHID) with their corresponding 95% confidence intervals.

Results: With both methods, the frequency of suicidal ideation in pediatric patients on atomoxetine was 0.37% (5/1357) versus 0% (0/851) in those on placebo; MHRR of 2.92 (95% CI, 0.63, 13.57; p=0.172) and MHID of 0.46 (95% CI, 0.09, 0.83; p=0.016). In addition, the FDA method classified 1 case in the atomoxetine group as a suicide attempt. The Lilly method classified 2 cases in the atomoxetine group and 1 case in the placebo group as suicide attempts. In adults, there was no statistically significant finding with either method.

Conclusions: Suicidal ideation was significantly more frequent in pediatric trials in patients treated with atomoxetine as compared to placebo.

BACKGROUND

- Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most common psychiatric disorders in children and adolescents. Adolescents with ADHD are at higher risk for suicide attempt compared with the healthy population.
- Atomoxetine, a selective inhibitor of norepinephrine transporter with low affinity for serotonin and dopamine transporters, is approved in the US and Canada for the treatment of ADHD in children, adolescents, and adults.
- The present analysis was conducted to examine suicidality in atomoxetine trials following the Committee for Medicinal Products for Human Use (CHMP) in the EU, as well as the US FDA, recommending a warning on pediatric suicidality for a list of compounds including atomoxetine.

METHODS

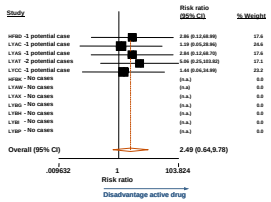
- Potential suicide or self-harm related events were identified by a computerized text string search of all electronically available data in Eli Lilly and Company's Clinical Trials database including all adverse events (reported and coded) and narratives for 12 pediatric and 9 adult double-blind, placebo-controlled trials of atomoxetine.
- A review of the identified events retrieved with these terms was conducted and events unrelated to suicidality or self-harm were excluded. All events that occurred before randomization and more than 1 day after last dose were excluded.
- A meta-analysis using the Maentel-Haenzel Risk Ratio (MHRR) and Maentel-Haenzel Incidence Difference (MHID) with 95% confidence intervals across the studies for atomoxetine relative to placebo was then calculated for the remaining events that were categorized as being suicide-related events. These included both suicidal behavior and suicidal ideation.

RESULTS

FDA Request for Data on "Possibly Suicide-related" Adverse Events in Placebo-controlled Atomoxetine Trials

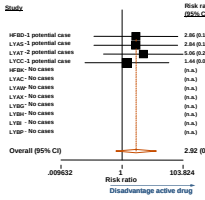
- Eli Lilly and Company provided results of 2 analyses to comply with the FDA request:
  - FDA standard approach for evaluating suicide-related events in clinical trials
  - Eli Lilly and Company Psychobehavioral Safety Working Group (PSWG) approach using slightly different event terms (more inclusive), categorization, and analysis methods
- For Eli Lilly and Company internal decision making, the PSWG methods were used.

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



Overall Risk ratio (95% CI)
2.49 (.64, 9.78; p=.190)

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



Overall Risk ratio (95% CI)
2.92 (.63, 13.57; p=.172)

***PSWG methods resulted in the same events of interest as in FDA analysis.**

Pediatric Atomoxetine Study Results

Meta-analysis (MHID) of Suicide-related Behaviors or Ideation in Acute Pediatric Placebo-controlled Atomoxetine Studies Using FDA Methods*

Outcome	Atomoxetine (*N*=1357) *n* (%)	Placebo (*N*=851) *n* (%)	*p*-value[b]
Suicidal behavior[a] or ideation	6 (0.44)	0 (0.0)	.010
Suicidal behavior[a]	1 (0.07)	0 (0.0)	.398
Suicide ideation	5 (0.37)	0 (0.0)	.016

[a] Suicidal behavior includes "completed suicide," "suicide attempts," and "preparatory acts toward imminent suicidal behavior."
[b] Mantel-Haenszel incidence difference stratified by study
* Includes all pediatric studies for all conditions. No suicide-related events reported in the enuresis study (LYBH), comorbid ADHD and depression study (LYAX), or comorbid ADHD and anxiety study (LYBP).

Patient Characteristics of Identified Pediatric Patient Events

- **Origins:** 5 Caucasians; 2 African descent; 1 other
- **Subtypes of ADHD:** 3/8 inattentive; 1/8 hyperactive/impulsive; 4/8 mixed
- **Stimulant use:** 5/8 naïve; 3/8 previously used

Narratives of Identified Pediatric Patient Events Using the FDA Methodology

- **Case 1. *Non-fatal suicide attempt:*** 9-year old male with diagnoses of ADHD, dysthymia, anxiety-specific phobias, oppositional defiant disorder (ODD), and past history of depression. Seventeen days after atomoxetine was started, patient took 15 pills of study drug reported as serious adverse event verbatim term of "took 5 doses of study medication at once". Patient evaluated in emergency room (ER) and discharged. Patient had no known history of suicidal ideation, suicide attempts, non-suicidal self-harm, or psychiatric hospitalizations. At study initiation, patient's baseline Children's Depression Rating Scale (CDRS) total score was 45 and item 13 score was 1 (understands the word "suicide" but does not apply term to self), which was highest rating patient received for item 13. Patient was receiving atomoxetine 0.79 mg/kg/day BID at time of event. Patient reported no concomitant medications or associated adverse events during event. Patient continued taking study drug and completed study. Patient would have been considered a treatment responder. ADHD RS score declined from a baseline high of 40 to 24 at visit prior to event.
- **Case 2. *Suicidal ideation:*** 12-year old male with diagnosis of ADHD randomized to atomoxetine. Experienced adverse event of 'suicidal ideation' reported 10 days after randomization. Comments on case report form stated, "Doctor noted suicidal ideation present, in context of school stress. Patient has no suicidal plan or intent either now or in the past. Ideation deemed 'adjustment reaction' to school stressors. Patient not at suicidal risk". Patient had no known history of suicidal ideation, suicide attempts, non-suicidal self-harm, aggressive or hostile behavior, or psychiatric hospitalizations. Patient not hospitalized and event resolved 3 days after it began. Patient not discontinued from study at time of event, but discontinued from study for other reasons after 25 days on atomoxetine. Patients' atomoxetine dose had not changed after randomization and was 0.48 mg/kg/day at time of event. Patient would have been considered a treatment nonresponder as ADHD RS score declined from 34 to 28 at discontinuation from study.
- **Case 3. *Suicidal ideation:*** 9-year old male with diagnoses of ADHD and a movement disorder, randomized to treatment with atomoxetine. Twenty-five days after first starting atomoxetine, investigator comments noted "patient endorsed item 9 of Children's Depression Inventory with a score of 1, which indicates that the patient has thought about suicide but would not carry through with it". Patient's history of suicidal ideation, attempts, non-suicidal self-harm, aggressive or hostile behavior, or psychiatric hospitalizations was unknown. At study initiation, patient's baseline CDRS total score was 21 and item 13 score was 1 (understands the word "suicide" but does not apply term to self). Item 13 score remained unchanged throughout study. Patient was receiving atomoxetine at a dose of approximately 1.0 mg/kg/day at time of event. Patient was not hospitalized and continued in study through completion of double-blind phase. Patient would have been considered a treatment responder as ADHD RS score declined from 36 to 23 by end of study.
- **Case 4. *Suicidal ideation:*** 7-year old male with diagnosis of ADHD, randomized to atomoxetine treatment. He experienced adverse event of suicidal ideation after 31 days of atomoxetine treatment and event resolved by next day. No other details about event were recorded. Patient had no known history of suicidal ideation, suicide attempts, non-suicidal self-harm, aggressive or hostile behavior, or psychiatric hospitalizations. Patient was receiving atomoxetine 1.40 mg/kg/day at the time of event. Patient was not hospitalized and continued into open-label study. Patient would have been considered a treatment nonresponder since ADHD RS score increased from 31 to 37 at visit one day after event.
- **Case 5. *Suicidal ideation:*** 12-year old male with diagnoses of ADHD and ODD, randomized to atomoxetine treatment. Approximately 28 days after starting study drug, investigator noted on case report form comments, "School suggested to mother that patient was depressed based on a statement by patient at school that he might bring a gun and kill someone. He saw a psychologist since the last study visit who diagnosed him as depressed and suicidal. He stopped medication. I am unable to get any symptoms of depression or suicidal ideas from him or his mother. It is unclear when the statement about the gun occurred – before or after the study protocol started – they do not remember". Patient discontinued from study. Patient had no known history of suicidal ideation, suicide attempts, or self-harm. Investigator did not collect information on psychosocial stressors. Patient was taking atomoxetine 0.95 mg/kg/day prior to the event. Patient would have been considered a treatment nonresponder as ADHD RS score declined from 36 to 30 by visit when event was recorded.
- **Case 6. *Suicidal ideation:*** 8-year old male with diagnosis of ADHD randomized to atomoxetine treatment. He experienced adverse events of suicidal ideation, agitation, and affect lability 9 days after starting study drug and discontinued from study due to suicidal thoughts after 16 days of study drug. Patient history of suicidal ideation, suicide attempts, non-suicidal self-harm, aggressive or hostile behavior, or psychiatric hospitalizations was unknown. Patient not hospitalized and is unknown if seen in ER. No additional information is available about the suicidal thoughts. Patient was receiving atomoxetine at approximately 0.55 mg/kg/day at time of event. Patient would have been considered a treatment responder since ADHD RS score declined from 50 to 35 by time he discontinued from study

Narratives of Identified Pediatric Patient Events Using the PSWG Methodology

- **Case 7. *Self-injurious behavior, intent unknown*:** Identified only by PSWG methodology. 9-year old male with diagnosis of ADHD randomized to atomoxetine treatment. Case report form comments from 29 days after start of atomoxetine stated, "Subject took 3 capsules on Sunday plus 6 of Monday's capsules on Sunday. Vomit induced with return of all 9 capsules. Subject did not re-dose on Sunday. Overdose will not be considered as an adverse event due to parents' statement that all 9 capsules were accounted for." Patient's history of suicidal ideation, attempts, non-suicidal self-harm, aggressive or hostile behavior, or psychiatric hospitalizations was unknown. Patient was on 0.80 mg/kg/day at time of event. Unknown if this event resulted in treatment in ER or hospitalization. Patient continued treatment and completed both acute and open-label phases of study. Patient would have been considered a treatment responder, as ADHD RS score declined from baseline 50 to 19 at visit closest to event.
- **Case 8. *Self-injurious behavior, intent unknown*:** Identified only by PSWG methodology. 8-year old male with diagnoses of ADHD and ODD, randomized to placebo. Overdose of 2 days worth of capsules was documented in comments of case report form, but not as adverse event, 24 days after start of study drug. Patient's history of suicidal ideation, attempts, non-suicidal self-harm, aggressive or hostile behavior, or psychiatric hospitalizations was unknown. Patient was lost to follow-up after event. Patient's only CDRS total score was 28 at baseline, with suicidal ideation score of 1 ("Understands the word 'suicide' but does not apply the term to self"). Patient would have been considered a treatment nonresponder since ADHD RS score declined from 54 to 52 at last visit prior to event.

Adult Atomoxetine Study Results

Meta-analysis (MHID) of Suicide-related Behaviors or Ideation in Acute Adult Placebo-controlled Atomoxetine Studies Using FDA Methods

Outcome	Atomoxetine	Placebo	*p*-value[b]
All Conditions (MDD and ADHD)	(*N*=1718) *n* (%)	(*N*=1072) *n* (%)	
Suicidal behavior[a] or ideation	15 (0.87)	10 (0.93)	.465
Suicidal behavior[a]	**1 (0.06)**	**2 (0.19)**	**.313**
Suicide ideation	14 (0.81)	8 (0.75)	.252
Separated by Condition **Historic MDD Studies**	(*N*=1177) *n* (%)	(*N*=667) *n* (%)	
Suicidal behavior[a] or ideation	15 (1.27)	9 (1.35)	.329
ADHD Studies	(*N*=541) *n* (%)	(*N*=405) *n* (%)	
Suicidal behavior[a] or ideation	0 (0.0)	1 (0.25)	.346

[a] Suicidal behavior includes "completed suicide," "suicide attempts," and "preparatory acts toward imminent suicidal behavior."
[b] Mantel-Haenszel incidence difference stratified by study
MDD=Major Depression Disorder, ADHD=Attention-Deficit/Hyperactivity Disorder

Of the 25 total events of suicidal behavior or ideation (15 in atomoxetine; 10 in placebo), 24 were in depression studies and 1 was in an ADHD study (placebo).

ADHD and Suicide Risk

- Children with ADHD have increased risk for comorbidities, including conduct disorders, depression, anxiety disorders, and tic disorders.
  - Comorbid 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 risks compared with controls:
  - Intentional self-injury was 1.7 times more likely in patients with ADHD.
    - 0.70% of patients with ADHD, 0.25% of controls, p<.001
  - Suicide attempts were 2.1 times more likely in patients with ADHD.
    - 0.48% of patients with ADHD, 0.14% of controls, p<.001
- ADHD appears to increase the risk of suicide, especially in males, via increasing severity of comorbid conditions, particularly conduct disorders and depression.

Other ADHD Medications

- It does not appear that a similar analysis of suicidal 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).
  - Exclusion criteria or pre-trial eliminates patients unable to tolerate stimulants (sample bias)
- 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.
- Of 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 remission, defined as 40% reduction in ADHD RS total score, is 5 for atomoxetine (compared with 4 for MPH) and 272 for ideation.
- Changes to Strattera® label are being made.
- Additional research regarding suicidal ideation and behavior in treated and untreated patients with ADHD is needed.

References

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