

Meta-analysis of Aggression or Hostility Events in Atomoxetine Pediatric Trials

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ABSTRACT

Objective. To assess the potential risk of events related to aggression or hostility in acute clinical trials of atomoxetine for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents.

Background. Aggressive behavior or hostility has been observed in children and adolescents as part of the clinical symptomatology of ADHD and also as possible treatment emergent adverse events associated with medications indicated for the treatment of ADHD.^{1,2} The present analysis examines the incidence of aggression or hostility events and the relationship between atomoxetine use and these events in clinical trial data.

Methods. Potential aggression or hostility events were identified by a computerized text-string search of all electronically available content (adverse events, comments, etc.) from 11 acute double-blind placebo-controlled studies of atomoxetine (atomoxetine *n*=1308, placebo *n*=806) and three acute double-blind comparator-controlled studies of atomoxetine in pediatric ADHD trials. Three of the placebo-controlled studies also contained a methylphenidate arm and those data were combined with the data from the three comparator studies for analysis (atomoxetine *n*=566, methylphenidate *n*=472). Seventy-one terms or partial terms related to aggression or hostility were identified (i.e., "aggress", "ability", "threat"). Each occurrence of these terms was reviewed for relevance and false hits (e.g., "rater availability") were excluded. All events occurring prior to randomization or more than 1 day after last dose in the acute period were also excluded. For the remaining events, Mantel-Haenszel risk ratios (MHRR) were calculated across studies for atomoxetine relative to placebo and atomoxetine relative to methylphenidate.

Results. In the 11 placebo-controlled trials of atomoxetine, there were 21 aggression/hostility events (1.6%) in atomoxetine patients and 9 (1.1%) in placebo patients. The overall MHRR for the occurrence of aggression/hostility-related events with atomoxetine relative to placebo was 1.33 (95% C.I.: 0.67, 2.64). In the 6 active comparator-controlled trials of atomoxetine, there were 7 aggression/hostility events (1.2%) in atomoxetine patients and 4 (0.8%) in methylphenidate patients. The overall MHRR with atomoxetine relative to methylphenidate was 0.96 (95% C.I.: 0.29, 3.19).

Conclusions. The current meta-analysis of clinical trial data of children and adolescents treated with atomoxetine showed a potentially higher risk of aggression or hostility events based on a numerically (but not statistically significantly) higher risk compared with placebo. The risk of hostility or aggression events was not significantly different from that seen with methylphenidate. Patients beginning treatment for ADHD should be monitored closely for the appearance or worsening of aggressive behavior or hostility.

INTRODUCTION

- Aggressive behavior is associated with various psychiatric disorders in children, including attention-deficit/hyperactivity disorder (ADHD).^{1,3}
- Children with both ADHD and aggression have worse outcomes than those with either problem alone.^{4,5}
- Childhood aggression can disrupt family and peer relationships and has been associated with an increased risk of lifetime diagnoses of major depression, drug abuse disorder, and antisocial personality disorder.⁶
- Although pharmacotherapies for ADHD generally reduce/treat aggression, there have been some case reports of apparent treatment-emergent aggression with these drugs.^{2,7}

OBJECTIVE

To assess the potential risk of events related to aggression or hostility in acute clinical trials of atomoxetine for the treatment of ADHD in children and adolescents.

METHODS

Studies included in analysis:

- Data from 14 clinical trials of atomoxetine in children and adolescents with ADHD were sorted into two databases (Table 1):
 - A placebo-controlled database was composed of 11 acute double-blind placebo-controlled studies of atomoxetine (atomoxetine *n*=1308, placebo *n*=806).
 - An active comparator database was composed of 6 trials including 3 acute double-blind studies of atomoxetine versus methylphenidate and 3 acute double-blind placebo-controlled studies that also included a methylphenidate arm (atomoxetine *n*=566, methylphenidate *n*=472).

Procedure:

- Potential aggression or hostility events were identified for review by a computerized text-string search (Table 2) of all electronically available content (adverse events, comments, etc.).
- Each occurrence of the terms was reviewed and false hits (e.g., "rater availability" as a match for "ability") were excluded.

Table 1. Summary of Studies Included

Study Code	Study Design	Placebo-Controlled Database	Active Comparator Database
HFBK	Double blind, placebo controlled (9 wks)	✓	✓
LYAC	Fixed dose-response (8 wks)	✓	✓
LYAT	Once-daily dosing (6 wks)	✓	✓
LYAW	Once-daily dosing and efficacy in the school setting (7 wks)	✓	✓
LYBG	Once-daily dosing and evening efficacy (8 wks)	✓	✓
LYBI	Double blind versus comparator (6 wks)	✓	✓
LYBP	Double blind, placebo controlled ADHD and comorbid anxiety disorder (12 wks)	✓	✓
LYAX	Double blind, placebo controlled ADHD and comorbid depressive disorder (9 wks)	✓	✓
LYAS	Double blind, placebo controlled ADHD and comorbid tic disorders (18 wks)	✓	✓
LYCC	Double blind, placebo controlled, assessment of morning dose or evening dose (6 wks)	✓	✓
LYAU	Double blind, functional MRI (6 wks)	✓	✓
LYAV	Double blind, sleep and neuropsychological functioning (7 wks)	✓	✓
LYBR	Double blind, safety and efficacy (8 wks)	✓	✓

- The remaining potential events were manually reviewed by two independent health care professionals (at least one of whom was a physician) who were blinded to treatment:
 - Each event was assigned to one of 9 categories (Table 3).
 - Consensus was obtained between the two reviewers with a third person providing arbitration if necessary.
- All events occurring prior to randomization or more than 1 day after last dose in the acute period were excluded.
- Patients were required to have taken at least one dose of study drug to be included in the analyses.

Statistical analyses:

- Primary outcome was aggression or hostility events (Categories 1-6, Table 3).
- Incidence rates were calculated by dividing the number of events by the total number of patients who took at least one dose of study drug in each treatment group
- Mantel-Haenszel risk ratios (MHRR) and 95% confidence intervals for atomoxetine relative to placebo and for atomoxetine relative to methylphenidate were calculated⁸

Table 2. Text Strings Used in Search

abuse	bit	disrupt	hostil	lac	slash
abusive	burn	drown	hurt	mani	social
agitat	confront	dying	immolat	mutilat	suffocat
aggress	cut	explos	inflict	poison	tantrum
aggravat	damag	fight	injur	opposi	temper
altercat	danger	firearm	intent	outburst	thinking
anger	dead	gas	irritab	personality	threat
angry	death	gun	jail	punch	uncoop
araru	defian	harm	kick	rifle	violen
assault	destruct	hate	kill	scream	violit
attack	die	hit	knife	shoot	yell
belliger	disinhibit	homicid	liability	shot	

Table 3. Categories

Category 1	Aggressive behavior with physical harm directed toward another person(s)
Category 2	Aggressive behavior with physical harm directed toward animals
Category 3	Aggressive behavior with physical harm directed toward objects
Category 4	Aggressive behavior with nonspecific information
Category 5	Aggressive behavior with indirect or no potential for direct physical harm
Category 6	Hostility without aggression
Category 7*	Anger without hostility or aggressive behavior
Category 8*	Violent ideation with no anger, hostility or aggressive behavior
Category 9*	Does not meet case definition

*Category does not meet definition of aggression or hostility, these events were not included in the analysis of the primary outcome.

RESULTS

Table 4. Demographics

	Placebo-controlled Database		Active Comparator Database	
	Atomoxetine <i>n</i> =1313	Placebo <i>n</i> =806	Atomoxetine <i>n</i> =567	Methylphenidate <i>n</i> =473
No. of Clinical Trials	11		6	
Age in Years, M ± SD	10.5 ± 2.4	10.7 ± 2.5	9.9 ± 2.0	10.0 ± 2.3
Age Group, <i>n</i> (%)				
6 <12 years	995 (75.8)	576 (71.3)	467 (82.4)	371 (78.4)
12 <18 years	318 (24.2)	232 (28.7)	100 (17.6)	102 (21.6)
Female, %	25.7	25.1	21.7	22.6
Caucasian, %	73.1	74.5	48.1	45.7
DSM-IV Subtype, %				
Hyperactive/impulsive	2.0	1.9	2.3	2.1
Inattentive	27.6	31.8	26.7	31.9
Combined	70.4	66.3	71.0	66.0
Comorbid ODD, %	36.4	33.8	36.1	30.4

Note: Demographics represent all randomized patients. Only patients who received at least one dose of study drug were included in the analyses below. ODD = oppositional defiant disorder.

Event categorization:

- For the primary outcome (Categories 1-6):
 - No events were assigned to Categories 2, 3, or 6.
 - Events were assigned to Categories 1, 4, and 5 with the majority being assigned to Category 4.

Incidence of aggression or hostility events:

- In the placebo-controlled database, incidence rates were 1.6% (*n*=21/1308) for atomoxetine patients and 1.1% (*n*=9/806) for placebo patients.
- In the active comparator database, incidence rates were 1.2% (*n*=7/566) for atomoxetine patients and 0.8% (*n*=4/472) for methylphenidate patients.

Figure 1. Risk Ratios and 95% CI for Aggression or Hostility Events from ADHD Placebo-controlled Studies

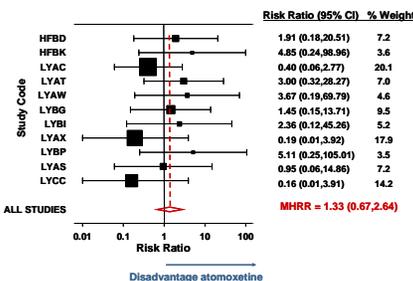
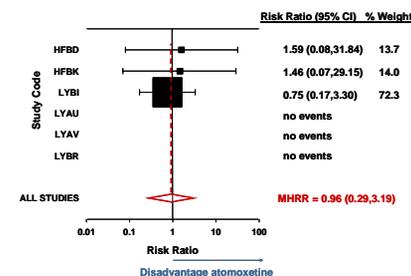


Figure 2. Risk Ratios and 95% CI for Aggression or Hostility Events from ADHD Active Comparator Studies



SUMMARY AND CONCLUSION

- Events related to hostility or aggression were generally infrequent during these trials.
- Children and adolescents treated with atomoxetine showed a potentially higher risk of aggression or hostility events based on a numerically (but not statistically significantly) higher risk compared with placebo (MHRR=1.33, 95% CI: 0.67, 2.64).
- The risk of hostility or aggression events with atomoxetine was not significantly different from that seen with methylphenidate (MHRR=0.96, 95% CI: 0.29, 3.19).
- Children and adolescents taking atomoxetine for ADHD should be monitored closely for the emergence or worsening of aggressive behavior or hostility.

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