Atomoxetine Tolerability in Pediatric and Adult Patients Receiving Different Dosing Strategies

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ABSTRACT

Objective: Examine how different dosing schedules and recent stimulant therapy effect incidence, time to onset, and duration of common treatment-emergent adverse events (TEAEs) during atomoxetine treatment.

Method: Post hoc analyses including safety data (open-ended questions) from 22 pediatric and 3 adult atomoxetine trials (1998–2009) in patients with attention-deficit/hyperactivity disorder. Most common TEAEs were determined by incidence rates and frequency of consumer and clinician inquiries. Onset and duration of TEAEs with slow versus fast titration, once-daily versus twice-daily dosing, and previous stimulant exposure were compared among treatment groups using Kaplan-Meier methods.

Results: In pediatric patients, the most commonly reported TEAEs were abdominal pain, decreased appetite, fatigue, nausea, somnolence, and vomiting; time to onset of TEAEs was significantly shorter for once-daily versus twice-daily dosing for all TEAEs ($P \leq .007$) and for fast versus slow titration for abdominal pain, decreased appetite, and somnolence (all P values $\leq .009$); duration of TEAEs with once-daily dosing was significantly longer for decreased appetite ($P = .001$) and nausea ($P = .041$); and more common in stimulant-naive patients versus patients with prior stimulant use were abdominal pain, decreased appetite, and fatigue ($P \leq .047$). In adult patients, the most commonly reported TEAEs (erectile dysfunction data were excluded) were nausea, insomnia, decreased appetite, urinary hesitation/urinary retention, and fatigue; insomnia had a significantly shorter time to onset and longer duration with twice-daily versus once-daily dosing ($P \leq .032$) and fast versus slow titration ($P \leq .007$).

Conclusions: Time to onset and resolution of TEAEs appear dependent on dosing schedule and titration speed. These findings can help to better manage tolerability issues and set appropriate expectations for clinicians and patients during atomoxetine titration, potentially improving treatment adherence and success.

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Attention-deficit/hyperactivity disorder (ADHD) is an early-onset, neurobehavioral disorder[1] that affects 3%–10% of school-age children in the United States.[2] One-third to two-thirds of children with ADHD are estimated to continue to have symptoms as adults.[2–6] Atomoxetine, a non-stimulant treatment for ADHD approved by the US Food and Drug Administration, is a selective inhibitor of the presynaptic norepinephrine transporter. The efficacy of atomoxetine for treating ADHD has been demonstrated in both acute and maintenance studies in children and adolescents when administered once daily[7–9] and twice daily.[10–12] In adults with ADHD, atomoxetine efficacy has been demonstrated in acute trials when administered once daily[13] and twice daily,[13,14] and sustained improvement of ADHD symptoms was demonstrated in two 6-month placebo-controlled trials when administered once daily.[15,16]

However, successful treatment of psychiatric disorders is hindered by poor adherence to medical treatment.[17,18] Among other factors, adherence is affected by a medication's profile of treatment-emergent adverse events (TEAEs).[19,20] Dosing schedule and rate of titration can affect tolerability.[2] Having a clearer understanding of what TEAEs to expect, when they might occur, and how long they might last as well as how to dose in the context of possible TEAEs could support clinicians in managing tolerability issues and in titrating medication with fewer TEAEs. Better informing patients about potential tolerability issues and helping them to set appropriate expectations would be expected to improve adherence.

Previous studies of atomoxetine tolerability have provided preliminary information regarding the effects of dosing schedule and titration speed on the incidence of TEAEs during treatment across multiple trials in the pediatric population,[21] as well as in a single adult trial[15]; however, the effects of these different approaches to dosing atomoxetine on the onset and duration of common TEAEs have not been fully determined.

The analyses presented here explored how characteristics (incidence, time to onset, and duration) of common TEAEs associated with atomoxetine in both pediatric and adult populations are affected by different dosing strategies (slow vs fast titration, once-daily vs twice-daily dosing, and previous stimulant exposure vs stimulant naïveté) in safety data from 22 pediatric[7–9,11,12,22–37] and 3 adult trials.[13,15,16] Specifically, these analyses provide data to better inform and aid clinicians in managing the dosing and titration of atomoxetine, in managing tolerability issues, and in setting appropriate expectations for patients, with the ultimate goal of improving treatment adherence and the overall quality of response.

Clinical Points

- In pediatric patients treated with atomoxetine, time to onset for common treatment-emergent adverse events (TEAEs) was shorter for once-daily versus twice-daily dosing and for fast versus slow titration. Time after onset to resolution was longer for once-daily versus twice-daily dosing for some TEAEs. Stimulant-naive patients experienced more TEAEs.
- In adult patients treated with atomoxetine, variation in TEAEs was limited to insomnia (shorter time to onset and longer duration with twice-daily dosing and fast titration of atomoxetine), decreased appetite (occurred only when atomoxetine was given once daily or with slow titration), and nausea (longer duration with slow titration).
- In patients who experience TEAEs during treatment with atomoxetine, it may be beneficial to change the dosing schedule from once daily to twice daily, fast to slow, and/or morning to evening.

METHOD

Data Sources

Atomoxetine clinical trial databases at Eli Lilly and Company were used to extract all data used in this study. Included in the analyses were all double-blind, randomized, and placebo-controlled pediatric trials sponsored by Eli Lilly and Company that were available at the time of data cutoff. For the adult dataset, all trials that included twice-daily and once-daily dosing or titration schedules with slow titration, low starting doses, or both were used. For both pediatric and adult datasets, results from all included trials were previously published individually. From an operational perspective, the individual trial datasets were merged to create a larger overall database to facilitate better analysis of safety information. For this article, we accessed this larger database and retrieved the necessary information.

Selection and Study Characteristics

Data were based on analyses of integrated safety data from 22 pediatric[7–9,11,12,22–37] and 3 adult trials[13,15,16] of atomoxetine (1998–2009) in patients with attention-deficit/hyperactivity disorder. The pediatric dataset comprised 2,287 atomoxetine patients and 1,334 placebo patients (age 6–18 years; study durations: 6 weeks to 17 months; atomoxetine dose range: 0.5 mg/kg/d to 3.0 mg/kg/d). The adult dataset comprised 678 atomoxetine patients and 424 placebo patients (age ≥ 18 years; study durations: 6 to 15 months; atomoxetine dose range: 25 mg/d to 100 mg/d). In pediatric patients, slow titration was defined as atomoxetine 0.5 mg/kg/d for 7 days, then atomoxetine 0.8 mg/kg/d for 7 days, followed by atomoxetine 1.2 mg/kg/d; fast titration was defined as atomoxetine 0.5 mg/kg/d for 7 days, followed by atomoxetine 1.2 mg/kg/d. In adult patients, slow titration was defined as atomoxetine 40 mg/d for 7 days followed by atomoxetine 80 mg/d; fast titration was defined as atomoxetine 40 mg/d for 3 days followed by atomoxetine 80 mg/d. All study protocols were approved by institutional review boards at each study site or country. After receiving a complete description of the study, all patients and/or their authorized legal representatives provided written informed consent before participation.

Elicitation of Treatment-Emergent Adverse Events

Treatment-emergent adverse events were collected by open-ended discussion at every patient visit in all included trials. In a subset of the pediatric trials, TEAEs were additionally collected with the Barkley Behavior and Adverse Events Questionnaire-Modified[38] at every visit.

Statistical Analysis

All patients who were randomized to atomoxetine or placebo and who received study drug were included in the analyses. Patient characteristics were summarized across treatment groups separately for pediatric and adult trials.

The proportions of patients experiencing TEAEs while taking placebo or atomoxetine were calculated and summarized separately for each TEAE. For the pooled pediatric data, TEAE rates are presented for the 6 most common adverse events experienced at least twice as often with atomoxetine compared with placebo in this meta-analysis or within the data presented in the atomoxetine package insert (abdominal pain, decreased appetite, fatigue, nausea, somnolence, and vomiting). These TEAEs were compared between subgroups of patients dosed using different approaches (twice-daily vs once-daily dosing, slow titration vs fast titration) as well as for subgroups with different histories of prior treatment (prior stimulant use vs stimulant naïveté) using a logistic regression with effects for subgroup, treatment, and a subgroup-by-treatment interaction. For the pooled adult data, TEAE rates for the most common TEAEs (based on the prescribing information and a high number of consumers and health care professionals who called the Lilly call center seeking information about these TEAEs: nausea, insomnia, decreased appetite, urinary hesitation and/or urinary retention, and fatigue) were examined in subgroups dosed and titrated differently. Erectile dysfunction is not discussed in this article, as it will be covered in an article more thoroughly discussing sexual TEAEs. Because of study design differences (1 adult study did not include placebo), comparisons of TEAE rates between dosing subgroups in adults were conducted via Fisher exact test based on only atomoxetine patient data.

Time to onset (defined as the number of days from randomized beginning of titration until the first occurrence of the adverse event) and time to resolution of the event (defined as the number of days from the start of the event until the last stop date) were summarized for different dosing/patient history subgroups using Kaplan-Meier methods, with median comparisons made via Wilcoxon signed rank tests. While all event onset times were observed, events that were ongoing at the time of study discontinuation were considered censored because it is unknown when or if the corresponding event resolved.

Table 1. Baseline Demographics[a]

	Adult Patients			Pediatric Patients		
Variable	Placebo (N = 424)	Atomoxetine (N = 678)	Total (N = 1,201)[b]	Placebo (N = 1,334)	Atomoxetine (N = 2,287)	Total (N = 3,621)
Age, y						
n	424	678	1,201	1,334	2,286	3,620
Mean (SD)	39.8 (8.8)	39.0 (8.6)	39.1 (8.8)	10.5 (2.4)	10.3 (2.5)	10.4 (2.5)
Gender						
n	424	678	1,201	1,334	2,286	3,620
Female, n (%)	228 (53.8)	304 (44.8)	570 (47.5)	283 (21.2)	472 (20.6)	755 (20.9)
Male, n (%)	196 (46.2)	374 (55.2)	631 (52.5)	1,051 (78.8)	1,814 (79.4)	2,865 (79.1)
Race						
n	423	678	1,201	1,297	2,247	3,544
White, n (%)	359 (84.7)	598 (88.2)	1,050 (87.4)	989 (76.3)	1,631 (72.6)	2,620 (73.9)
African, n (%)	3 (0.7)	2 (0.3)	5 (0.4)	97 (7.5)	159 (7.1)	256 (7.2)
Hispanic, n (%)	21 (5.0)	24 (3.5)	46 (3.8)	75 (5.8)	137 (6.1)	212 (6.0)
Asian, n (%)	32 (7.5)	42 (6.2)	79 (6.6)	100 (7.7)	267 (11.9)	367 (10.4)
Other, n (%)	9 (2.1)	12 (1.8)	21 (1.7)	36 (2.8)	53 (2.4)	89 (2.5)

[a]Includes only patients with treatment-emergent adverse events.
[b]Patients without an adverse event are only included in the overall sample size.
Abbreviations: N = total number of participants, n = number of patients in the specified category.

Table 2. Treatment-Emergent Adverse Events (TEAEs)[a]

Patients	Atomoxetine, n (%)	Placebo, n (%)	Total, n (%)	*P* Value[b]
Pediatric				
N	2,287	1,334	3,621	
Patients with ≥ 1 TEAE	1,697 (74.2)	827 (62.0)	2,524 (69.7)	< .001
Decreased appetite	467 (20.4)	68 (5.1)	535 (14.8)	< .001
Headache	431 (18.8)	199 (14.9)	630 (17.4)	.003
Abdominal pain upper	276 (12.1)	103 (7.7)	379 (10.5)	< .001
Nausea	259 (11.3)	62 (4.6)	321 (8.9)	< .001
Vomiting	248 (10.8)	75 (5.6)	323 (8.9)	< .001
Somnolence	213 (9.3)	42 (3.1)	255 (7.0)	< .001
Fatigue	202 (8.8)	51 (3.8)	253 (7.0)	< .001
Nasopharyngitis	144 (6.3)	82 (6.1)	226 (6.2)	.887
Cough	123 (5.4)	82 (6.1)	205 (5.7)	.334
Irritability	115 (5.0)	39 (2.9)	154 (4.3)	.003
Abdominal pain	109 (4.8)	31 (2.3)	140 (3.9)	< .001
Adult				
N	719	482	1,201	
Patients with ≥ 1 TEAE	661 (91.9)	391 (81.1)	1,052 (87.6)	< .001
Nausea	229 (31.9)	39 (8.1)	268 (22.3)	< .001
Insomnia	106 (14.7)	35 (7.3)	141 (11.7)	< .001
Decreased appetite	86 (12.0)	17 (3.5)	103 (8.6)	< .001
Urinary hesitation and/or retention	39 (5.4)	4 (0.8)	43 (3.6)	.025
Fatigue	93 (12.9)	40 (8.3)	133 (11.1)	.014

[a]Erectile dysfunction data were excluded.
[b]*P* Values are from Fisher exact test.
Abbreviations: N = total number of participants, n = number of patients in the specified category.

Statistical tests were performed at a 2-sided significance level of .05. All statistical analyses were performed using SAS software, version 9.1 (Cary, North Carolina).

RESULTS

Baseline demographics for all patients are shown in Table 1. Pediatric patients were predominantly male (atomoxetine, 79.4%; placebo, 78.8%) and white (atomoxetine, 72.6%; placebo, 76.3%), with a comparable mean age in both treatment groups (atomoxetine, 10.3 years; placebo, 10.5 years). In adult patients, a slightly higher percentage was male in the atomoxetine group (55.2% male; 44.8% female) versus placebo (46.2% male; 53.8% female); this was also true for white ethnicity (atomoxetine, 88.2%; placebo, 84.7%). Mean age in adults was comparable between the atomoxetine (39.0 years) and placebo (39.8 years) groups.

Treatment-emergent adverse events with an incidence of ≥ 5% in the pediatric or adult placebo or atomoxetine groups are shown in Table 2. Treatment-emergent adverse events that were significantly different between treatment groups had a higher incidence in patients in the atomoxetine groups.

In pediatric patients, TEAEs were similar to those seen in previous pediatric trials and were consistent with the prescribing information.[39] Rates of abdominal pain, fatigue, nausea, and somnolence were significantly greater for once-daily dosing versus twice-daily dosing ($P \leq .036$), with the reporting rates of abdominal pain and fatigue also being significantly greater with fast titration compared with slow titration ($P \leq .044$). Significantly more stimulant-naive patients reported abdominal pain, decreased appetite, and fatigue compared with patients who used stimulants previously ($P \leq .047$).

In adult patients, TEAEs were similar to those seen in previous adult trials[13,15,16] and consistent with the prescribing information.[39] The reporting rates for decreased appetite, nausea, and vomiting were significantly greater for once-daily dosing versus twice-daily dosing ($P \leq .037$). In contrast, insomnia occurred significantly more often with twice-daily versus once-daily dosing ($P < .001$) in the atomoxetine group. Additionally, rates of decreased appetite, vomiting, and urinary hesitation and/or retention were significantly larger for slow titration versus fast titration ($P \leq .027$), while insomnia occurred more frequently with fast titration versus slow titration ($P < .001$). No significant differences were observed in the frequency of any of the examined TEAEs between stimulant-naive patients and patients with prior stimulant use.

Table 3. Time Course of Treatment-Emergent Adverse Events: Onset and Resolution[a,b]

	Time to Onset[c]				Time After Onset to Resolution[d]			
Patients	N	Median, d	Range	*P* Value	N	Median, d	Range	*P* Value
Pediatric								
Abdominal pain								
Atomoxetine	408	8.0	1–86	.019	373	1.0	0–373	.015
Placebo	136	14.5	1–88		129	1.0	0–129	
Decreased appetite								
Atomoxetine	458	8.0	1–118	.940	321	27.0	1–891	<.001
Placebo	66	9.5	1–94		53	11.0	1–406	
Fatigue								
Atomoxetine	197	2.0	1–58	<.001	151	11.0	1–532	.807
Placebo	50	8.0	1–68		38	10.0	1–187	
Nausea								
Atomoxetine	256	7.5	1–95	.053	237	3.0	1–532	.017
Placebo	62	14.0	1–68		61	2.0	1–28	
Somnolence								
Atomoxetine	240	2.0	1–81	<.001	202	7.0	0–421	.232
Placebo	45	8.0	1–93		40	7.0	0–105	
Vomiting								
Atomoxetine	248	18.0	1–83	.097	243	1.0	1–320	.322
Placebo	75	25.0	1–99		75	1.0	1–18	
Adult								
Nausea								
Atomoxetine	224	4.0	1–198	.012	184	15.0	1–309	<.001
Placebo	38	13.0	1–139		36	3.5	1–120	
Insomnia								
Atomoxetine	135	7.0	1–193	.004	101	23.0	1–182	.745
Placebo	54	16.5	1–182		37	21.0	1–210	
Decreased appetite								
Atomoxetine	85	2.0	1–148	.226	46	39.0	1–270	.129
Placebo	17	5.0	1–43		14	25.0	1–181	
Urinary hesitation and/or retention								
Atomoxetine	38	3.5	1–66	.087	19	24.0	2–312	.590
Placebo	4	125.0	1–182		3	17.0	3–50	
Fatigue								
Atomoxetine	91	8.0	1–145	.404	56	27.0	1–226	.182
Placebo	40	14.5	1–162		30	17.0	2–173	

[a]Includes only patients with treatment-emergent adverse events.
[b]Erectile dysfunction data were excluded.
[c]Number of days from randomized beginning of titration until the first occurrence of the adverse event.
[d]Number of days from the start of the event until the last stop date.
Abbreviation: N = total number of participants.

The time courses of TEAE onset and resolution for the atomoxetine and placebo groups for both pediatric and adult patients are shown in Table 3. In pediatric patients, fatigue ($P<.001$) and somnolence ($P<.001$) had an earlier onset (days) and a similar time to resolution in the atomoxetine group versus the placebo group; abdominal pain had an earlier onset ($P=.019$) and longer time to resolution ($P=.015$) in the atomoxetine group compared with the placebo group. Time after onset to resolution for decreased appetite ($P<.001$) and nausea ($P=.017$) was significantly longer in the atomoxetine group compared with the placebo group in pediatric patients. In adult patients, time to onset of insomnia ($P=.004$) was significantly shorter in the atomoxetine group compared with the placebo group. Nausea had an earlier onset ($P=.012$) and longer time to resolution ($P<.001$) in the atomoxetine group compared with the placebo group in adults.

Time course of TEAEs as a function of once-daily versus twice-daily dosing is shown in Table 4 for both pediatric and adult patients. In pediatric patients, median time to onset of the evaluated TEAEs was shorter when atomoxetine was given once daily compared with twice daily ($P\leq.007$). Time after onset to resolution for decreased appetite ($P=.001$) and nausea ($P=.041$) was significantly longer when atomoxetine was given once daily versus twice daily. In adults, time to onset was longer for insomnia when atomoxetine was given once daily versus twice daily ($P=.001$). Time after onset to resolution for insomnia ($P=.032$) was significantly longer when atomoxetine was given twice daily versus once daily, and decreased appetite occurred only in adult patients given atomoxetine once daily.

Time course of TEAEs as a function of slow versus fast titration is shown in Table 5 for both pediatric and adult patients. In pediatric patients, time to onset was significantly longer for slow titration compared with fast titration for abdominal pain ($P<.001$), decreased appetite ($P=.009$), and somnolence ($P=.001$) (Table 5); time after onset to resolution was not significantly different between slow and fast titration for any of the measured TEAEs. In adults, time to onset of insomnia was shorter in patients on fast versus slow titration ($P=.002$). Time to resolution of nausea in adults was longer during slow versus fast titration ($P=.006$), and time to resolution of insomnia was longer during fast versus slow titration ($P=.007$). In adults, decreased appetite occurred only in patients with slow titration.

Time course for TEAEs was also compared in patients with prior stimulant exposure and those who were stimulant-naive (see Supplementary eTable 1 at PSYCHIATRIST.COM) for both pediatric and adult patients. Time to onset of somnolence was shorter in pediatric patients with prior stimulant exposure compared with stimulant-naive patients (median = 1 day vs 3 days, $P=.022$). Duration of nausea was shorter for pediatric patients with prior stimulant exposure compared with stimulant-naive patients (median = 2 days vs 3 days, $P=.001$). No significant differences ($P\geq.050$) between adult patients with prior stimulant exposure and those who were stimulant-naive were observed.

DISCUSSION

Presented here are the first extensive analyses examining onset and duration of common TEAEs (except erectile dysfunction) in pediatric and adult patients treated with atomoxetine. Onset and duration were compared for slow versus fast titration, once-daily versus twice-daily dosing, and previous stimulant exposure versus stimulant naïveté.

Time to onset and resolution of several common TEAEs in pediatric patients showed significant differences between dosing groups. The time to onset and duration of TEAEs appear to depend upon when the atomoxetine dose was

Table 4. Time Course of Treatment-Emergent Adverse Events: Once-Daily Versus Twice-Daily Dosing[a]

	Time to Onset[b]				Time After Onset to Resolution[c]			
Patients	N	Median, d	Range	*P* Value	N	Median, d	Range	*P* Value
Pediatric								
Abdominal pain								
Once daily	305	6.0	1–86	<.001	280	1.0	0–373	.866
Twice daily	184	17.0	1–85		170	1.0	0–200	
Decreased appetite								
Once daily	320	7.0	1–94	<.001	240	29.0	1–616	.001
Twice daily	164	15.5	1–118		109	18.0	1–891	
Fatigue								
Once daily	161	2.0	1–68	.003	127	10.0	1–532	.911
Twice daily	56	6.0	1–53		42	13.0	1–116	
Nausea								
Once daily	189	7.0	1–64	<.001	180	3.0	1–532	.041
Twice daily	90	16.5	1–95		85	2.0	1–35	
Somnolence								
Once daily	179	2.0	1–93	.007	159	8.0	0–421	.242
Twice daily	90	5.0	1–81		71	7.0	0–214	
Vomiting								
Once daily	172	15.0	1–99	<.001	170	1.0	1–320	.669
Twice daily	123	29.0	1–80		122	1.0	1–22	
Adult								
Nausea								
Once daily	203	5.0	1–198	.152	165	15.0	1–309	.454
Twice daily	21	2.0	1–68		19	12.0	1–65	
Insomnia								
Once daily	99	9.0	1–193	.001	77	20.0	1–182	.032
Twice daily	36	2.0	1–54		24	46.5	1–135	
Decreased appetite								
Once daily	85	2.0	1–148	…	46	39.0	1–270	…
Twice daily	0	0	0		0	0	0	
Urinary hesitation and/or retention								
Once daily	34	4.0	1–66	.228	17	24.0	2–312	.836
Twice daily	4	2.0	1–13		2	54.5	3–106	
Fatigue								
Once daily	82	8.5	1–145	.565	51	27.0	1–226	.816
Twice daily	9	7.0	1–56		3	17.0	5–113	

[a]Erectile dysfunction data were excluded.
[b]Number of days from randomized beginning of titration until the first occurrence of the adverse event.
[c]Number of days from the start of the event until the last stop date.
Abbreviation: N = total number of participants.
Symbol: … = not calculated.

given (once daily vs twice daily) and how quickly the titration occurred (fast vs slow).

Pediatric patients dosed once daily versus twice daily had an earlier onset of all TEAEs analyzed here. In this patient population, decreased appetite and nausea also had a longer duration with once-daily dosing, while the durations of all other TEAEs were not significantly different between the once-daily and twice-daily dosing subgroups. Pediatric patients undergoing fast titration of atomoxetine showed earlier onset of abdominal pain, decreased appetite, and somnolence. These results are similar to the results of a previous post hoc meta-analysis[21] of 5 trials in pediatric patients, which concluded that the risk of TEAEs within the first few weeks of treatment may be lower if patients are dosed twice daily and titrated to the total daily dose over the first week or more slowly. Additionally, whether a patient previously used stimulant treatment for ADHD appeared to affect TEAE expectations; patients with prior stimulant use experienced a shorter time to onset for somnolence, and stimulant-naive patients showed a longer time to resolution for nausea. Because no other studies have examined the effect of prior stimulant use on TEAEs in pediatric patients, our results highlight the potential impact of this historical context.

Somnolence has been associated with atomoxetine exposure in pediatric populations.[40–42] Similar to the preliminary pediatric meta-analysis,[21] the overall incidence of somnolence seen in the current analyses was higher among patients dosed once daily versus those dosed twice daily. Dosing on a once-daily versus twice-daily schedule, or titrating fast rather than slow resulted in an earlier onset of somnolence between 1 and 2 days. Pediatric patients previously treated with stimulants also had an earlier onset (1 to 2 days) of somnolence; this is noteworthy because in some of the included trials stimulant washout occurred within 24 to 48 hours of starting atomoxetine. As stimulant medications wear off, rebound sedation may occur. The duration of somnolence was not significantly different between stimulant-naive patients and patients with prior stimulant use. In a previous trial[3] comparing morning and evening dosing of atomoxetine in pediatric patients, both dosing methods decreased core ADHD symptoms and evening dosing produced fewer reports of somnolence. Therefore, in cases where sleepiness occurs during the morning, it may be appropriate to give the once-daily dose at bedtime or split the dose and give it twice daily.

With the exception of nausea and insomnia, the onsets and durations of TEAEs were not significantly different from placebo (although overall incidence rates were significantly higher) for adult patients treated with atomoxetine. In this patient population, insomnia had a shorter time to onset and longer time to resolution with twice-daily dosing ($P \leq .032$) and fast titration ($P \leq .007$). Based on this finding, it may be appropriate to administer atomoxetine once daily and use slower titration in adults; however, nausea had a longer time to resolution with slow titration ($P = .006$). In summary, time to onset and duration of both insomnia and nausea appear to depend upon when the atomoxetine dose was given (once daily vs twice daily) and how quickly the titration occurred (fast vs slow). The lack of a significant difference between dosing schedules and titration for all other TEAEs is similar to what has been seen in individual studies with adult ADHD patients.[13,15,16]

Limitations

This was a retrospective analysis of studies conducted over a range of time; differences in design between studies conducted earlier compared to those conducted later need to be considered. In earlier studies, patients were mostly dosed

Table 5. Time Course of Treatment-Emergent Adverse Events: Slow Versus Fast Titration[a]

	Time to Onset[b]				Time After Onset to Resolution[c]			
Patients	N	Median, d	Range	*P* Value	N	Median, d	Range	*P* Value
Pediatric								
Abdominal pain								
Slow	297	11.0	1–86	<.001	276	1.0	0–129	.394
Fast	207	6.0	1–85		189	2.0	0–373	
Decreased appetite								
Slow	265	10.0	1–118	.009	174	22.0	1–891	.396
Fast	233	7.0	1–94		179	27.0	1–532	
Fatigue								
Slow	134	4.0	1–68	.098	107	11.0	1–82	.317
Fast	94	2.0	1–58		70	13.0	1–532	
Nausea								
Slow	166	10.5	1–95	.183	151	2.0	1–163	.191
Fast	130	7.0	1–78		125	3.0	1–532	
Somnolence								
Slow	135	6.0	1–93	.001	111	7.0	0–421	.383
Fast	135	1.0	1–78		120	8.5	0–286	
Vomiting								
Slow	178	21.0	1–99	.088	173	1.0	1–93	.143
Fast	124	15.0	1–79		124	1.0	1–320	
Adult								
Nausea								
Slow	166	7.0	1–198	.072	130	21.0	1–309	.006
Fast	58	2.0	1–68		54	7.0	1–80	
Insomnia								
Slow	77	9.0	1–193	.002	59	17.0	1–182	.007
Fast	58	2.0	1–54		42	40.5	1–136	
Decreased appetite								
Slow	85	2.0	1–148	…	46	39.0	1–270	…
Fast	0	0	0		0	0	0	
Urinary hesitation and/or retention								
Slow	33	4.0	1–66	.063	17	24.0	2–312	.836
Fast	5	2.0	1–13		2	54.5	3–106	
Fatigue								
Slow	73	10.0	1–145	.219	47	27.0	1–226	.881
Fast	18	5.0	1–76		7	26.0	5–113	

[a]Erectile dysfunctional data were excluded.
[b]Number of days from randomized beginning of titration until the first occurrence of the adverse event.
[c]Number of days from the start of the event until the last stop date.
Abbreviation: N = total number of participants.
Symbol: … = not calculated.

twice daily, while later studies used predominantly once-daily dosing. Another potential limitation is that the studies examined here included both US patients and patients outside the United States; regional differences, therefore (eg, diet), may have influenced our results. In addition, while the pediatric population was large (22 studies), the adult population included patients from only 3 studies, therefore limiting our ability to definitively examine dosing strategies in adults. Finally, erectile dysfunction data were excluded from the current analyses.

Clinical Implications and Conclusions

Time to onset and time after onset to resolution for certain common TEAEs varied significantly depending on dosing schedule (once daily vs twice daily), titration (fast vs slow), and prior stimulant use in pediatric patients. The variation in TEAEs seen in adult patients was limited to insomnia (shorter time to onset and longer duration with twice-daily dosing and fast titration of atomoxetine), decreased appetite (occurred only when atomoxetine was given once daily or with slow titration), and nausea (longer duration with slow titration).

Given the findings above, in patients experiencing TEAEs, it may be beneficial to change the dosing schedule from once daily to twice daily, fast to slow, and/or morning to evening. The results of our analyses can provide guidance to both clinicians and patients in setting appropriate expectations related to tolerability and potentially minimize problems with adherence in the first few weeks of treatment. The clinical implications for pediatric patients include titrating atomoxetine slowly and using a twice-daily schedule when initiating treatment with atomoxetine. We observed distinct differences between pediatric and adult patients: insomnia seemed to show a stronger association with twice-daily dosing in adult patients compared with once-daily dosing. In adults, it may be appropriate to administer atomoxetine once daily and titrate slowly to minimize the occurrence of insomnia or delay its onset and shorten its duration, compared to dosing twice daily and fast titration. However, nausea and decreased appetite were more strongly associated with slow titration in adult patients, underlining the importance of individualized treatment strategies based on each patient's needs and priorities.

Drug names: atomoxetine (Strattera).
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Potential conflicts of interest: **Dr Ruff** is a full-time employee of Lilly USA. **Dr Allen** is an employee and stock shareholder of Eli Lilly and has received grant/research support from Eli Lilly. **Dr Greenhill** receives research support from Rhodes Pharmaceuticals and Shire and honoraria from the American Academy of Child and Adolescent Psychiatry. **Dr Newcorn** is a consultant for Alcobra, Eli Lilly, and Shire; receives research support from Eli Lilly, Shire, and Ortho-McNeill-Janssen; and is on the advisory boards of Alcobra, Biobehavioral Diagnostics, Neos, Shionogi, Shire, and Otsuka. **Ms Wietecha** is an employee and stock shareholder of Lilly USA.
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Supplementary Material

Article Title: Atomoxetine Tolerability in Patients Receiving Different Dosing Strategies

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List of Supplementary Material for the article

1. eTable 1 Time Course of Treatment-Emergent Adverse Events: Prior Stimulant use versus Stimulant Naïveté

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Supplementary eTable 1. Time Course of Treatment-Emergent Adverse Events: Prior Stimulant use versus Stimulant Naïveté

	Time-to-Onset (Days)				Time After Onset to Resolution (Days)			
Pediatric Patients	**N**	**Median**	**Range**	***P*-Value**	**N**	**Median**	**Range**	***P*-Value**
Abdominal pain								
Prior use	220	11.0	1-69	.171	200	1.0	0-200	.978
Never used	259	8.0	1-85		240	1.0	0-373	
Decreased appetite								
Prior use	189	7.0	1-94	.495	133	26.0	1-337	.877
Never used	281	9.0	1-118		194	22.0	1-891	
Fatigue								
Prior use	101	3.0	1-56	.692	82	12.5	1-300	.653
Never used	115	3.0	1-68		83	11.0	1-532	
Nausea								
Prior use	134	12.0	1-95	.054	126	2.0	1-91	.001
Never used	144	6.0	1-80		133	3.0	1-532	
Somnolence								
Prior use	118	1.0	1-81	.022	97	7.0	0-286	.272
Never used	135	3.0	1-93		117	10.0	0-421	
Vomiting								
Prior use	143	21.0	1-79	.271	140	1.0	1-27	.163
Never used	147	18.0	1-99		145	1.0	1-320	
	Time-to-Onset (Days)				**Time After Onset to Resolution (Days)**			
Adult Patients	**N**	**Median**	**Range**	***P*-Value**	**N**	**Median**	**Range**	***P*-Value**
Nausea								
Prior use	60	8.0	1-103	.212	50	12.0	1-159	.471
Never used	163	3.0	1-198		133	15.0	1-309	
Insomnia								
Prior use	45	7.0	1-150	.810	34	15.5	1-119	.164
Never used	90	6.5	1-193		67	28.0	1-182	
Decreased appetite								
Prior use	18	4.5	1-48	.147	11	19.0	4-210	.316
Never used	66	2.0	1-148		35	40.0	1-270	
Urinary hesitation and/or urinary retention								
Prior use	11	3.0	1-66	.961	6	11.0	2-312	.438
Never used	27	4.0	1-58		13	36.0	3-130	
Fatigue								
Prior use	27	5.0	1-62	.258	13	16.0	3-113	.050
Never used	64	12.5	1-145		41	29.0	1-226	

Abbreviations: N = total number of participants.