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ORIGINAL RESEARCH ARTICLE

Profile of Sexual and Genitourinary Treatment-Emergent Adverse Events Associated with Atomoxetine Treatment: A Pooled Analysis

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Abstract

Background Attention-deficit hyperactivity disorder (ADHD) is a neuropsychiatric disorder that begins in childhood. Atomoxetine is a selective inhibitor of the presynaptic norepinephrine transporter. Several studies have demonstrated the safety and efficacy of atomoxetine in the treatment of ADHD.

Objective The objective of this analysis was to provide additional information on the frequency, time to onset and time to resolution of sexual and genitourinary (GU) treatment-emergent adverse events (TEAEs) reported during atomoxetine treatment in clinical trials.

Methods Data from all adult atomoxetine placebo-controlled ADHD trials were pooled for this analysis, for a total of 3,314 patients (atomoxetine, $n = 1{,}738$; placebo, $n = 1{,}576$). Additionally, data from all adolescent patients (baseline age $\geq$13 to <18 years) within all ADHD placebo-controlled trials were pooled for analysis, for a total of 538 patients (atomoxetine, $n = 329$; placebo, $n = 209$). Rates of sexual and GU TEAEs were summarized by sex for each age group. Time to onset and resolution of sexual and GU TEAEs were summarized and compared using Kaplan–Meier methods.

Results Overall, the baseline characteristics of randomized patients in the atomoxetine and placebo groups were similar. Profiles of sexual and GU TEAEs for atomoxetine appeared clinically similar to placebo in female patients and in adolescent male patients. Adult male patients reported relatively more sexual and GU TEAEs when taking atomoxetine compared with placebo, with libido decreased (4.6 vs. 3.0 %), dysuria (3.7 vs. 1.5 %), urinary hesitation (6.9 vs. 2.4 %), urine flow decreased (2.5 vs. 0.6 %), ejaculation disorder (2.8 vs. 1.1 %) and erectile dysfunction (8.0 vs. 1.9 %) being the most common. The time to onset of the most common TEAEs in adult male patients tended to occur relatively early in dosing: within the first 2 weeks for GU TEAEs, and during the second and third week of dosing for erectile and ejaculation issues. The median time to resolution for these events ranged from around 3–8 weeks after event onset, depending on the event. While the common sexual and GU TEAEs showed numerically higher percentages of discontinuations in atomoxetine-treated patients compared with placebo, most incidences of the sexual and GU TEAEs were not considered severe.

Conclusions The sexual and GU TEAE profiles of patients taking atomoxetine were generally similar to those of patients taking placebo in the female and adolescent male populations, with greater frequency of TEAEs reported in adult males taking atomoxetine compared with placebo. The time to onset of the TEAEs tended to be shorter, and time to resolution tended to be longer in adult male patients treated with atomoxetine compared with those receiving placebo. The conclusions must be interpreted with caution because the TEAEs were likely underreported.

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1 Introduction

Attention-deficit hyperactivity disorder (ADHD) is a neuropsychiatric disorder that begins in childhood. The prevalence

in school-aged children in the US is estimated to be 3–7 % [1]. Of those children with ADHD, one- to two-thirds are estimated to continue to have symptoms as adults [2, 3]. The National Comorbidity Survey Replication of adults (18–44 years of age) estimated the prevalence of ADHD in adults to be 4.4 % in the US [4]. Fayyad et al. [5] reported the prevalence of ADHD in adults to be 3.4 % (range 1.2–7.3 %) in the Americas, Europe and the Middle East. In adults, ADHD is associated with impairments in time management, organization and goal-oriented activity, difficulties in relationships and poor motor vehicle driving performance, in addition to psychiatric comorbidities and substance abuse disorders [3, 6, 7].

Atomoxetine is a selective inhibitor of the presynaptic norepinephrine transporter. Several studies have demonstrated the tolerability and efficacy of atomoxetine for children and adolescents; they have not revealed any major issues with regard to safety [8–11]. The efficacy of atomoxetine for treating ADHD in adults was originally demonstrated in two placebo-controlled registration trials that examined its treatment effect on core ADHD symptoms (as described in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition) [12]. Two 6-month placebo-controlled trials in adults with ADHD further demonstrated the sustained improvement of ADHD with atomoxetine treatment [13, 14]. Additionally, atomoxetine treatment may continue to reduce ADHD symptoms over time in adults and children [12, 13, 15–17].

Atomoxetine appears to impair sexual function in some patients. The incidence of sexual adverse events reported by at least 2 % of adult patients taking atomoxetine in placebo-controlled trials included erectile dysfunction, dysmenorrhoea, ejaculation delayed/ejaculation disorder, libido decreased and irregular menstruation [18]. In most clinical trials, changes in sexual desire, sexual performance and sexual satisfaction have not been well studied because patients and physicians may be hesitant to discuss them. Consequently, the estimates of the incidence of sexual adverse events cited are likely to underestimate the actual incidence. There are no adequate, well-controlled studies examining sexual dysfunction with atomoxetine treatment.

Atomoxetine also appears to impair urinary function in some patients. The incidence of genitourinary (GU) adverse events reported by at least 2 % of adult patients taking atomoxetine in placebo-controlled trials included dysuria, urinary hesitation and urinary retention [18]. In two acute adult ADHD placebo-controlled trials the rates of urinary retention (1.7 %, 9/540) and urinary hesitation (5.6 %, 30/540) were increased among atomoxetine patients compared with placebo patients (0 %, 0/402, urinary retention; 0.5 %, 2/402, urinary hesitation) [18]. There are no studies specifically examining sexual dysfunction and GU adverse events with atomoxetine treatment. Pooled analysis of the limited existing data may provide further information on sexual and GU treatment-emergent adverse events (TEAEs) in atomoxetine-treated patients.

The primary objective of this analysis was to provide additional information on the frequency, time to onset and time to resolution of sexual and GU TEAEs reported during atomoxetine treatment in clinical trials.

2 Methods

In the present analysis we used the Eli Lilly and Company (Lilly) atomoxetine database and included patients from published and unpublished randomized clinical trials of atomoxetine that had been completed and analysed prior to September 2011. These analyses included all patients in the Lilly atomoxetine database who were enrolled in ADHD double-blind, placebo-controlled trials of atomoxetine (Strattera®, Indianapolis, IN, USA) [18] who were randomized to atomoxetine or placebo and received study drug. The studies involved several countries and varied from 10 weeks to 6 months in length. The number and frequency of visits varied, depending on the study. Data from all adult patients (defined as having a baseline age $\geq$18 years) were pooled for this analysis [a total of 3,314 patients (atomoxetine, $n = 1{,}738$; placebo, $n = 1{,}576$)]. Additionally, data from all adolescent patients (defined as having a baseline age $\geq$13 to $<$18 years) were pooled for analysis [a total of 538 patients (atomoxetine, $n = 329$; placebo, $n = 209$)]. As these are analyses across multiple studies (9 adult trials and 15 adolescent trials), the analyses presented here were defined well after study completion and are considered post hoc.

2.1 Measures

Summaries were made based on numbers of patients with treatment-emergent GU and/or sexual adverse events. Adverse events were elicited by non-probing inquiry at each visit and recorded regardless of perceived causality. The reporting of adverse events is comparable across trials since all Lilly trials follow a standard protocol for adverse event collection and reporting. A patient was said to have experienced a TEAE if he/she reported an adverse event after receiving study drug that either had not been experienced during the study baseline period or had been experienced in a milder form during the study baseline period. The adverse event terms recorded by site personnel were mapped and coded with Medical Dictionary for Regulatory Activities (MedDRA® v.12) dictionary terms.[1] A comprehensive list

[1] MedDRA® terminology is the medical terminology developed under the auspices of the International Conference on Harmonization of technical requirements for Registration of Pharmaceuticals for Human Use (ICH).

of all reported TEAEs was generated from the Lilly atomoxetine database. From this list, the medical reviewers selected all events that were deemed to belong to either GU or sexual categories. For each TEAE, the time to onset (defined as the number of days from the start of study drug to the start of the TEAE) and the time to resolution (defined as the number of days from the start of the TEAE until the event stopped) were calculated.

Patients were not prompted to report sexual and GU adverse events in clinical trials. Although sexual functioning was specifically assessed using the Arizona Sexual Experiences Scale in two randomized, double-blind, placebo-controlled trials in adults with ADHD [12], adverse events were not captured from this scale and this scale was not included in the current pooled analysis.

TEAEs were categorized (using a form) by the investigator at each study site. Investigators were asked to rate TEAEs as mild, moderate or severe based upon the discomfort, health risk, interference with activity or any combination of the three. While these ratings were subjective and most likely to be inconsistent across patients, they did allow for severity comparisons between groups and probably reflect what patients actually thought.

2.2 Statistical Analyses

Data from 9 adult clinical trials and 15 paediatric/adolescent clinical trials were pooled for this analysis. These analyses included all patients in the Lilly atomoxetine database who were randomized to atomoxetine or placebo and who had received study drug. Patient characteristics, including cytochrome P450 (CYP) 2D6 genotype, prior stimulant use and ADHD subtype were summarized across treatment groups. The proportion of patients experiencing treatment-emergent sexual or GU adverse events while taking placebo or atomoxetine were calculated separately for each adverse event for adult patients and adolescent patients, and a Fisher exact test was used for comparison. The proportion of severe adverse events and the proportion of events resulting in study discontinuation were similarly summarized; however, no formal statistical tests were performed as these comparisons would be likely to be significantly underpowered since underlying proportions were expected to be much lower than those reported overall. In general, all adult comparisons were at least 80 % powered to detect a twofold increase in incidence when the underlying placebo-reporting rate is 3.5 % or more.

Time to onset and resolution of sexual and GU TEAEs were summarized and compared using Kaplan–Meier methods. Time to onset is defined as the number of days from randomized dosing start until the first occurrence of the adverse event. Time to resolution is defined as the number of days from the start of event until the last stop date. For events that were ongoing at the time of study discontinuation, the time to resolution was considered to be no earlier than the duration of the event at the time of discontinuation within the Kaplan–Meier comparison of median time. Histograms summarizing the observed values are based on all available uncensored data.

Because many sexual and GU TEAEs are sex-specific, all summaries detailed above were compiled separately for male and female patients.

3 Results

3.1 Demographics

Patient demographics are shown in Table 1. The mean age of the adult patients was 36.5 years. Baseline characteristics of adult randomized patients in the atomoxetine and placebo groups were similar. Overall, of adult randomized patients, 44.2 % were female, the majority were Caucasian (73.7 %), they did not have previous stimulant use (71.8 %) and they presented with the combined subtype of ADHD (66.7 %). The mean age of the adolescent patients was 14.7 years. Baseline characteristics of adolescent randomized patients in the atomoxetine and placebo groups were similar. The majority of adolescent randomized patients were male (74.6 % placebo and 80.9 % atomoxetine), Caucasian (79.4 % placebo and 76.9 % atomoxetine) and had previous stimulant use (66.2 % placebo and 64.1 % atomoxetine). The adolescent randomized patients presented with a split of the inattentive subtype (50.8 % placebo and 45.9 % atomoxetine) and the combined subtype of ADHD (47.7 % placebo and 51.9 % atomoxetine). The percentage of CYP2D6 extensive metabolizers was higher than the percentage of poor metabolizers in adolescents (68.6 vs. 4.1 %) and adults (48.0 vs. 10.9 %). There was a large percentage of unknown status for both adolescents (26.6 %) and adults (41.0 %). Due to a large percentage of patients with unknown status, a subgroup analysis would not accurately represent the two populations.

3.2 Sexual and Genitourinary Treatment-Emergent Adverse Events (GU TEAEs)

The most commonly reported sexual and GU TEAEs for adults and adolescents in the atomoxetine and placebo groups are shown in Table 2 by System Organ Class (SOC), separately for male and female patients. Summary GU/sexual TEAE tables for male (Table 1) and female (Table 2) adults, and male (Table 3) and female (Table 4) adolescents are provided in the electronic supplementary

Table 1 Summary of demographic characteristics

Variable	Adult			Adolescent		
	Placebo ($N = 1,576$)	Atomoxetine ($N = 1,738$)	Total ($N = 3,314$)	Placebo ($N = 209$)	Atomoxetine ($N = 329$)	Total ($N = 538$)
Age (years)						
Mean (SD)	36.2 (10.5)	36.8 (10.4)	36.5 (10.4)	14.6 (1.2)	14.7 (1.3)	14.7 (1.3)
Range	17.6–67.5	18.2–76.7	17.6–76.7	13.0–17.9	13.0–18.0	13.0–18.0
Sex [n (%)]						
Female	696 (44.2)	769 (44.2)	1,465 (44.2)	53 (25.4)	63 (19.1)	116 (21.6)
	880 (55.8)	969 (55.8)	1,849 (55.8)	156 (74.6)	266 (80.9)	422 (78.4)
Race [n (%)]						
Caucasian	1,147 (72.8)	1,294 (74.5)	2,441 (73.7)	166 (79.4)	253 (76.9)	419 (77.9)
African	79 (5.0)	79 (4.5)	158 (4.8)	14 (6.7)	19 (5.8)	33 (6.1)
Hispanic	109 (6.9)	118 (6.8)	227 (6.8)	10 (4.8)	16 (4.9)	26 (4.8)
Native American	1 (0.1)	0 (0.0)	1 (0.0)	NA	NA	NA
Asian	219 (13.9)	223 (12.8)	442 (13.3)	15 (7.2)	37 (11.2)	52 (9.7)
Other	21 (1.3)	24 (1.4)	45 (1.4)	4 (1.9)	4 (1.2)	8 (1.5)
CYP2D6 genotype[a] [n (%)]						
EM	773 (49.0)	818 (47.1)	1,591 (48.0)	149 (71.3)	220 (66.9)	369 (68.6)
PM	183 (11.6)	178 (10.2)	361 (10.9)	14 (6.7)	8 (2.4)	22 (4.1)
Unknown	619 (39.3)	740 (42.6)	1,359 (41.0)	45 (21.5)	98 (29.8)	143 (26.6)
Error	1 (0.1)	2 (0.1)	3 (0.1)	NA	NA	NA
Intermediate	NA	NA	NA	1 (0.5)	3 (0.9)	4 (0.7)
Previous stimulant use [n (%)]						
No. of patients	1,572	1,734	3,306	201	304	505
No	1,131 (71.9)	1,244 (71.7)	2,375 (71.8)	68 (33.8)	109 (35.9)	177 (35.0)
Yes	441 (28.1)	490 (28.3)	931 (28.2)	133 (66.2)	195 (64.1)	328 (65.0)
ADHD subtype [n (%)]						
No. of patients	1,575	1,736	3,311	199	318	517
Combined	1,047 (66.5)	1,160 (66.8)	2,207 (66.7)	95 (47.7)	165 (51.9)	260 (50.3)
Hyperactive/impulsive	23 (1.5)	18 (1.0)	41 (1.2)	3 (1.5)	7 (2.2)	10 (1.9)
Inattentive	505 (32.1)	558 (32.1)	1,063 (32.1)	101 (50.8)	146 (45.9)	247 (47.8)

Percentages are based on the number of non-missing values in each group

ADHD attention-deficit hyperactivity disorder, *CYP* cytochrome P450, *EM* extensive metabolizers, *N* all randomized patients who took at least one dose of study drug; *n* number of patients in the specified category, *NA* not applicable, *PM* poor metabolizers, *SD* standard deviation

[a] Summary includes only PM and EM of atomoxetine. Patients with unknown, missing or other values were excluded

material. The rates of treatment-emergent events looked relatively similar between adolescent and adult female patients. Male adult patients reported relatively more sexual and GU adverse events when taking atomoxetine versus placebo. The most common TEAEs reported by male adults (occurring in at least 2 % of patients taking atomoxetine and more than in placebo) included libido decreased (4.6 vs. 3.0 %), dysuria (3.7 vs. 1.5 %), urinary hesitation (6.9 vs. 2.4 %), urine flow decreased (2.5 vs. 0.6 %), ejaculation disorder (2.8 vs. 1.1 %) and erectile dysfunction (8.0 vs. 1.9 %). Of these six common TEAEs, the only TEAE that was not statistically different between atomoxetine and placebo in adult males was libido decreased ($p = 0.069$). While these six TEAEs did occur more often in male adults taking atomoxetine, they were generally mild to moderate in severity, with only 0.4 % of male adults experiencing severe erectile dysfunction, 0.1 % experiencing severe urinary hesitation or decreased urine flow and 0.3 % experiencing severely decreased libido (Table 3). For some of the TEAEs, the percentage of severe TEAEs was similar between atomoxetine and placebo.

In adolescents there were no sexual adverse events falling into the category of psychiatric disorders (per MedDRA® classification) [libido decreased, orgasm abnormal, orgasm sensation decreased and premature ejaculation]

Table 2 Summary of the most common sexual and genitourinary treatment-emergent adverse events by SOC

MedDRA® SOC Adverse event (preferred term)	Male adult patients			Female adult patients		
	Atomoxetine $N = 969$ [*n* (%)]	Placebo $N = 880$ [*n* (%)]	*p*-value	Atomoxetine $N = 769$ [*n* (%)]	Placebo $N = 696$ [*n* (%)]	*p*-value
Psychiatric disorders sexual adverse events[a]	67 (6.9)	33 (3.8)		12 (1.6)	3 (0.4)	
Libido decreased	45 (4.6)	26 (3.0)	0.069	9 (1.2)	2 (0.3)	0.068
Renal and urinary disorders	193 (19.9)	68 (7.7)		19 (2.5)	17 (2.4)	
Dysuria	36 (3.7)	13 (1.5)	0.003	3 (0.4)	2 (0.3)	1.000
Urinary hesitation	67 (6.9)	21 (2.4)	<0.001	5 (0.7)	1 (0.1)	0.221
Urine flow decreased	24 (2.5)	5 (0.6)	0.001	1 (0.1)	0 (0)	1.000
Reproductive system and breast disorders	170 (17.5)	47 (5.3)		52 (6.8)	40 (5.8)	NA
Ejaculation disorder	27 (2.8)	10 (1.1)	0.012	NA	NA	NA
Erectile dysfunction	78 (8.0)	17 (1.9)	<0.001	NA	NA	NA
	Male adolescent patients			Female adolescent patients		
	Atomoxetine $N = 261$ [*n* (%)]	Placebo $N = 154$ [*n* (%)]	*p*-value	Atomoxetine $N = 62$ [*n* (%)]	Placebo $N = 52$ [*n* (%)]	*p*-value
Psychiatric disorders sexual adverse events[a]	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA
Renal and urinary disorders	3 (1.2)	3 (2.0)	0.675	2 (3.2)	0 (0)	0.499
Reproductive system and breast disorders	0 (0)	0 (0)	NA	4 (6.5)	3 (5.8)	1.000

MedDRA® Medical Dictionary for Regulatory Activities, *N* all randomized patients who took at least one dose of study drug, *n* number of patients in the specified category, *NA* not applicable, *SOC* System Organ Class

[a] Psychiatric disorders (SOC) sexual adverse events (preferred terms) included libido decreased, orgasm abnormal, orgasm sensation decreased and premature ejaculation

Table 3 Summary of the most common severe sexual and genitourinary treatment-emergent adverse events by SOC

MedDRA® SOC Adverse event (preferred term)	Overall		Adult male patients	
	Atomoxetine $N = 1,738$ [*n* (%)]	Placebo $N = 1,576$ [*n* (%)]	Atomoxetine $N = 969$ [*n* (%)]	Placebo $N = 880$ [*n* (%)]
Psychiatric disorders sexual adverse events[a]	7 (0.40)	4 (0.25)	5 (0.52)	3 (0.34)
Libido decreased	5 (0.29)	4 (0.25)	3 (0.31)	3 (0.34)
Renal and urinary disorders	8 (0.46)	8 (0.51)	8 (0.83)	5 (0.57)
Dysuria	1 (0.06)	1 (0.06)	1 (0.10)	1 (0.11)
Urinary hesitation	1 (0.06)	0 (0)	1 (0.10)	0 (0)
Urine flow decreased	1 (0.06)	0 (0)	1 (0.10)	0 (0)
Reproductive system and breast disorders	19 (1.09)	13 (0.82)	10 (1.03)	6 (0.68)
Ejaculation disorder	0 (0)	1 (0.06)	0 (0)	1 (0.11)
Erectile dysfunction	4 (0.23)	2 (0.13)	4 (0.41)	2 (0.23)

MedDRA® Medical Dictionary for Regulatory Activities, *N* all randomized patients who took at least one dose of study drug, *n* number of patients in the specified category, *SOC* System Organ Class

[a] Psychiatric disorders (SOC) sexual adverse events (preferred terms) included libido decreased, orgasm abnormal, orgasm sensation decreased, and premature ejaculation

Table 4 Summary of the most common sexual and genitourinary treatment-emergent adverse events for adult male patients resulting in discontinuation

Adverse event (MedDRA® preferred term)	Atomoxetine $N = 969$ [*n* (%)]	Placebo $N = 880$ [*n* (%)]
Erectile dysfunction	12 (1.24)	3 (0.34)
Urinary hesitation	6 (0.62)	3 (0.34)
Libido decreased	3 (0.31)	1 (0.11)
Ejaculation disorder	3 (0.31)	1 (0.11)
Dysuria	2 (0.21)	0 (0)
Urine flow decreased	2 (0.21)	0 (0)

N all randomized patients who took at least one dose of study drug, *n* number of patients in the specified category

(Table 2). There were a few renal and urinary disorders in adolescents (male: atomoxetine 1.2 %, placebo 2.0 %; female: atomoxetine 3.2 %, placebo 0.0 %). The percentage of reproductive system and breast disorders in female adolescents (atomoxetine 6.5 %, placebo 5.8 %) was similar to that reported in female adults.

The majority of sexual and GU TEAEs leading to discontinuation were in men. A summary of the most common sexual and GU TEAEs resulting in discontinuation for all adult male patients in the atomoxetine and placebo groups is shown in Table 4. The common sexual and GU TEAEs resulted in a higher percentage of discontinuations in atomoxetine-treated patients compared with placebo. The only GU or sexual TEAE leading to discontinuation in women was pollakiuria (frequent urination) [$n = 1$, 0.13 % atomoxetine; $n = 0$ placebo].

3.3 Onset and Duration

The median time to onset of the most common sexual and GU TEAEs in adult male patients are summarized in Table 5. In general, these events tended to occur relatively early in dosing, with median times of onset for atomoxetine patients occurring within the first 2 weeks for GU TEAEs, and during the second and third week of dosing for erectile and ejaculation issues. The median time to resolution of the most common sexual and GU TEAEs in adult male patients are summarized in Table 6. Median times to resolution for these events ranged from around 3–8 weeks depending on the event. The distributions of time to onset and time to resolution for the six most common sexual and GU TEAEs in all atomoxetine-treated adult male patients are shown in Fig. 1.

4 Discussion

4.1 Mechanism of Action

The mechanism of action for atomoxetine for treatment efficacy in ADHD has not been established, although it is thought to be a selective inhibitor of the presynaptic norepinephrine transporter [8]. In rats, atomoxetine hydrochloride selectively inhibits presynaptic norepinephrine reuptake, resulting in increased synaptic norepinephrine [19]. Atomoxetine has relatively low affinity for serotonin and dopamine uptake processes [20–24]. The increase in GU TEAEs with atomoxetine may be due to the non-selective peripheral effect on the adrenergic nerve endings on the smooth muscle cells in both the urethral sphincter and the arteries [25, 26].

Table 5 Summary of median time to onset (in days) of the most common sexual and genitourinary treatment-emergent adverse events for adult male patients

Adverse event (MedDRA® preferred term)	Atomoxetine				Placebo			
	N	Mean	Median	SD	N	Mean	Median	SD
Libido decreased	44	28.2	15.5	45.4	25	57.2	42.0	48.0
Dysuria	34	23.2	11.0	32.4	12	100.3	97.0	79.1
Urinary hesitation	66	15.2	6.5	19.8	21	137.4	163.0	61.2
Urine flow decreased	23	10.7	4.0	14.0	5	104.8	104.0	64.9
Ejaculation disorder	27	31.4	19.0	38.9	10	129.1	105.5	68.5
Erectile dysfunction	77	24.6	8	39.4	17	66.9	53.0	53.7

N number of patients reporting this adverse event, *SD* standard deviation

Table 6 Summary of median time to resolution (in days) of the most common sexual and genitourinary treatment-emergent adverse events for adult male patients

Adverse event (MedDRA® preferred term)	Atomoxetine				Placebo			
	N	Mean	Median	SD	N	Mean	Median	SD
Libido decreased	24	63.1	52.0	46.4	12	43.3	36.5	29.4
Dysuria	23	34.1	24.0	27.5	7	18.1	7.0	22.3
Urinary hesitation	28	56.7	42.5	62.5	9	42.3	38.0	32.9
Urine flow decreased	10	51.8	44.5	37.5	3	52.0	52.0	50.0
Ejaculation disorder	18	27.3	22.0	25.7	6	24.3	11.5	26.2
Erectile dysfunction	45	49.4	28.0	55.3	7	17.6	15.0	10.1

N number of patients reporting this adverse event, *SD* standard deviation

4.2 Sexual and GU TEAEs

Sexual and GU TEAEs occurred in a higher percentage of atomoxetine-treated male patients compared with placebo-treated male patients. The time to onset of sexual and GU TEAEs tended to be shorter, and the time to resolution tended to be longer, in male patients treated with atomoxetine compared with those receiving placebo. If patients and physicians are aware of the average time of onset and the average duration for these sexual and GU TEAEs they may be better able to manage them and remain compliant with their treatments.

In adolescents there were no sexual TEAEs and only a few GU TEAEs reported. Sexual and GU TEAEs did not appear to be a significant concern in adolescents in this study. However, the underreporting of sexual TEAEs in adolescents (post-pubescent) [27] could contribute to the difference in sexual TEAEs reported between adult and adolescent (post-pubescent) males. The difference in frequency of sexual and GU TEAEs between older and younger patients may also be due to the aging process, since these TEAEs may increase with normal aging.

Female adolescents and female adults showed similar rates of reproductive system and breast disorders. In these analyses, female adults had lower percentages of TEAEs compared with male adults.

Sexual TEAEs have been reported with other ADHD treatments. Methylphenidate HCl extended release [US Package Insert (USPI)] [28] reported libido decreased ($\geq$1 % of adults) and erectile dysfunction (<1 %). Lisdexamfetamine (USPI) [29] adverse reactions were reported at a rate of less than 2 % in adults and included decreased libido and erectile dysfunction. Patients using dextroamphetamine and amphetamine salts [30] reported impotence and changes in libido. In addition, sexual and GU TEAEs have been reported with reboxetine, a drug with a mechanism of action similar to that of atomoxetine that is approved in Europe for the acute treatment of depressive illness/major depression [31]. Reboxetine (UK Summary of Product Characteristics) [31] reports GU (urinary hesitancy, sensation of incomplete bladder emptying, urinary tract infection) and sexual (erectile dysfunction, ejaculatory pain, ejaculatory delay, testicular disorder-primarily pain) TEAEs in the label from adult trials. The similar mechanism of action of atomoxetine and reboxetine and the similar reports of sexual and GU TEAEs with these compounds might suggest that a similar mechanism of action contributes to the GU and sexual TEAEs.

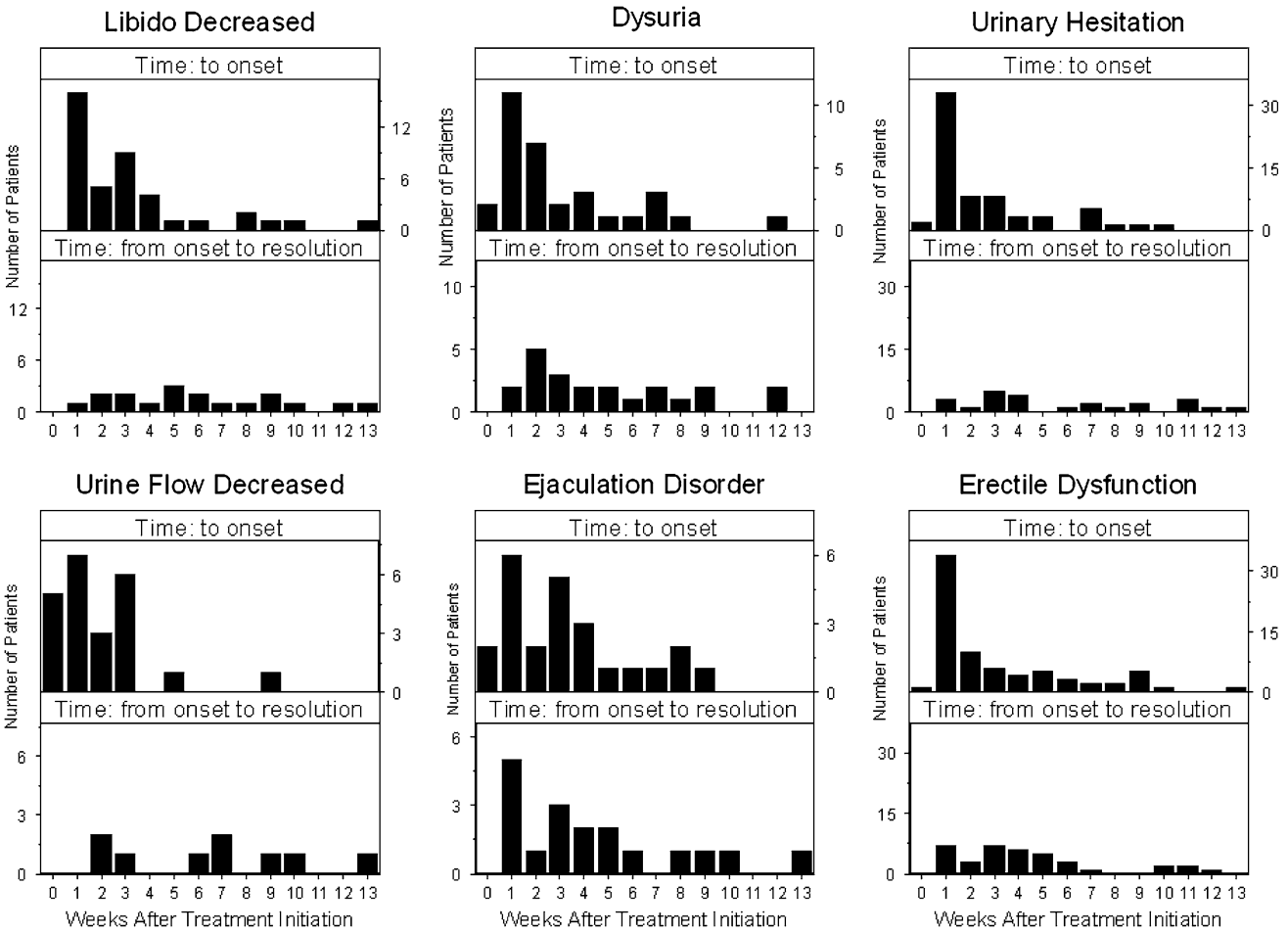

Fig. 1 Time to onset and duration of the most common sexual and GU TEAEs in adult male patients. Histograms of the time to onset and duration of the most common sexual and GU TEAEs in adult male patients within placebo-controlled atomoxetine trials; libido decreased, dysuria, urinary hesitation, urine flow decreased, ejaculation disorder and erectile dysfunction. Because few observations occurred after 13 weeks, the x-axes were restricted to 13 weeks. *GU* genitourinary, *TEAEs* treatment-emergent adverse events

4.3 Limitations

The findings of this post hoc study are limited by several factors. This post hoc analysis is limited by the nature of adverse event reporting. Adverse event reporting is dependent on patient recall and is generally not reported well. In addition, patients and physicians may be reluctant to discuss sexual adverse events and therefore these adverse events can be underreported. Most of the studies in this analysis did not specifically investigate sexual adverse events, which may also contribute to the underreporting of sexual adverse events. No formal statistical tests were performed on the proportion of severe adverse events and the proportion of events resulting in study discontinuation; these comparisons would be likely to be significantly underpowered since underlying proportions were expected to be much lower than those reported overall.

5 Conclusion

A greater frequency of sexual and GU TEAEs was reported in adult males taking atomoxetine compared with those taking placebo. The time to onset of the TEAEs tended to be shorter, and time to resolution tended to be longer in adult male patients treated with atomoxetine compared with those receiving placebo. The sexual and GU TEAE profiles of patients taking atomoxetine were generally similar to those of patients taking placebo in the adult female and adolescent male and female populations. If patients and physicians are aware of the average time of onset and the average duration for these sexual and GU TEAEs they may be better able to manage them and remain compliant with their treatment.

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Conflicts of interest The authors contributed to the study concept and design; collection, analysis, and interpretation of data; preparation of the manuscript; and decision to publish the data. Dr Camporeale, Mrs Day, Dr Ruff and Dr Kelsey are full-time employees of, and minor stockholders in, Eli Lilly and Company. Dr Arsenault and Mr Williams are full-time employees of inVentiv Health Clinical. Dr Arsenault is also a former employee of, and minor stockholder in, Eli Lilly and Company.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed, text revision. Washington, DC: American Psychiatric Press; 2000.
2. Wender PH, Wolf LE, Wasserstein J. Adults with ADHD: an overview. Ann N Y Acad Sci. 2001;931:1–16.
3. Wilens TE, Dodson W. A clinical perspective of attention-deficit/hyperactivity disorder into adulthood. J Clin Psychiatry. 2004;65(10):1301–13.
4. Kessler RC, Coccaro EF, Fava M, et al. The prevalence and correlates of DSM-IV intermittent explosive disorder in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2006;63(6):669–78.
5. Fayyad J, De Graaf R, Kessler R, et al. Cross-national prevalence and correlates of adult attention-deficit hyperactivity disorder. Br J Psychiatry. 2007;190:402–9.
6. Kessler RC, Adler L, Barkley R, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. Am J Psychiatry. 2006;163(4):716–23.
7. Barkley RA. Major life activity and health outcomes associated with attention-deficit/hyperactivity disorder. J Clin Psychiatry. 2002;63(Suppl. 12):10–5.
8. Michelson D, Faries D, Wernicke J, et al. Atomoxetine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled, dose-response study. Pediatrics. 2001;108(5):E83.
9. Michelson D, Allen AJ, Busner J, et al. Once-daily atomoxetine treatment for children and adolescents with attention deficit hyperactivity disorder: a randomized, placebo-controlled study. Am J Psychiatry. 2002;159(11):1896–901.
10. Allen AJ, Kurlan RM, Gilbert DL, et al. Atomoxetine treatment in children and adolescents with ADHD and comorbid tic disorders. Neurology. 2005;65(12):1941–9.
11. Kelsey DK, Sumner CR, Casat CD, et al. Once-daily atomoxetine treatment for children with attention-deficit/hyperactivity disorder, including an assessment of evening and morning behavior: a double-blind, placebo-controlled trial. Pediatrics. 2004;114(1):e1–8.
12. Michelson D, Adler L, Spencer T, et al. Atomoxetine in adults with ADHD: two randomized, placebo-controlled studies. Biol Psychiatry. 2003;53(2):112–20.
13. Adler LA, Spencer T, Brown TE, et al. Once-daily atomoxetine for adult attention-deficit/hyperactivity disorder: a 6-month, double-blind trial. J Clin Psychopharmacol. 2009;29(1):44–50.
14. Young JL, Sarkis E, Qiao M, et al. Once-daily treatment with atomoxetine in adults with attention-deficit/hyperactivity disorder: a 24-week, randomized, double-blind, placebo-controlled trial. Clin Neuropharmacol. 2011;34(2):51–60.
15. Durell T, Adler L, Wilens T, et al. Atomoxetine treatment for ADHD: younger adults compared with older adults. J Atten Disord. 2010;13(4):401–6.
16. Wietecha LA, Williams DW, Herbert M, et al. Atomoxetine treatment in adolescents with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2009;19(6):719–30.
17. Adler LA, Liebowitz M, Kronenberger W, et al. Atomoxetine treatment in adults with attention-deficit/hyperactivity disorder and comorbid social anxiety disorder. Depress Anxiety. 2009;26(3):212–21.
18. Strattera® (atomoxetine). US prescribing information. Indianapolis: Eli Lilly and Company; 2011.
19. Bymaster FP, Katner JS, Nelson DL, et al. Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity disorder. Neuropsychopharmacology. 2002;27(5):699–711.
20. Bolden-Watson C, Richelson E. Blockade by newly-developed antidepressants of biogenic amine uptake into rat brain synaptosomes. Life Sci. 1993;52(12):1023–9.
21. Tatsumi M, Groshan K, Blakely RD, et al. Pharmacological profile of antidepressants and related compounds at human monoamine transporters. Eur J Pharmacol. 1997;340(2–3):249–58.
22. Gehlert DR, Schober DA, Gackenheimer SL. Comparison of (R)-[3H]tomoxetine and (R/S)-[3H]nisoxetine binding in rat brain. J Neurochem. 1995;64(6):2792–800.
23. Wong DT, Threlkeld PG, Best KL, et al. A new inhibitor of norepinephrine uptake devoid of affinity for receptors in rat brain. J Pharmacol Exp Ther. 1982;222(1):61–5.
24. Wilens TE. Mechanism of action of agents used in attention-deficit/hyperactivity disorder. J Clin Psychiatry. 2006;67(Suppl. 8):32–8.
25. Sumner CR, Schuh KJ, Sutton VK, et al. Placebo-controlled study of the effects of atomoxetine on bladder control in children with nocturnal enuresis. J Child Adolesc Psychopharmacol. 2006;16(6):699–711.
26. Viktrup L, Pangallo BA, Detke MJ, et al. Urinary side effects of duloxetine in the treatment of depression and stress urinary incontinence. Prim Care Companion J Clin Psychiatry. 2004;6(2):65–73.
27. Scharko AM. Selective serotonin reuptake inhibitor-induced sexual dysfunction in adolescents: a review. J Am Acad Child Adolesc Psychiatry. 2004;43(9):1071–9.
28. CONCERTA® (methylphenidate HCl) extended-release tablets CII. US prescribing information. Titusville: Ortho-McNeil-Janssen Pharmaceuticals; 2010.
29. Vyvanse (lisdexamfetamine dimesylate) capsule. US prescribing information. Wayne: Shire LLC; 2012.
30. Adderall (dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate and amphetamine sulfate) tablet. US prescribing information. Wayne: Shire US Inc.; 2006.
31. Edronax (reboxetine) 4 mg tablets: summary of product characteristics. Kent: Pharmacia Limited; 2011.