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ORIGINAL INVESTIGATION

Efficacy and safety of atomoxetine for attention-deficit/hyperactivity disorder in children and adolescents—meta-analysis and meta-regression analysis

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Abstract
Objectives The objective of this study was to evaluate the efficacy and safety of atomoxetine in children and adolescents.
Materials and methods We searched for studies published between 1985 and 2006 through Medline, PubMed, PsychInfo and Cochrane Central Register of Controlled Trials (CENTRAL 2006 Issue 3) using keywords related to atomoxetine and attention-deficit/hyperactivity disorder (ADHD) and scanned though reference lists. We included nine randomized placebo-controlled trials (atomoxetine: placebo=1,150:678).
Results Atomoxetine was superior ($p<0.01$) to placebo in reducing ADHD symptoms across different scales (Attention-Deficit/Hyperactivity Disorder Rating Scale-IV, Conners' Parent and Teacher Rating Scales-Revised:Short Form, Clinical Global Impression-Severity) rated by different raters (parent, teacher, clinician). The number-needed-to-treat (NNTs) for treatment response and relapse prevention were 3.43 (95% CI, 2.79–4.45) and 10.30 (95% CI, 5.89–40.62), respectively. High baseline ADHD symptoms ($p=0.02$) was associated with greater reduction in ADHD symptoms, whereas male gender ($p=0.02$), comorbid oppositional defiant disorder (ODD) status ($p=0.01$) and ADHD hyperactive/impulsive subtype ($p=0.01$) were associated with smaller reductions. The commonest adverse events were gastrointestinal [appetite decrease, number-needed-to-harm (NNH)=8.81; abdominal pain, NNH=22.48; vomiting, NNH=29.96; dyspepsia, NNH=49.38] and sleep related (somnolence, NNH=19.41). Young age ($p=0.03$) and high baseline hyperactive/impulsive symptoms ($p<0.01$) were associated with more adverse events, whereas ADHD inattentive subtype ($p=0.04$) was associated with less adverse events. Quality of life using Child Health Questionnaire (CHQ) improved ($p<0.01$) with atomoxetine treatment. Both ADHD and ODD symptoms ($p<0.01$) were reduced in comorbid ADHD+ODD, and ODD status was not associated with more adverse events. Efficacy and side effects were not altered by comorbid general anxiety disorder or major depression.
Conclusions Atomoxetine is efficacious in reducing ADHD symptoms. It may have a role in treating comorbid ODD or depression, and probably in comorbid anxiety.

Keywords Atomoxetine · Efficacy · Side effects · Meta-analysis · Meta-regression

Abbreviations

ADHD	attention-deficit/hyperactivity disorder
OR	odds ratio
NNH	number-needed-to-harm
NNT	number-needed-to-treat

Introduction

Atomoxetine[1] (formerly known as tomoxetine) is a new drug approved by the Food and Drug Administration (FDA) of the USA (in 2002) and various national drug

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[1] Drug name: Generic name (Trade name): Atomoxetine (Strattera)

regulatory agencies (UK in 2004) for the treatment of attention-deficit/hyperactivity disorder (ADHD). It is the first non-stimulant drug approved for ADHD treatment and also the first drug approved for treatment of ADHD in adult patients. It is a selective presynaptic norepinephrine reuptake inhibitor originally developed as an antidepressant. The FDA updated the labelling of atomoxetine with bold warnings about its potential for severe liver injury (US Food and Drug Administration, available at http://www.fda.gov/medwatch/SAFETY/2004/Strattera_PI.pdf, accessed May 2007), based on a teenager and an adult who were treated for several months and who recovered after discontinuation of the drug. Since then three children were reported to develop hepatitis after atomoxetine treatment (Lim et al. 2006; Stojanovski et al. 2007).

Previous pooled analyses (Kratochvil et al. 2006, Wilens et al. 2006) found atomoxetine to be superior to placebo in reducing ADHD symptoms in children and adolescents. As the results from relapse-prevention trials are now available, we aimed to quantify the efficacy (in standardised mean difference, SMD, and number-needed-to-treat, NNT; see "Materials and methods") of atomoxetine in achieving relapse prevention and (as previously reported) treatment response and to identify patient characteristics associated with higher drug efficacy. As the side effects profile is also important in the clinical choice of drug and dosage, we aimed to quantify the side effects in number-needed-to-harm (NNH; see "Materials and methods") and to identify patient characteristics associated with higher side effects.

Oppositional defiant disorder (ODD) is the most common comorbid condition in ADHD, and it affects 30–60% of children with ADHD (Biederman et al. 1991; Goldman et al. 1998; Jensen et al. 2001). At present, no medication is approved for the treatment of ODD, and behavioural interventions are the mainstay of treatment. Laboratory studies (Bymaster et al. 2002) in rodents suggest that atomoxetine increases dopamine and norepinephrine release in the prefrontal cortex, a mechanism similar to methylphenidate, but it does not increase dopamine in the striatum or nucleus accumbens. As the latter sites of the brain are involved in substance abuse and are not affected by atomoxetine, this drug appears an attractive alternative in children with comorbid conduct disorder at risk of substance abuse (Wilens et al. 2006). In this study, we aimed to investigate the efficacy of atomoxetine in reducing ADHD and ODD symptoms in children with comorbid ADHD and ODD. Anxiety and depressive disorders are common comorbidities in ADHD (25 and 15–75%, respectively; Biederman et al. 1991). Children with comorbid ADHD and anxiety are reported to experience less behavioural response (Taylor et al. 1987; Pliszka 1989), develop tics and dysphoric symptoms (Tannock and Schachar 1992), and have less improvements in working memory (Tannock et al. 1995) with methylphenidate treatment, although other studies found methylphenidate to be useful (Livingstone et al. 1990; Tannock et al. 1995), and others found no differential response in either comorbid status (Diamond et al. 1999; The MTA Cooperative Group 1999). No study has compared efficacy of stimulants in ADHD children with and without depressive disorder, but antidepressants are widely accepted to be useful in the treatment of comorbid depression in ADHD (Pliszka 1998). We aimed to investigate the efficacy and safety of atomoxetine in reducing ADHD symptoms in these subgroups.

Children with ADHD often have academic (Faraone et al. 2001; Todd et al. 2002), family (Johnston and Mash 2001) and social difficulties (Bagwell et al. 2001; Greene et al. 2001; Maedgen and Carlson 2000), and improvement in quality of life (QoL) is a desirable quality of any ADHD treatment. Atomoxetine has been reported to be associated with improvements in QoL after treatment (Perwien et al. 2004), and we aimed to use pooled data to investigate these findings.

This paper aims to: (1) quantify (in SMDs and NNTs) the efficacy of atomoxetine in achieving treatment response and relapse prevention and identify patient characteristics associated with higher drug efficacy, (2) to quantify (in NNHs) the adverse events of atomoxetine and to identify patient characteristics associated with more adverse events, (3) to investigate the efficacy and safety of atomoxetine in ADHD comorbid with ODD, anxiety and depressive disorders and (4) to evaluate the effect of atomoxetine on QoL measures after treatment.

Materials and methods

We searched for published trials on atomoxetine and attention-deficit/hyperactivity disorder (ADHD) published between January 1985 to September 2006, through Medline, PubMed, PsychInfo and Cochrane Central Register of Controlled Trials (CENTRAL 2006 Issue 3) and scanned though reference lists. We used two search terms for atomoxetine ("atomoxetine" and "tomoxetine"), five terms for ADHD ("attention-deficit/hyperactivity disorder", "ADHD", "minimal brain dysfunction", "hyperkinetic disorder" and "attention-deficit"), and used the "AND" search string to narrow down the search to overlapping studies. Whole texts were retrieved and read.

Inclusion and exclusion criteria for atomoxetine trials

Studies were included if they fulfilled the following inclusion criteria: (1) study design was randomized, placebo-controlled trial (RCT); (2) atomoxetine was used to treat attention-deficit/hyperactivity disorder of any subtype; (3) atomoxetine

(single dose or different doses) was compared to placebo; (4) study was conducted in children and adolescents; (5) efficacy outcomes were assessed with validated Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV; DuPaul et al. 1998); and (6) adverse events, withdrawals or dropouts were reported.

We excluded studies that did not provide enough written data for our calculations.

Data extraction

Data were extracted according to a fixed protocol: author, year of study, number of study subjects (atomoxetine-treated, placebo-treated), number of study sites, duration of study, age range of study subjects, percentages of ADHD subtypes, percentages of comorbidities, dosages of atomoxetine (fixed, variable, optimum), baseline efficacy measure scores, posttreatment improvement in efficacy measure scores, number of each reported adverse event, number of withdrawals or dropouts, mean final dosages of treatment, duration of treatment, and percentages of subjects discontinued due to adverse events. Information was noted and described herein as such if inadequate data were given.

Two of the investigators (C.J. and K.J.) independently rated and extracted data from each study, and any disagreements were resolved through discussion to obtain a consensus before including data in the analysis.

Quality assessment

Atomoxetine randomized placebo-controlled trials (Table 1) were assessed for methodological quality using the instrument published by Jadad et al. Each study was given a score from 0 to 5, according to randomization (+2), double-blinding (+2) and withdrawals or dropouts (+1), and higher scores indicate better methodological quality.

Efficacy and QoL measures

The primary efficacy measures were ADHD-RS-IV Total, Inattentive symptom and Hyperactive/impulsive symptom scores. The ADHD-RS-IV was chosen because our preliminary search identified it as the most commonly used assessment instrument in atomoxetine trials, and it was specified as one of our inclusion criteria. Other ("secondary") efficacy measures included Conners' Parent and Teacher Rating Scales-Revised:Short Form (CPRS-R:S and CTRS-R:S; Conners 1997), and the Clinical Global Impression-Severity (CGI-S; Guy 1976). The Oppositional Index on the CPRS-R:S was used to assess ODD symptoms. We included different instruments to give us different perspectives from the raters, which included the parents (CPRS-R:S), teachers (CTRS-R:S) and the clinicians (ADHD-RS-IV and CGI-S).

We used the psychosocial summary score on the parent-administered Child Health Questionnaire (CHQ; Landgraf et al. 1996) as our QoL and functional outcome measure.

Statistical analysis for efficacy and QoL measures

To establish the efficacy of atomoxetine compared to placebo in reducing ADHD symptoms and improving QoL, a set of meta-analyses (Table 2) was performed on atomoxetine randomized placebo-controlled trials involving ADHD+/-ODD subjects (Table 1). To investigate the efficacy of atomoxetine compared to placebo in reducing ADHD and ODD symptoms, we performed another set of meta-analyses (Table 3) on atomoxetine RCTs that included only comorbid ADHD+ODD subjects (Table 1).

Results on posttreatment improvements were standardized using Glass's Δ, which adjusted the effect sizes by the standard deviation of the placebo group, to derive standardized mean differences (SMDs). This method was

Table 1 Quality appraisal of included studies

	Randomization		Double blinding		Withdrawal and dropouts	Total score
	Yes?	Appropriate?	Yes?	Appropriate?	Yes?	
ADHD+/−ODD						
Buitelaar et al. 2006	+1	+1	+1	+1 (Placebo)	+1	5
Kelsey et al. 2004	+1	0	+1	+1 (Placebo)	+1	4
Michelson et al. 2001	+1	+1	0	0 (Placebo)	+1	3
Michelson et al. 2002	+1	0	+1	+1 (Placebo)	+1	4
Michelson et al. 2004	+1	+1	+1	+1 (Placebo)	+1	5
Spencer et al. 2002	+1	0	+1	+1 (Placebo)	+1	4
Weiss et al. 2005	+1	+1	+1	+1 (Placebo)	+1	5
ADHD+ODD only						
Kaplan et al. 2004	+1	+1	+1	+1 (Placebo)	+1	5
Newcorn et al. 2005	+1	0	+1	+1 (Placebo)	+1	4

Table 2 Meta-analyses of efficacy, functional outcomes and quality of life measures, and meta-regression of primary efficacy measures

	Atomoxetine (*n*)	Placebo (*n*)	Standardised mean differences (SMD; 95% CI)	Test for overall effect		Test for heterogeneity			
				Z score	*P* value	χ^2	I^2 (%)	*P* value	τ^2 statistic
Efficacy									
ADHD-RS-IV									
Total score	1,013	602	−0.638 (−0.761, −0.516)	10.19	0.00*	12.66	28.9	0.18	0.0112
Inattentive symptoms	1,013	602	−0.558 (−0.658, −0.457)	10.87	0.00*	8.09	0.0	0.53	0.0000
Hyperactive/impulsive symptoms	1,013	602	−0.548 (−0.727, −0.369)	5.99	0.00*	27.26	67.0	0.01*	0.0549
CTRS-R:S ADHD Index	451	287	−0.342 (−0.634, −0.050)	2.30	0.02*	6.55	69.5	0.03*	0.0460
CPRS-R:S ADHD Index	887	708	−0.616 (−0.847, −0.384)	5.22	0.00*	36.07	77.8	0.00*	0.0957
CGI-S	727	438	−0.638 (−0.829, −0.448)	6.58	0.00*	10.32	51.5	0.06	0.0284
Functional outcomes and quality of life									
CHQ psychosocial summary score[a]	576	287	0.467 (0.249, 0.685)	10.19	0.00*	12.66	28.9	0.18	0.0112
Meta-regression adjustments[b]									
ADHD-RS-IV									
Total score	1,013	602	−0.643 (−0.750, −0.537)	11.83	0.00*	6.17	0.0	0.72	0.0000
Inattentive symptoms	1,013	602	−0.575 (−0.661, −0.488)	12.97	0.00*	8.47	0.0	0.49	0.0000
Hyperactive/impulsive symptoms	1,013	602	−0.535 (−0.809, −0.261)	3.82	0.00*	1.43	0.0	0.99	0.0000

ADHD-RS-IV: Buitelaar et al. (2006), Kelsey et al. (2004), Michelson et al. (2001), Michelson et al. (2002), Michelson et al. (2004), Spencer et al. (2002) and Weiss et al. (2005).
CHQ: Buitelaar et al. (2006), Michelson et al. (2001) and Michelson et al. (2004).
CTRS-R:S: Buitelaar et al. (2006), Michelson et al. (2002) and Michelson et al. (2004).
CPRS-R:S: Buitelaar et al. (2006), Michelson et al. (2001), Michelson et al. (2002), Michelson et al. (2004), Spencer et al. (2002) and Weiss et al. (2005).
CGI: Kelsey et al. (2004), Michelson et al. (2002), Michelson et al. (2004), Spencer et al. (2002) and Weiss et al. (2005).
I^2 variation in SMD attributable to heterogeneity; τ^2 variance between the included studies; *ADHD-RS-IV* ADHD Rating Scale IV; *CHQ* Child Health Questionnaire; *CTRS-R:S* Conners' Teacher Rating Scale-Revised:Short Form; *CPRS-R:S* Conners' Parent Rating Scale-Revised:Short Form; *CGI-S* Clinical Global Impression Severity Score
*$p<0.05$
[a] Increase in CHQ score indicates improved symptoms; for all other measures, decrease in score indicates improved symptoms.
[b] Adjusted for significant confounders in Table 4. Notice both I^2 and τ^2 were reduced after adjustment, and the heterogeneity for hyperactive/impulsive symptoms was no longer statistically significant.

chosen because different dosages of medication were used that might alter the observed variability of the treatment response. The SMDs facilitate comparison of different scales, and it was used to ensure that results were comparable across studies.

As our preliminary analysis detected heterogeneity across the studies, weighted averages of SMDs were calculated using the inverse variance method for the random effects model. Heterogeneity between studies and in the meta-analysis estimates was evaluated by the χ^2 test.

Meta-regression analysis (Table 4) was used to assess and adjust the effects of potential covariates on the meta-analysis estimates derived from the primary efficacy measures of atomoxetine RCTs that involved ADHD+/-ODD subjects. Study characteristics (duration of follow up, number of study sites, atomoxetine:placebo ratio, dosage of drug, per cent discontinued due to side effects), subject characteristics (mean age of subjects, per cent ADHD hyperactive/impulsive subtype,per cent ODD) and study quality (Jadad total score, randomization score, double-blinding score) were included in the analysis.

Publication bias was assessed by visual inspection, Begg's and Egger's tests.

We quantified the efficacy of atomoxetine (Table 5) in bringing about a treatment response (defined as reduction of ≥25% in ADHD-RS-IV total score from baseline) and for relapse prevention (defined as reduction of ≥25% in ADHD-RS-IV total score from baseline, and a CGI-S score of 1 or 2) in terms of number-need-to-treat (NNT), which indicates the average number of patients that have to be treated with atomoxetine to result in one treatment response or to prevent one relapse (i.e. the smaller the NNT, the more

Table 3 Meta-analyses on the efficacy of atomoxetine in reducing ADHD and ODD symptoms in comorbid ADHD/ODD

	ATM (*n*)	PLA (*n*)	Standardised mean differences (SMD; 95% CI)	Test for overall effect		Test for heterogeneity			
				Z score	*P* value	χ^2	I^2 (%)	*P* value	τ^2 statistic
Efficacy									
ADHD-RS-IV									
Total score	137	76	−0.699 (−0.954, −0.444)	5.38	0.00*	0.95	0.0	0.814	0.0000
Inattentive symptoms	137	76	−0.692 (−0.946, −0.437)	5.33	0.00*	0.90	0.0	0.825	0.0000
Hyperactive/impulsive symptoms	137	76	−0.595 (−0.846, −0.344)	4.65	0.00*	1.11	0.0	0.775	0.0000
CPRS-R:S ADHD Index	137	76	−0.749 (−1.015, −0.482)	5.51	0.00*	0.63	0.0	0.891	0.0000
CPRS-R:S Oppositional	137	76	−0.422 (−0.702, −0.142)	2.95	0.00*	3.55	15.6	0.314	0.0129
CGI-S	137	76	−0.598 (−0.849, −0.347)	4.67	0.00*	0.99	0.0	0.805	0.0000

Included Kaplan et al. (2004) and Newcorn et al. (2005).
I^2 variation in SMD attributable to heterogeneity; τ^2 variance between the included studies; *ADHD-RS-IV* ADHD Rating Scale IV; *CPRS-R:S* Conners' Parent Rating Scale-Revised:Short Form; *CGI-S* Clinical Global Impression Severity Score.
*$p<0.05$

efficacious). We calculated the NNTs for individual studies and as a summary measure for all studies (with and without the studies with only comorbid ADHD+ODD subjects).

Statistical analysis for treatment-emergent adverse events

Treatment-emergent adverse events (Table 6) were pooled from atomoxetine RCTs involving ADHD+/-ODD subjects, and Fisher's exact test was performed to detect differences in the incidence of adverse events between atomoxetine-treated and placebo-treated groups. Number-needed-to-harm (NNH) was calculated for each adverse event to indicate the average number of patients that have to be treated with atomoxetine to result in one adverse event (i.e. larger the NNH, less common are adverse events). For each adverse event, meta-regression analyses were used to identify dose–response relationship between mean final dose and relative risk increase (RRI) of adverse events and to identify duration–response relationship between mean duration of atomoxetine treatment and RRI of adverse events. A final meta-regression

Table 4 Meta-regression analysis of potential factors

	Regression coefficient (95% CI)	*Z* score	*P* value
Study characteristics			
Duration of study	−0.01 (−0.02, −0.01)	−2.59	0.01*
Number of study sites	−0.02 (−0.03, −0.01)	−2.82	0.01*
Atomoxetine:placebo ratio	−0.03 (−0.24, 0.18)	−0.26	0.79
Dosage of drug	0.22 (−0.13, 0.57)	1.26	0.21
Per cent discontinued due to side effects	0.09 (−0.03, 0.20)	1.45	0.15
Subject characteristics			
Mean age of subjects	−0.14 (−0.36, 0.07)	−1.31	0.19
% Men	−0.01 (−0.03, −0.01)	−2.30	0.02*
% ADHD hyperactive/impulsive subtype	−0.09 (−0.16, −0.02)	−2.43	0.01*
% ADHD inattentive subtype	0.01 (−0.01, 0.02)	0.57	0.57
% ADHD mixed subtype	−0.01 (−0.02, 0.02)	−0.17	0.86
% Oppositional defiant disorder	−0.02 (−0.03, −0.01)	−2.50	0.01*
% General anxiety disorder	−0.01 (−0.15, 0.12)	−0.16	0.87
% Major depression	0.02 (−0.10, 0.15)	0.35	0.72
Baseline ADHD-RS-IV Total	0.01 (0.00, 0.02)	2.44	0.02*
Baseline ADHD-RS-IV Inattention	0.02 (0.00, 0.04)	2.45	0.01*
Baseline ADHD-RS-IV Hyper/Imp	0.03 (0.00, 0.05)	2.38	0.02*
Study Quality			
Total score	−0.06 (−0.22, 0.09)	−0.83	0.41
Randomization	−0.24 (−0.48, −0.03)	−2.19	0.03*
Double blinding	0.02 (−1.28, 0.17)	0.28	0.78

*$p<0.05$

Table 5 Number-needed-to-treat (NNT) for treatment response and relapse prevention

	Treatment response				Relapse prevention			
	Atomoxetine	Placebo	NNT	(95% CI)	Atomoxetine	Placebo	NNT	(95% CI)
Buitelaar et al. 2006					2/81	10/82	10.28	(5.69, 53.24)
Kelsey et al. 2004	67/107	15/45	3.40	(2.18, 7.85)				
Michelson et al. 2001	–	–	–	–				
Michelson et al. 2002	50/84	26/83	3.54	(2.34, 7.29)				
Michelson et al. 2004					65/292	47/124	6.39	(3.93, 17.06)
Spencer et al. 2002; Study 1	41/64	15/61	2.53	(1.80, 4.25)				
Spencer et al. 2002; Study 2	37/63	24/60	5.34	(2.77, 73.12)				
Weiss et al. 2005	69/100	22/51	3.86	(2.36, 10.49)				
Sub-total	264/418	102/300	3.42	(2.75, 4.52)				
Kaplan et al. 2004	34/52	16/44	3.44	(2.07, 10.19)				
Newcorn et al. 2005	–	–	–	–				
Total	298/470	118/344	3.43	(2.79, 4.45)	67/373	57/206	10.30	(5.89, 40.62)

model (Table 7) involving all types of adverse events was used to investigate the effects of subject characteristics and dosage characteristics on the RRI of adverse events associated with atomoxetine.

We used the 95% confidence interval for all calculations, and p values of <0.05 were considered to be statistically significant. All statistical calculations were performed by STATA™ version 8.0.

Statistical analysis for publication bias

We used funnel plots to assess for publication bias by the statistical methods of Begg's test and Egger's test. The funnel plot is based on the symmetry assumption about representative data: when the estimated effect sizes are plotted against their standard errors, a symmetrical plot is formed showing increasing variability of effect sizes around the true value as the standard error increases, and any asymmetries could be due to unrepresentativeness of the data.

Results

An initial search identified 1,750 articles. Sixteen articles were clinical trials that used atomoxetine to treat ADHD patients, two studies of which were conducted in adults (Spencer et al. 1998; Michelson et al. 2003), two studies did not have placebo control groups (Kratochvil et al. 2001; Spencer et al. 2001), two studies compared atomoxetine and methylphenidate osmotic release oral system (OROS) (Kemner et al. 2005; Starr and Kemner 2005), one study compared atomoxetine and methylphenidate (Kratochvil et al. 2005), one study only involved comorbid ADHD+ODD subjects but did not provide enough data (Hazell et al. 2006), and all were excluded. Table 1 lists the seven atomoxetine RCTs (Buitelaar et al. 2006; Kelsey et al. 2004; Michelson et al. 2001, 2002, 2004; Spencer et al. 2002; Weiss et al. 2005) that included ADHD+/-ODD subjects and two atomoxetine RCTs (Kaplan et al. 2004; Newcorn et al. 2005) that only included comorbid ADHD+ODD subjects. The seven studies included 1,615 ADHD+/-ODD subjects (atomoxetine:placebo=1,013:602), and the two studies included 213 comorbid ADHD+ODD subjects (atomoxetine:placebo=137:76). The average total score for methological quality was 4.33/5, the lowest total score was 3, and the highest total score was 5. All studies were randomized, provided information on withdrawals and dropouts, and all but one study were double-blinded.

Efficacy of atomoxetine versus placebo in ADHD+/-ODD

The SMDs for reduction in ADHD symptoms (Table 2) were all statistically significant ($p<0.01$) regardless of the instrument (ADHD-RS-IV, CPRS/CTRS-R:S, CGI-S) and type of rater (clinician, parent or teacher). The overall NNTs for treatment response were 3.43 (2.79, 4.45) and 3.42 (2.75, 4.52), with and without the two studies with only comorbid ADHD+ODD subjects, respectively (Table 5). The overall NNT for relapse prevention was 10.30 (5.89, 40.62).

QoL and functional outcomes after atomoxetine in ADHD+/-ODD

The SMD for improvement of QoL and functional outcomes was statistically significant (Table 2).

Efficacy of Atomoxetine Versus Placebo in comorbid ADHD+ODD

The SMDs for reduction in ADHD (clinician-rated ADHD-RS-IV and CGI-S and parent-rated CPRS-R:S) and ODD symptoms (parent-rated CPRS-R:S) were statistically significant (Table 3).

Table 6 Treatment-emergent adverse events and their number-needed-to-harm (NNH)

	Meta-analysis					Meta-regression analysis	
	Atomoxetine (n=717)	Placebo (n=484)	P value[a]	NNH[b]	(95% CI)	Dose–response relationship; P values	Duration–response relationship; P values
Appetite decrease	111	20	0.00*	8.81	(6.88, 12.25)	0.58	0.81
Somnolence	71	23	0.00*	19.41	(12.43, 44.31)	0.71	0.78
Abdominal pain	103	48	0.02*	22.48	(12.27, 133.48)	0.73	0.53
Vomiting	58	23	0.02*	29.96	(16.42, 171.01)	0.76	0.80
Dyspepsia	16	1	0.00*	49.38	(31.45, 114.87)	–	–
Dizziness	15	1	0.01*	53.03	(33.24, 131.15)	0.44	0.30
Nausea	50	25	0.20	55.30	(22.12, −110.45)	0.91	0.43
Nervousness	30	12	0.11	58.65	(26.87, −320.60)	0.88	0.02*
Fatigue	13	1	0.01*	62.24	(37.54, 182.01)	–	–
Rash	21	7	0.09	67.44	(32.14, −681.76)	0.87	0.08
Asthenia	18	5	0.07	67.68	(34.08, 4,889.98)	0.58	0.24
Infection	11	1	0.02*	75.32	(43.21, 293.13)	0.20	–
Insomnia	14	5	0.21	108.75	(43.95, −229.41)	0.13	–
Pruritus	6	0	0.04*	119.50	(66.50, 588.10)	–	–
Fever	17	8	0.39	139.25	(43.31, −114.60)	0.80	0.67
Pain	11	5	0.46	199.55	(56.36, −129.53)	0.66	–
Emotional lability	6	4	0.98	9,639.65	(94.62, −96.52)	–	–
Headache	124	86	0.83	−210.83	(25.55, −20.56)	0.96	0.36
Depression	3	5	0.20	−162.69	(248.42, −61.28)	0.99	–
Accidental injury	12	13	0.23	−98.78	(141.43, −36.61)	0.59	0.06
Diarrhoea	6	9	0.12	−97.78	(283.14, −41.69)	0.96	–
Cough	26	30	0.04*	−38.87	(−3,972.98, −19.53)	0.12	0.42
Pharyngitis	55	52	0.07	−32.54	(328.66, −15.50)	0.79	0.75
Rhinitis	76	78	0.01*	−18.12	(−64.93, −10.54)	0.97	0.49

The treatment-emergent adverse events from the 292 atomoxetine-treated and 124 placebo-treated subjects in Michelson et al. (2004) were not included due to insufficient data, but it stated that "gastroenteritis and pharyngitis were more common on atomoxetine, whereas increased appetite was more common on placebo".

Of the seven atomoxetine studies, only Spencer et al. (2002) mentioned a patient discontinued because of "tic-like movements", and there was no mention of tics as a side effect in the other studies.

[a] Fisher's exact test for difference

[b] A negative NNH indicates that the adverse event is more common in the placebo-treated population. The most common adverse events related to atomoxetine should therefore have a positive and small NNH (i.e. appetite decrease).

*p<0.05

Meta-regression analysis of atomoxetine's efficacy

Of the five study characteristics examined, only duration of study (regression coefficient −0.01; p=0.01) and number of study sites (regression coefficient −0.02; p=0.01) were found to be significant (Table 3). Six subject characteristics were found to be significant: men (regression coefficient −0.01; p=0.02), ADHD hyperactive/impulsive subtype (regression coefficient −0.09; p=0.01), oppositional defiant disorder (regression coefficient −0.02; p=0.01), baseline ADHD-RS-IV total score (regression coefficient 0.01; p= 0.02), inattention score (regression coefficient 0.02; p= 0.01) and hyperactivity/impulsivity score (regression coefficient 0.03; p=0.02).

The meta-regression adjusted SMDs are shown in the bottom half of Table 2. All were statistically significant (p< 0.01), and τ^2 statistics were all reduced to zero.

Treatment-emergent adverse events of atomoxetine

Of all the treatment-emergent adverse events examined, six adverse events were significantly more common in the atomoxetine-treated group compared to placebo-treated group (Table 4). They were (commonest event listed first): decrease in appetite (NNH 8.81; p<0.01), somnolence (NNH 19.41; p<0.01), abdominal pain (NNH 22.48; p= 0.02), vomiting (NNH 29.96; p=0.02), dyspepsia (NNH 49.38; p<0.01), dizziness (NNH 53.03; p=0.01), fatigue

Table 7 Meta-regression analysis on atomoxetine associated adverse events

	Regression coefficient (95% CI)	*Z* score	*P* value
Subject characteristics			
Mean age of subjects	−0.58 (−1.09,−0.08)	−2.28	0.03*
% Men	0.03 (−0.06, 0.12)	0.74	0.46
% ADHD hyperactive/impulsive subtype	0.19 (−0.21, 0.59)	0.93	0.36
% ADHD inattentive subtype	−0.06(−0.11,−0.01)	−2.11	0.04*
% ADHD mixed subtype	0.05 (−0.01, 0.11)	1.96	0.05
% Oppositional defiant disorder	0.03(−0.01, 0.08)	1.51	0.13
% General anxiety disorder	0.35 (−0.04, 0.75)	1.81	0.07
% Major depression	−0.11 (−0.35, 0.12)	−0.93	0.35
% with comorbidity	0.01 (−0.01, 0.03)	1.09	0.28
Baseline ADHD-RS-IV Total	0.46(0.19, 0.72)	3.46	0.00*
Baseline ADHD-RS-IV Inattention	0.46(−0.55, 1.48)	0.91	0.36
Baseline ADHD-RS-IV Hyper/Imp	0.53(0.24, 0.83)	3.58	0.00*
Treatment characteristics			
Mean final dosage	0.18 (−0.58, 0.94)	0.47	0.64
Duration of treatment	−0.01(−0.05, 0.04)	−0.32	0.75

*$p<0.05$

(NNH 62.24; $p=0.01$), infection (NNH 75.32; $p=0.02$) and pruritus (NNH 119.5; $p=0.04$).

Meta-regression analysis of treatment-emergent adverse events

Of all the subject characteristics examined, four were found to be significant: mean age of subjects (regression coefficient −0.58; $p=0.03$), ADHD inattentive subtype (regression coefficient −0.06; $p=0.04$), baseline ADHD-RS-IV total score (regression coefficient 0.46; $p<0.01$) and hyperactivity/impulsivity score (regression coefficient 0.53; $p<0.01$). Mean final dose ($p=0.64$) and duration of atomoxetine treatment ($p=0.75$) were not significantly associated with relative risk increase in adverse events (Table 5). No dose–response relationship was identified between mean final doses and relative risk increases for any of the adverse events, and only one adverse event (nervousness, $p=0.02$) demonstrated duration–response relationship although it was not found to be significantly more common in atomoxetine-treated group ($p=0.11$; right side of Table 4).

Publication bias

Begg's test with continuity correction did not detect publication bias ($p=0.28$), but Egger's test detected significant publication bias ($p=0.04$).

Discussion

This is the first meta-analysis to quantify the side effects of atomoxetine in children and adolescents and to investigate the moderating effects of age, gender, ADHD subtype, baseline ADHD symptoms and comorbid anxiety and depression statuses on the efficacy and safety of atomoxetine.

Efficacy of atomoxetine versus placebo

We found atomoxetine to be efficacious in reducing ADHD symptoms (in SMDs), whether rated by parents, teachers or clinicians or by different psychometric instruments and is consistent with previous trial data. The NNTs for treatment response with and without comorbid ADHD were highly similar, both around 3.4, similar to the NNT of 3.8 (±0.21) reported by Banaschewski et al. (2006), and they compare favourably to the NNTs required for the treatment of adult depression (NNT=0.5; Geddes and Butler 2002), obsessive–compulsive disorder (NNT=9; Soomro 2002) and schizophrenia (NNT=0.25 to 20; Leucht et al. 1999). The NNT required for relapse prevention (NNT=10.30; 95% CI, 5.89, 40.62) was significantly larger than that required for treatment response (NNT=3.43; 95% CI, 2.79, 4.45), which was consistent with our finding that longer duration of treatment was associated with lower drug efficacy (see "Drug Tolerance?").

We also found significant improvements in QoL and functional outcome measures after atomoxetine treatment, consistent with Perwien et al. (2004).

Gender and psychiatric comorbidity

We found that atomoxetine may be more efficacious in female ADHD patients and in those patients without comorbid ODD.

Few studies (if any) have compared the efficacy of atomoxetine in the two genders. Biederman et al. (2002) found atomoxetine to be efficacious and well tolerated in school-age girls, but there was no comparison between boys

and girls. A post hoc analysis in school-age girls found that 18-day treatment with mixed amphetamine salts extended release achieved greater improvements than atomoxetine in classroom behaviour, attention and academic performance (Swanson, Kotkin, Atkins, M/Flynn, Pelham Scale (SKAMP) deportment and attention subscales and the number of maths problems attempted; Biederman et al. 2006), although it has to be said atomoxetine takes 6–8 weeks rather than 18 days to achieve its full effect.

A number of studies have examined the effect of comorbid ODD on the efficacy of atomoxetine in the management of ADHD. Kaplan et al. (2004) concluded that atomoxetine was efficacious only in reducing ADHD symptoms but not ODD symptoms, in comorbid ADHD+ODD patients. In contrast, Newcorn et al. (2005). found that atomoxetine was efficacious in reducing both ADHD and ODD symptoms, although comorbid ADHD+ODD patients required higher doses of atomoxetine compared to ADHD-ODD patient. Our meta-analysis of both studies (Table 5) suggests that atomoxetine was efficacious in reducing both ADHD and ODD symptoms in ADHD+ODD patients. Although in a recent meta-analysis (Biederman et al. 2007), the reduction in ODD symptoms was not significant whether in ADHD+ODD or ADHD-ODD patients. However, the authors suggested that reduction in ODD symptoms was related to the magnitude of ADHD symptom reduction, as a high correlation was found between changes in ADHD-RS-IV total score and CPRS-R: S oppositional score. It is possible that the different conclusions reached are due to different levels of ADHD symptom reduction in different study populations. Our larger sample (1,615 vs 512) may partly explain our significant finding. In terms of relapse rate, Hazell et al. (2006) found no such difference between the ODD comorbid status. Presence of comorbid ODD was predictive of smaller improvements in psychosocial measures after atomoxetine treatment (Perwien et al. 2004).

It was thought that the therapeutic reduction in ADHD symptoms in ADHD+ODD may be less than in ADHD-ODD, although such difference was not found (Biederman et al. 2007). The finding of higher drug efficacy in girls maybe due to (1) a genuine greater efficacy in this gender (no study has compared the genders) or (2) due to a lower prevalence of comorbid ODD in this gender and ODD is associated with lower ADHD symptoms reduction (but contradicts Biederman et al. 2007). The former explanation may be further explained by the relatively less severe externalizing or disruptive behaviours in girls (Biederman et al. 2002; Gaub and Carlson 1997), which upon drug treatment may appear to improve more than boys in the eyes of the instrument raters.

Gender (p=0.46) and comorbid ODD (p=0.13) were not found to alter atomoxetine's side effects.

We did not detect significant moderation of atomoxetine's efficacy (p=0.87 and p=0.72 respectively) and adverse events (p=0.07 and p=0.35 respectively) by general anxiety disorder (GAD) or major depression. GAD reached borderline significance in association with greater side effects (coefficient 0.35, p=0.07). Thus, atomoxetine appeared to be as efficacious in GAD and depression and as safe in depression but may have more adverse events in ADHD comorbid with GAD.

The MTA study (The MTA Cooperative Group 1999) found behavioural therapy to be particularly efficacious in reducing hyperactivity/impulsivity symptoms in comorbid anxiety group compared to non-comorbid group, comparable to medication alone or combined (medication and psychosocial) treatments. As atomoxetine may be associated with more adverse events in comorbid GAD, the preferred treatment in this group may be stimulants with or without behavioural treatment. Biederman et al. (1993) found desipramine to be as equally efficacious in reducing ADHD symptoms in either ADHD+/−depression comorbid status. Desipramine (Rapport et al. 1993; Pataki et al. 1993) or fluoxetine (Gammon and Brown 1993) can be combined with methylphenidate to treat comorbid depression. In an 8-week comparison trial (Kratochvil et al. 2005) between atomoxetine alone and combined atomoxetine and fluoxetine, greater reduction in depressive symptoms was achieved with combined treatment, and it suggests atomoxetine to be an alternative to methylphenidate in combination with fluoxetine for treatment of comorbid depressive symptoms.

Age

A strong negative association was found between age and atomoxetine's side effects (coefficient −0.58, p=0.03). No association was found between age and atomoxetine's efficacy.

ADHD subtypes and baseline symptomatology

The hyperactive/impulsive subtype experienced significantly lower efficacy of atomoxetine (p=0.01), and inattentive subtype experienced significantly less side effects (p=0.04). These suggest atomoxetine to be more efficacious and safer for the inattention subtype. A post hoc analysis (Heiligenstein et al. 2001) on the study of Spencer et al. (2002) found atomoxetine to be efficacious in reducing inattention, and significant reduction was achieved during the first week and was maintained throughout the 9-week study. Addition of fluoxetine to atomoxetine (compared to atomoxetine alone) was associated with greater reduction in ADHD-RS-IV inattentive symptoms (not total or hyperactivity/impulsive symptoms) but was only marginally significant (p=0.059; Kratochvil et al. 2005). Fluoxetine alone reduced inattentive symptoms, but not hyperactive symptoms, in ADHD with comorbid depression (Quintana et al. 2007).

Greater baseline ADHD symptom scores on ADHD-RS-IV total, inattention and hyperactivity/impulsivity domains were significantly associated with greater symptom score reduction but greater baseline scores on total and hyperactivity/impulsivity domains were also associated with more side effects. This could be due to higher dosage titration (and associated side effects) for patients with greater symptoms; however, it was unlikely, as dose–response relationships were not found in our results. Inattentive subtype patients with high baseline symptoms may benefit from atomoxetine as greater efficacy can be achieved with no significant elevation of side effects.

Drug tolerance?

Trials with longer treatment duration were found to have smaller summary estimates, which may suggest a loss of efficacy with long-term atomoxetine treatment (tolerance). Wilens et al. (2006) commented that there was "little evidence of any clinically significant drug tolerance...based on the continued response without dose adjustments other than to account for increased body weight." Although statistically we found evidence of drug tolerance, this may not be clinically apparent on the individual patients, particularly because the regression coefficient is small (−0.01; $p=0.01$). Methylphenidate also appears to have acute tolerance (Swanson et al. 1999), and an optimum dosing regimen (e.g. frequency of doses) has to take this into account.

Study characteristics and study quality

The number of study sites was negatively associated with summary estimate sizes ($p=0.01$). This could be due to difficulty in coordinating different trial centres, which resulted in variations (e.g. protocol violations) in the execution of trials.

Trials that are better randomized also had smaller summary estimates ($p=0.03$). As all included atomoxetine studies are randomized, the main difference lies in the quality of randomization and disclosure by the authors of the method of randomization. Trial investigators in a randomized (subjects blinded) study that has inadequate concealment of randomization information may result in investigator observer bias.

Adverse events

The most common side effects of atomoxetine include gastrointestinal (appetite decrease, abdominal pain, vomiting, dyspepsia), sleep disturbance (somnolence), and other general symptoms (dizziness, fatigue).

Meta-regression has identified high baseline ADHD-RS-IV total score and hyperactivity/impulsivity score to be associated with more adverse events with atomoxetine, and the effect sizes are moderate to large (regression coefficient 0.46 and 0.53 respectively; $p<0.01$). Mean age of subjects is found to be protective of adverse events, and the effect size is large (regression coefficient −0.58; $p=0.03$).

No dose–response relationship was identified for any of the adverse events, and only one adverse event, nervousness, exhibited duration–response relationship. Michelson et al. (2001) has identified dose–response relationship for two adverse events associated with atomoxetine, namely, infection and pruritus (both $p<0.05$), out of a list of 21 adverse events. Furthermore, both adverse events were among the least common on the list and could be a result of zero cell computation. It is therefore likely that adverse events associated with atomoxetine are more idiosyncratic rather than dose-dependent. Our finding of a significant duration–response relationship should be interpreted with caution, as the NNH for that event was not statistically significant. Furthermore, as we performed a large number of statistical tests, there remains a possibility of false positive "significant findings".

Recommendations

The European Treatment Guideline on ADHD (Banaschewski et al. 2006) recommends that atomoxetine should be preferred as first choice if: (1) there is comorbid substance abuse, tics or anxiety; (2) there is a strong preference for a non-stimulant; (3) there is a strong preference for 24-h action; (4) a child has failed to respond to immediate-release methylphenidate; or (5) a child has suffered adverse events on immediate-release methylphenidate.

Atomoxetine has a theoretical advantage over methylphenidate because its action spares the striatum and nucleus accumbens (Bymaster et al. 2002) that are affected in substance abuse, particularly in comorbid ODD patients who are at risk of substance abuse (Wilens et al. 2006). Our evidence suggests that atomoxetine may be efficacious in reducing both ADHD and ODD symptoms, and comorbid ODD did not predict more adverse events of the drug. The therapeutic reduction in ADHD symptoms (Biederman et al. 2007) and relapse rate of ADHD (Hazell et al. 2006) appeared to be independent of ODD status, although ODD status predicted lesser psychosocial improvements (Perwien et al. 2004).

More recent studies (Livingstone et al. 1990; Tannock et al. 1995; Diamond et al. 1999; The MTA Cooperative Group 1999) have shown methylphenidate to be equally efficacious in ADHD+/-comorbid anxiety, rejecting earlier suggestions that comorbid anxiety may reduce the efficacy of methylphenidate, and atomoxetine may have a lesser role in this comorbid group than previously thought. The MTA study found behavioural therapy to be particularly effica-

cious in comorbid anxiety (The MTA Cooperative Group 1999), and the preferred treatment may be stimulants alone or in combination with behavioural therapy in this group of patients. Our evidence also suggests more adverse events in comorbid anxiety patients treated with atomoxetine (p=0.07), although the efficacy of atomoxetine was no different in this comorbid group. Atomoxetine may be considered in comorbid anxiety patients who satisfy options (2) to (5) of the European Guideline above.

Atomoxetine may have a greater role in comorbid depression, where it serves as an alternative to methylphenidate used in combination with fluoxetine, in children who satisfy options (2) to (5) of the European Guideline above. Kratochvil et al. (2005) found that atomoxetine-fluoxetine combination can achieve greater reduction in depressive symptoms over atomoxetine alone. We found atomoxetine to be equally efficacious and safe in ADHD+/-depression.

Limitations

We chose not to perform Bonferroni's or Holm's methods of adjustment for multiple testing as some researchers (Perneger 1998) raised doubts about their underlying assumptions and false negative rates. We prefer to caution the readers in the interpretation of p values that were marginally significant (such as p=0.04), rather than missing important associations, such as side effects, due to too conservative multiple testing adjustments. The limitation of this approach is that some of our "significant findings" may have been false positives.

Although Egger's test detected significant publication bias (p=0.04) with results biased toward larger standardised mean differences, this publication bias was unlikely to render the summary estimates less significant as the 95% confidence intervals were far away from 0 SMD. To investigate this point, we performed trim-and-fill analysis, but no filling was required statistically, and the summary estimates were significant before and after the analysis (both p<0.01).

Heterogeneity is a potential problem, but only ADHD-RS-IV hyperactivity/impulsivity score had significant heterogeneity (p=0.01; I^2=67.0%; τ^2 statistic=0.0549), not total score (p=0.18; I^2=28.9%; τ^2 statistic=0.0112) and inattention score (p=0.53; I^2=8.09%; τ^2 statistic<0.0001). After meta-regression adjustments, the heterogeneity was no longer significant, and I^2 and τ^2 statistics are reduced to zero reflecting adequate adjustment. This small degree of heterogeneity is due in part to the high quality of the included trials that used similar methodologies and assessment instruments.

Another limitation is the generalizability of aggregate findings to individual patients. Individual responses (therapeutic or side effects) may be quite variable and can be quite different from the aggregate findings in this study.

Conclusion

Atomoxetine was superior to placebo in reducing ADHD symptoms. The NNTs for treatment response and relapse prevention were 3.4 and 10.3, respectively. Patients with higher baseline ADHD symptoms experienced greater reduction in ADHD symptoms. Male gender, comorbid ODD status and ADHD hyperactive/impulsive subtype were associated with smaller reduction in ADHD symptoms. The commonest adverse events were gastrointestinal (appetite decrease, abdominal pain, vomiting, dyspepsia) and sleep related (somnolence). Young age and high baseline hyperactive/impulsive symptoms were associated with more adverse events, whereas ADHD inattentive subtype was associated with less adverse events. QoL improved with atomoxetine treatment. Atomoxetine may reduce both ADHD and ODD symptoms, and comorbid ODD was not associated with more adverse events. It may have less role in comorbid anxiety than previously thought, but it may be a good alternative to methylphenidate used in combination with fluoxetine in comorbid depression.

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