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REVIEW

Efficacy and Safety of Atomoxetine in the Treatment of Children and Adolescents with Attention Deficit Hyperactivity Disorder

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Abstract: Several non-stimulant medications have been used in the treatment of attention deficit hyperactivity disorder (ADHD). Atomoxetine, was introduced in 2002. The safety and efficacy of atomoxetine in the treatment of ADHD for children, adolescents, and adults has been evaluated in over 4000 patients in randomized controlled studies and double blinded studies as well as in recent large longitudinal studies. This paper provides an updated summary of the literature on atomoxetine, particularly in relation to findings on the short- and long-term safety of atomoxetine in children and adolescents arising from recent large longitudinal cohort studies. Information is presented about the efficacy, safety, and tolerability of this medication.

Keywords: atomoxetine, children, adolescents, ADHD, safety, efficacy

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Introduction

Several non-stimulant medications have been used in the treatment of attention deficit hyperactivity disorder (ADHD). The non-stimulant atomoxetine was introduced in the United States in 2002. The safety and efficacy of atomoxetine in the treatment of ADHD for children, adolescents, and adults has been evaluated in over 4000 patients in randomized controlled studies and double blinded studies, as well as in recent large longitudinal studies.[1–6]

Though stimulant medications are frequently used as first-line agents, atomoxetine may also be considered as an initial choice, particularly in the presence of select comorbid disorders including active substance abuse, anxiety disorder, or tic disorder.[7]

Atomoxetine mechanism of action

The mechanism of action of atomoxetine in the control and maintenance of ADHD symptoms is thought to be through the highly specific presynaptic inhibition of noradrenaline (NA), although the exact mechanism of action is not yet understood. Atomoxetine (Strattera®, Eli Lilly and Company) is a highly selective NA reuptake inhibitor, thereby increasing synaptic NA. It is the first nonstimulant medication approved by the United States Food and Drug Administration (FDA) for the treatment of attention deficit hyperactivity disorder (ADHD). It has a low affinity for serotonin or dopamine receptors,[8,9] and the regions of the brain affected by atomoxetine are limited. It acts almost exclusively in the prefrontal cortical (PFC) regions, which play a key role in attention and higher cognitive processes but not in other dopamine rich brain regions such as the nucleus accumbens and striatum.[9] In addition, atomoxetine increases NA in other brain regions, with a substantial density of NA transporters, such as the brain stem areas and subcortical structures.[10] Genetic and imaging evidence point to dysregulation of NA as having a central role in the pathophysiology of ADHD.[11] Hence, atomoxetine may be used either as the sole pharmacological agent or in combination with stimulant medications, which act directly to enhance dopaminergic activity to treat ADHD.

Atomoxetine is efficiently absorbed after oral administration (range 63%–94%), and its bioavailability is minimally affected by food. After oral administration, atomoxetine reaches a maximum plasma concentration within two hours. Atomoxetine is highly bound to albumin and does not affect the binding of other common medications.[12]

Atomoxetine metabolism

The metabolism of atomoxetine occurs primarily in the liver via the P450 (CYP2D6) system. The resulting conversion to 4-hydroxy-atomoxetine is glucuronidated and excreted in the urine. There are distinct differences within populations of CYP2D6 activity (extensive versus poor metabolizers). Genetic testing is available to detect the small percentage (<10%) of slow metabolizers who can have more than five times the blood level of medication and an extended half-life for a given dose. Atomoxetine has a plasma half-life of about five hours in extensive metabolizers.[13] Dosages of atomoxetine must also be reduced in patients with both renal and hepatic disease.[14] Response to atomoxetine should also be monitored more closely whenever a CYP450 2D6 inhibitor is added to or withdrawn from therapy, as dosage adjustment of atomoxetine may be necessary in extensive metabolizers. During co-administration, patients should be advised to contact their physician if they experience excessive adverse effects of atomoxetine such as dizziness, dry mouth, anorexia, sleep disturbances, and palpitations. Though atomoxetine does not induce or inhibit the cytochrome P450 (CYP2D6) system, it is involved in drug interactions that involve selective serotonin reuptake inhibitors (eg, fluoxetine and paroxetine) and other drugs (eg, quinidine) metabolized through this pathway, which may reduce atomoxetine clearance and cause higher peak plasma concentrations and slower elimination of atomoxetine.[12]

Atomoxetine has a low affinity for various receptors, such as serotonergic, cholinergic, histaminic, alpha1-adrenergic, and alpha2-adrenergic and hence is not involved in drug interactions with these agents.

Atomoxetine interactions

Atomoxetine should not be used within two weeks after discontinuing MAOI (monoamine oxidase inhibitors) or other drugs that affect brain monoamine concentrations. Atomoxetine should be prescribed with caution if a patient is taking asthma medications (albuterol or other beta2 agonists) or other medications with chronotropic or pressor effects. In

combination with either citalopram,[15] venlafaxine, or stimulants, involuntary movements have occurred.[16] These symptoms are likely to resolve after the discontinuation of atomoxetine.

The efficacy of atomoxetine, in addition to its safety and tolerability, in the treatment of ADHD are discussed in the Results section of this article. This review provides an updated summary of the literature on atomoxetine to that provided by Hammerness et al,[17] particularly in relation to findings on the short- and long-term safety of atomoxetine in children and adolescents arising from recent large longitudinal cohort studies.

While qualitative reviews of the literature, such as the information below, are useful for summarizing results and drawing conclusions about general trends, it remains important to appreciate that such reviews cannot easily evaluate the many factors associated with study design and measurement that may influence the apparent medication effect from the results of a single study.

Methods

Literature search

In accordance with our aim to extend the review of Hammerness et al,[17] we have included a literature search of studies since 2009 that report on the efficacy, safety, and tolerability of atomoxetine.

The literature search was undertaken on 14 June 2012. The other dates refer to the dates covered within the search using the different search engines and are the actual names of the search engines (e.g, "psychINFO (from 2002 through the first week of June 2012)" was the title of the search engine used), therefore, the different years listed (i.e, 2002 vs. 2009). Search terms were "ADHD" and "atomoxetine." Both words were entered separately, before search results for both words were combined with a limit for publication year set as 2009–current. An initial screen was undertaken on all search results where publication titles and abstracts were examined and publications filtered if they did not appear to meet eligibility criteria at the outset. Those which were not filtered out at the screening phase (including ones we were unsure of from the title and abstract) were subsequently assessed for eligibility by examination of the full-text article. Requests to the University of Sydney library or the corresponding author were made to obtain full-text for the articles which were not accessible online.

Journal papers were included in the review if they met the following criteria: clinical study utilizing atomoxetine as a treatment, human child or adolescent participants (<18 years of age) with a primary diagnosis of ADHD determined by a clinician or based on Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV), outcomes of either effect of atomoxetine on ADHD symptom measures and/or safety, and written in the English language. Excluded were monographs, reviews, meta-analyses and pooled analyses papers, books, case reports, articles not published by peer-reviewed scientific journals, papers available only in a language other than English, adult studies, trials without any adverse events reporting or efficacy outcomes in relation to ADHD symptom severity after atomoxetine treatment, animal studies, and papers reporting already-published data (in these cases, only one of the papers per study were included).

Outcomes of interest

The change in scores before and after treatment (mean and standard deviation [SD]) reflecting the efficacy of atomoxetine on behavioral and cognitive performance measures specifically were extracted from the literature. The numbers of participants who withdrew from a study because of a lack of efficacy of atomoxetine were also recorded. Where mean change data were not published, it was calculated using the published pre- and post-treatment values. The efficacy of atomoxetine in the treatment of ADHD was assessed through review of the effects of length of treatment, dosing, impact of age or prior stimulant use, and comorbid conditions. Information about the safety of atomoxetine, tolerability, and adverse events (type and frequency) were recorded and were compared with reports from earlier studies.

Results

The literature search for papers from 2009 yielded 183 results in total. After excluding papers that did not meet eligibility criteria as well as duplicates (eleven papers were duplicated), 33 papers met the criteria for the review of papers from 2009 (Fig. 1). Information from these papers and previously published data is summarized in regard to findings on mechanism of action, metabolism, efficacy, tolerability, and safety.

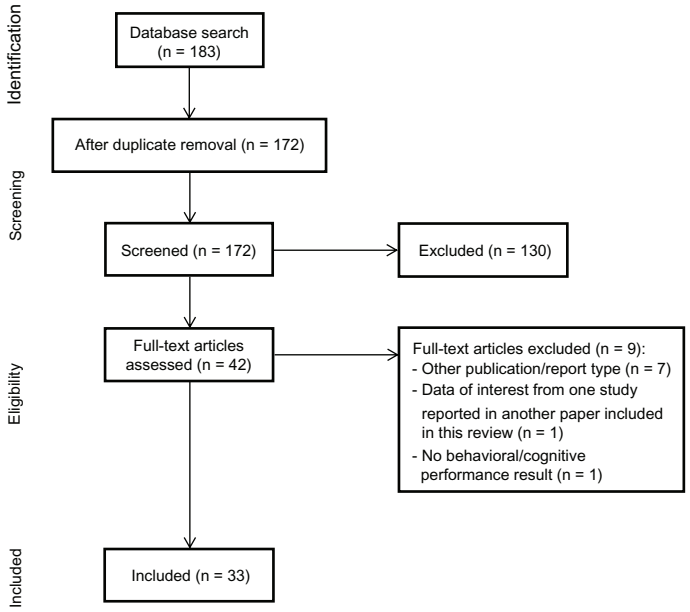

Figure 1. Literature flow chart.

Efficacy

The papers included in this review since 2009 observed the efficacy of atomoxetine on a wide spectrum of measures including reported ADHD symptoms, quality of life, other internalizing and externalizing symptoms, functioning and life participation, clinical global impressions, cognitive performance measures, family impact and functioning, perceived difficulties, school performance and academic functioning, and health outcomes (eg, risky behaviors and sleep habits) (Table 2). These measures included direct performance measures as well as perceived ratings by the child, parent, teacher, investigator, or clinician (Table 2). The findings of these papers are briefly summarized below, and further detail is provided in Tables 1 and 2.

Short-term treatment

For the purpose of this review, we have included papers that incorporated short-term post-treatment assessments at less than or equal to eight weeks. Twenty-one of the papers located from the literature search reported results within this time frame (Table 2). Within these short-term reports, improvements after atomoxetine treatment were observed from as early as two weeks, where Dittman et al, for example, reported an improvement in perceived difficulties and parent-rated ADHD symptoms.[18] This was the only study located using our search criteria which reported measures taken at a time point as early as two weeks.

Overall, the recent literature suggests that within eight weeks of treatment, atomoxetine was beneficial in significantly improving child-, parent-, clinician-, and teacher-rated ADHD symptoms, internalizing and externalizing behavior ratings, perceived difficulties, functioning and life participation, academic/school functioning, youth risk behavior, classroom behavior, depressive symptoms, sleep habits, and quality of life (Table 2). More objective performance measures of attention (continuous and switching) and executive abilities (the ability to organize, plan and anticipate) were also significantly improved after treatment with atomoxetine within this time period (Table 2). In those studies that incorporated a placebo arm, the improvements observed after treatment with atomoxetine were often superior to placebo across these measures (Table 2).

Within these studies, atomoxetine was either used as a sole treatment (at times comparing different doses or daily dose frequencies), or combined with behavioral therapy, psychotherapy in addition to behavior management, methylphenidate, mood stabilizers, or antipsychotic medications. These atomoxetine treatment arms were compared with treatment arms utilizing methylphenidate, ABT-089, and/or placebo or compared participants with ADHD to "healthy" controls or with participants with ADHD in addition to comorbid reading disorder, comorbid dyslexia. Other participant groups included within two of these studies had reading disorder alone and ADHD with comorbid bipolar disorder (Table 1). Six of the studies included did not have any comparison treatments or groups. Significant benefits were observed after treatment whether atomoxetine was used alone as a sole treatment or in combination with another medication or treatment modality. When combined with behavior therapy such as in Waxmonsky et al's studies,[19,20] greater benefits were reported in some (but not all) parent- and/or teacher-ratings on subscales pertaining to disruptive behaviors, social skills, academic performance, and impairment and depression ratings (Table 2). Methylphenidate in combination with atomoxetine may also provide superior benefits to symptom and behavior ratings beyond what atomoxetine alone provides, as further improvements to outcome measures were observed in a three-week atomoxetine plus methylphenidate phase following four weeks of atomoxetine alone.[21,22] When

comparing atomoxetine alone with methylphenidate, the effects from both treatments were comparable in that both treatments significantly improved behavior and cognitive measures.[23,24] Atomoxetine was superior to ABT-089 across symptom, behavior, and quality of life measures (Table 2).[25]

In cohorts with comorbid conditions, short-term benefits of atomoxetine treatment were consistently reported in ADHD symptom levels with no significant differences between groups, including groups with comorbid bipolar disorder, reading disorder, oppositional defiant disorder (ODD), or between inattentive and hyperactive-impulsive ADHD subtypes (Table 2). Further, de Jong et al also found a positive effect of atomoxetine compared with placebo on cognitive performance tasks including measures of visuospatial working memory and inhibition in their cohorts with ADHD, ADHD plus reading disorder, and in reading disorder alone.[26] Atomoxetine, however, had no significant effect on depression or mania ratings in those with comorbid bipolar disorder (although there were no comparison treatments or groups).[27]

Within these short-term studies, atomoxetine doses ranged from 0.2 to 1.8 mg/kg/d (Table 2). Investigations into atomoxetine dosing examined the effect of different dosing concentrations (two studies), fast versus slow titration (one study), or one versus two doses per day (one study). Cho et al[28] and Takahashi et al[29] examined atomoxetine doses of 0.2, 0.5, 1.2, and 1.8 mg/kg/d in 6 to 18 year olds, and their results suggest that the lower doses (0.2 and 0.5 mg/kg/d) were ineffective for improving ADHD symptom ratings, while significant benefits were observed with the higher doses (1.2 and 1.8 mg/kg/d). No differences were observed when participants adopted either a slow or fast titration schedule, and significant improvements to ADHD symptoms, life participation, family functioning, academic achievement, and some risky behavior ratings were observed after both titration schedules (Table 2).[30,31] In relation to one versus two daily doses, Waxmonsky et al found that one daily dose was superior to two daily doses in behavior and impairment ratings, where after eight weeks of treatment, significant benefits were observed in some of the measures only in those who took one daily dose (Table 2).[19,20] Additionally, Waxmonsky et al assessed participants every fortnight and found that improvements in parent-rated behaviors improved from the commencement of treatment (within the first fortnight) when one dose per day was taken, while benefits with two daily doses were first noticed halfway through the eight-week treatment period.

In summary, improvements in ADHD symptoms, behavior, functioning, quality of life, and cognitive performance measures are seen within the first 2 to 8 weeks of treatment with atomoxetine in children and adolescents with ADHD alone and in those with ADHD and comorbid disorders. Atomoxetine is also effective whether it is used alone or in combination with methylphenidate or other treatment modalities, and there is currently limited evidence that atomoxetine is more effective at higher doses and when taken as a single daily dose.

Long-term treatment

Long-term studies summarized in this section include those reporting results taken after treatment of more than eight weeks in duration. The two longest studies ran for either 10 months[32] or for eight weeks with an additional 40 week maintenance period.[30,31] Seventeen studies reported results from longer-term time points.

Overall, the results from the longer-term studies were consistent with the findings from the short-term studies, whereby atomoxetine improved many of the outcome measures even up to 10 months post-treatment (Table 2). Similar to the short-term reports, the longer-term studies compared atomoxetine to other treatments (stimulants[32] and methylphenidate[23,24]) and to placebo arms and combined atomoxetine treatment with other treatment modalities (motivational interviewing plus cognitive behavior therapy[33] and psychoeducation for parents[34]). Atomoxetine dosing was examined also in relation to fast versus slow titration[35,36] and compared low doses (0.8 mg/kg/d) to higher doses (1.4 mg/kg/d).[30,31] Cohorts used for comparisons included healthy controls and participants with ADHD with comorbid dyslexia (Table 2).

Three studies compared the efficacy of atomoxetine to methylphenidate or stimulant medication.[23,24,32] Bastiaens et al reported similar benefits in ADHD symptom ratings, quality of life, internalizing and externalizing symptoms, and functioning for both treatments (atomoxetine and stimulants) with no differences between treatments (Table 2).[32] However, the

Table 1. Participant characteristics.

Study	Design	N (% male)	Age (y)
Bastiaens et al[32]	Prospective, open-label study	75 (78.6%) Groups: ATMX: 33 (nr%) Stimulants: 42 (nr%)	Range: 6–12 Groups: ATMX: 8.9 ± 2.3 Stimulants: 9.0 ± 2.0
Kratochvil et al[39]	RCT-p (double-blind)	93 (67.7%) Groups: ATMX: 44 (47.3%) Placebo: 49 (52.7%)	Range: 5–6 Groups: ATMX: 6.1 ± 0.6 Placebo: 6.1 ± 0.5
Chang et al[76]	Prospective, open-label study	12 (58.3%)	Range: 6–14 Mean: 11.3 ± 3.2
Cho et al[77]	Multi-centre, randomized, open-label, parallel trial	153 (83.7%) Groups: 0.2 mg/kg/d: 51 (92.2%) 0.5 mg/kg/d: 54 (80.4%) 1.2 mg/kg/d: 48 (78.4%)	Range: 6–18 Mean: 9.8 ± 2.4
de Jong et al[78]	RX-p (double-blind)	83 (63.9%) Groups: ADHD: 16 (87.5%) ADHD+RD: 20 (75.0%) RD: 21 (38.1%) Controls: 26 (61.5%)	Range: 8–12 Groups: ADHD: **8.8 ± 1.3** ADHD+RD: 9.8 ± 1.2 RD: **9.9 ± 1.0** Controls: 9.3 ± 0.9
Dell'Agnello et al[79]	Multi-centre, RCT-p (double-blind)	137 (92.7%) Groups: ATMX: 105 (93.3%) Placebo: 32 (90.6%)	Range: 6–15 Groups: ATMX: 9.7 ± 2.2 Placebo: 10.0 ± 2.4
Dittman et al[35] and Wehmeier et al[37]	RCT-p (double-blind)	180 (84.4%) Groups: ATMX-fast titration: 60 (85.0%) ATMX-slow titration: 61 (86.9%) Placebo: 59 (81.4%)	Range: 6–17 Groups: ATMX-fast titration: 11.1 ± 2.9 ATMX-slow titration: 10.8 ± 3.4 Placebo: 11.1 ± 2.8
Dittman et al[80]	Multi-centre, open-label, single arm study	159 (78.6%) Combined subtype: nr Predominantly inattentive subtype: nr	Range: 12–17 Mean: 14.1 ± 1.53
Escobar et al[81]	Multi-centre RCT-p (double-blind)	151 (79.5%) Groups: ATMX: 100 (79.0%) Placebo: 51 (80.4%)	Range: 6–15 Groups: ATMX: 10.3 ± 2.5 Placebo: 10.3 ± 2.4
Gau and Shang[82]	Open-label follow-up study	30 (100.0%)	Range: 8–16 Mean: 10.7 ± 1.8

Comorbidities (n, %)	ADHD subtype recruited	Comments
Disruptive behavior disorders (15, 20%) Anxiety disorders (12, 16%) Autism (9, 12%) Tic disorders (4, 5%) Depressive disorders (2, 3%).	Any	
ODD (32, 34.4%) Enuresis (16, 17.2%) SAD (1, 1.1%) Phobia (8, 8.6%) Tics (1, 1.1%) Other (5, 5.4%).	Any	
Bipolar I (10, 83%) Bipolar II (2, 17%) ODD (7, 58%).	Any	
nr	Any	Korean study
(Comorbidities other than RD and ODD were excluded). N ODD nr.	Combined	Netherlands and Belgium
ODD (137, 100%) GAD (15, 10.9%) OCD (3, 2.2%) Panic disorder (3, 2.2%) SAD (5, 3.6%) Specific phobias (10, 7.3%) Adjustment disorder (1, 0.7%) Dysthymia (9, 6.6%) MDD (2, 1.5%) SPD (2, 1.5%) Other depressive disorder (1, 0.7%).	Any (~89% combined subtype)	Italy
ADHD only (2, 1.1%), ODD (74.4%), conduct disorder (24.4%), disruptive behavior disorder not otherwise specified (1, 0.6%), adjustment disorder with mixed disturbance of emotions and conduct (1, 0.6%).	Any (75.6% combined, 19.4% IA, 5.0% HI)	Germany
Psychiatric comorbidities (29, 18.2%), ODD (21, 13.2%), emotional disorder of childhood (4, 2.5%), depressed mood (2, 1.3%).	Any (50.9% combined, 45.9% IA, 3.1% nr)	Germany
ODD (38, 25.5%), tic disorder (25, 16.8%), affective disorders (5, 3.4%), anxiety disorders (19, 12.8%).	Any (63.1% combined, 32.9% IA, 4.0% HI)	Spain
ODD (11, 36.7%), conduct disorder (1, 3.3%), history of anxiety disorders (2, 6.7%).	Any (50.0% combined, 43.3% IA, 6.5% HI)	Taiwan

(*Continued*)

Table 1. (*Continued*)

Study	Design	N (% male)	Age (y)
Ghuman et al[83]	Open-label, prospective, pilot study	12 (75.0%)	Range: 3.56–5.76 Mean: 5.0 ± 0.72
Hammerness et al[84]	Open-label, prospective study	34 (79%)	Range: 6–17 Mean: 10.8 ± 3.0
Hammerness et al[21] and Wilens et al[85]	Single-site, open-label study	ATMX+MPH phase: 50 (76%)	Range: 6–17 Mean: 9.3 ± 2.5
Kratz et al[86]	Randomized cross-over (no blinding)	19 (78.9%)	Range: 7–10 Mean: 9.0 ± 1.06
Martenyi et al[40]	RCT-p, (double-blind)	105 (85.7%) Groups: ATMX: 72 (87.5%) Placebo: 33 (81.8%)	Range: 6–16 Mean: 9.8 ± 2.8
Maziade et al[87]	Single-site, pilot, open-label longitudinal study	42 (73.8%) Groups: ADHD: 21 (76.2%) Controls: 20 (75.0%)	Range: 6–10.5 Groups: ADHD: 8.0 ± 1.3 Controls: 8.0 ± 1.5
Mendez et al[88]	Multi-centre, open-label trial	228 (85.1%)	Range: 8–11 Mean: 9.6 ± 0.96
Montoya et al[89]	Pilot RCT-p	41 (nr%) Groups: ATMX: 28 (nr%) Placebo: 13 (nr%)	Range: 6–15 Mean: nr
Montoya et al[90]	Multi-centre RCT-p (double-blind)	151 (79.5%) Groups: ATMX: 100 (79.0%) Placebo: 51 (80.4%)	Range: 6–15 Mean: 10.3 ± 2.5
Svanborg[34]	Multi-centre RCT-p (double-blind)	99 (80.8%) Groups: ATMX: 49 (79.6%) Placebo: 50 (82.0%) [+4 sessions of psycho-education for parents]	Range: 7–15 Mean: 11.5 ± 2.2
Saylor et al[30] and Wietecha et al[91]	Multi-site, randomized study (double-blind)	*8 week phase:* 267 (64.0%) Slow titration: 135 (65.9%) Fast titration: 132 (62.1%) *40 week maintenance:* 178 (62.4%) 0.8 mg/kg/d: 88 (58.0%) 1.4 mg/kg/d: 90 (66.7%) *High risk (scores > 75% of sample for YRBS or scores < 75% of sample for CHIP-AE):* 5–68 (nr%)	Range: 13–16 *8 week phase:* Slow titration: 14.7 ± 1.1 Fast titration: 14.5 ± 1.0 *40 week maintenance:* 0.8 mg/kg/d:14.7 ± 1.1 1.4 mg/kg/d: 14.5 ± 1.0 *High risk (scores > 75% of sample for YRBS or scores < 75% of sample for CHIP-AE):* nr
Sumner et al[38]	Open-label, non-randomized, parallel pilot study	56 (70.0%) Groups: ADHD: 20 (75.0%) ADHD+dyslexia: 36 (66.7%)	Range: 10–16 Groups: ADHD: 12.7 ± 1.5 ADHD+dyslexia: 12.2 ± 2.0

Comorbidities (n, %)	ADHD subtype recruited	Comments
nr	Any (41.7% combined, 58.3 HI)	USA
nr	nr	USA; participants had previous (unsuccessful) trial of stimulant medication.
ODD (20, 40%), conduct disorder (2, 4%), MDD (1, 2%), panic disorder (1, 2%), agoraphobia (4, 8%), social phobia (5, 10%), specific phobia (7, 14%), OCD (1, 2%), GAD (3, 6%), SAD (9, 18%).	Any (54% combined, 38% IA, 8% HI)	USA
Dyslexia (5, 26.3%), emotional disorder (2, 10.5%).	Combined (57.9%) or IA (42.1%)	Germany
ODD (2, 1.9%), conduct disorder (5, 4.8%).	Combined (72.2%), IA (23.6%), HI (4.2%)	Russia
nr	Combined (28.6%), IA (71.4%)	Canada
Communication disability (26.6%), learning disability (93.7%), motor skill disability (24.1%).	Combined (61.8%), IA (36.0%), HI (2.2%)	China, South Korea, Taiwan Spain; newly diagnosed, treatment-naïve participants
ODD (25.5%), tic disorder (16.8%), affective disorders (3.4%), anxiety disorders (12.8%).	Combined (63.1%), IA (32.9%), HI (4.0%)	Spain, newly-diagnosed ADHD, treatment-naive
Depression (5.1%), ODD (20.2%), tics—any type (14.1%), motoric tics (14.1%), phonetic tics (11.1%).	Combined (77.8%), IA (18.2%), HI (4.0%)	Sweden
nr	*8 week phase:* combined (47.9%), IA (49.8%), HI (2.2%) *Maintenance:* Combined (44.9%), IA (52.2%), HI (2.8%) *High risk (scores $>$ 75% of sample for YRBS or scores $<$ 75% of sample for CHIP-AE):* nr	USA
nr	Combined (53.6%), IA (42.9%), HI (3.6%).	USA

(*Continued*)

Table 1. (*Continued*)

Study	Design	N (% male)	Age (y)
Takahashi et al[92]	Multi-centre, RCT-p (double-blind)	245 (85.3%) Groups: 0.5 mg/kg/d: 62 (83.9%) 1.2 mg/kg/d: 60 (86.7%) 1.8 mg/kg/d: 61 (86.9%) Placebo: 62 (83.9%)	Range: 6–17 Mean: 10.5 ± 2.5 Groups: 0.5 mg/kg/d: 10.3 ± 2.6 1.2 mg/kg/d: 10.6 ± 2.7 1.8 mg/kg/d: 10.5 ± 2.7 Placebo: 10.8 ± 2.0
Thurstone et al[33]	RCT	70 (78.6%) Groups: ATMX+MI/CBT: 35 (71.4%) Placebo+MI/CBT: 35 (85.7%)	Range: 13–19 Groups: ATMX+MI/CBT: 16.1 ± 1.4 Placebo+MI/CBT: 16.1 ± 1.8
Waxmonsky et al[19,20]	Open-label randomized trial	56 (80.4%) Groups: ATMX: 27 (77.8%) ATMX+BT: 29 (82.8%) Subsample: 55 (80.0%) 1 daily dose: 33 (75.8%) 2 daily doses: 22 (86.4%)	Range: 6–12 Mean: 8.6 ± 1.6 Groups: ATMX: 8.9 ± 1.5 ATMX+BT: 8.3 ± 1.6 Subsample: 1 daily dose: 8.8 ± 1.7 2 daily doses: 8.4 ± 1.4
Wehmeier et al[36]	Multi-centre, RCT-p (double-blind)	125 (77.6%) Groups: ATMX: 63 (75.6%) Placebo: 62 (80.6%)	Range: 6–12 Mean: 9.0 ± 1.8 Groups: ATMX: 9.1 ± 1.9 Placebo: 8.9 ± 1.6
Wilens et al[25] (study 1 only)	Multi-centre, RCT-p (double-blind)	271 (65.7%) Groups: ATMX: 49 (69%) ABT-089 (0.085): 32 (71%) ABT-089 (0.26): 25 (57%) ABT-089 (0.52): 32 (71%) ABT-089 (0.7): 27 (64%) Placebo: 46 (61%)	Range: 6–12 Mean: 8.6 Groups: ATMX: 8.7 ± 1.9 ABT-089 (0.085): 8.7 ± 1.8 ABT-089 (0.26): 8.4 ± 1.8 ABT-089 (0.52): 8.6 ± 1.8 ABT-089 (0.7): 8.7 ± 1.9 Placebo: 8.6 ± 1.9
Yang et al[23]	RCT (single-blind: assessors only)	188 (81.9%) Groups: ATMX: 57 (87.7%) MPH: 85 (81.2%) Controls (non-ADHD): 46 (76.1%)	Range: 7–14 Mean: 9.6 ± 2.0 Groups: ATMX: 9.9 ± 2.0 MPH: 9.5 ± 1.9 Controls (non-ADHD): 10.4 ± 1.8
Yildiz et al[24]	Prospective, randomized, open-label study	26 (84.6%) Groups: ATMX: 14 (92.9%) MPH: 11 (81.8%)	Range: 8–14 Mean: 9.97 Groups: ATMX: 9.8 ± 1.4 MPH: 10.2 ± 1.7

Comorbidities (n, %)	ADHD subtype recruited	Comments
ODD (33, 13.5%), conduct disorder (2, 0.8%).	Combined (34.3%), IA (61.2%), HI (4.5%).	Japan
Conduct disorder (37, 52.9%), MDD (20, 28.6%), alcohol use disorder (20, 28.6%), cannabis use disorder (67, 95.7%), nicotine dependence (40, 57.1%), cocaine use disorder (2, 2.9%), amphetamine use disorder (1, 1.4%), hallucinogen use disorder (1, 1.4%).	Combined (75.7%), IA (17.1%), HI (7.1%).	USA
ADHD only (10, 17.9%), ODD (24, 42.9%), conduct disorder (22, 39.3%).	Combined (85.7%), IA (12.5%), HI (1.8%).	USA
ADHD only (75, 60.0%), ODD (39, 31.2%), conduct disorder (21, 16.8%), tic disorder (1, 0.8%), mood disorder (1, 0.8%).	Combined (70.4%), IA (22.4%), HI (7.2%).	Germany
nr	Combined (80%), IA (17.7%), HI (2.2%).	USA
ODD (44, 31.0%), conduct disorder (2, 1.4%).	Combined (50.0%), IA (47.2%), HI (2.8%).	China
ODD (7), conduct disorder (6)	Combined (84.0%), IA (16.0%).	Turkey

Notes: ABT-089 = a novel alpha-sub 4 beta sub 2 neuronal nicotinic receptor partial agonist (numbers in parentheses indicate dosage in mg/kg). Numbers in **bold** indicate significant differences between those groups.
Abbreviations: RCT-p, randomized placebo-controlled trial; RX-p, randomized placebo-controlled cross-over study; M, male; RD, reading disorder; ODD, oppositional defiant disorder; ATMX, atomoxetine; MPH, osmotic release oral system methylphenidate; YRBS, youth risk behavior surveillance; CHIP-AE, child health and illness profile—adolescent edition; MI, motivational interviewing; CBT, cognitive behavioral therapy; BT, behavior therapy; SAD, separation anxiety disorder; GAD, generalized anxiety disorders; OCD, obsessive compulsive disorder; MDD, major depressive disorders; SPD, seasonal pattern disorders; IA, inattentive; HI, hyperactive-impulsive; nr, not reported/specified.

Table 2. Efficacy table.

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
Bastiaens et al[28]	ATMX: 1.2 ± 0.3 Stimulants: 1.2 ± 0.4 (Psychotherapy also encouraged)	Mean: 10 months	ADHD-RS	Both treatments: –7.6 ± 10.6 ATMX: –7.2 ± 10.1 Stimulants: –7.9 ± 11	<0.05* nr nr	
			HALFS: Parent	Both treatments: 1.8 ± 3.6 ATMX: 1.9 ± 2.7 Stimulants: 1.7 ± 4.2	<0.05* nr nr	
			CSI: Parent	Both treatments: –16.7 ± 27.6 ATMX: –16.8 ± 29.2 Stimulants: –16.6 ± 26.7	<0.05* nr nr	
			GAF: Psychiatrist	Both treatments: 8 ± 7.9 ATMX: 9.5 ± 7.3 Stimulants: 6.8 ± 8.3	<0.05* nr nr	
Kratochvil et al[35]	ATMX: 1.4 ± 0.4 Placebo: 1.5 ± 0.3 (psychoeducation & behavioural management strategies provided)	8 weeks	ADHD-RS: Total: Parent	ATMX improvement > Placebo ATMX: –13.2 ± 1.7 Placebo: –5.8 ± 1.2	0.009*	ES: 0.7
			ADHD-RS: HI: Parent	ATMX improvement > Placebo ATMX: –6.2 ± 1.0 Placebo: –2.8 ± 0.8	0.005*	
			ADHD-RS: IA: Parent	ATMX improvement > Placebo ATMX: –7.3 ± 0.8 Placebo: –2.5 ± 0.8	0.002*	
			ADHD-RS: Total: Teacher	ATMX improvement > Placebo ATMX: –12.5 ± 1.7 Placebo: –5.0 ± 1.4	0.02*	ES: 0.6
			ADHD-RS: HI: Teacher	ATMX: –5.4 ± 1.0 Placebo: –3.2 ± 0.9	0.08	
			ADHD-RS: IA: Teacher	ATMX improvement > Placebo ATMX: –6.6 ± 1.0 Placebo: –2.3 ± 0.8	0.04*	
Chang et al[71]	ATMX: 1.0 (in addition to current treatment with mood stabilizers/ antipsychotics)	8 weeks, weekly assessments	ADHD-RS	–16.9 ± 10.9	<0.0001*	ES: 0.73
			CDRS	–0.7 ± 6.7	0.71	
			YMRS	–0.5 ± 5.5	0.72	

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
Cho et al[24]	Range: 0.2 mg/kg/d: 0.01–0.35 0.5 mg/kg/d: 0.36–0.85 1.2 mg/kg/d: >0.85 (with dose escalation)	6 weeks	ADHD-RS: Parent	0.2 mg/kg/d: –9.6 0.5 mg/kg/d: –12.3 1.2 mg/kg/d: –14.5	0.024*	
			CGI-I	Greater improvement in Group 3 than Group 1 (mean scores: 2.8 and 3.29 respectively)	0.0025*	
de Jong et al[73]	ATMX: 1.11 ± 0.1	28 days	ADHD-RS: parent	ADHD: ATMX: –5.6 Placebo: –2.7 ADHD+RD: ATMX: –12.6 Placebo: –2.1	<0.001* (treatment effect)	
			Corsi block tapping task	*N correct sequences:* ADHD: ATMX: +1.9 Placebo: +2.2 ADHD+RD: ATMX: +2.0 Placebo: +0.2 RD: ATMX: +1.6 Placebo: +1.0 Controls: Second visit: +1.2	<0.006* (treatment effect)	
			Stop signal paradigm	*Stop signal reaction time:* ADHD: ATMX: +8.9 Placebo: –5.9 ADHD+RD: ADHD: –21.1 Placebo: +12.4 RD: ATMX: –23.1 Placebo: –30.7 Controls: Second visit: +3.5	0.07	
				Mean reaction time: ADHD: ATMX: –68.4 Placebo: –45.7 ADHD+RD: ATMX: –24.0 Placebo: –30.8 RD: ATMX: –40.8 Placebo: –42.3 Controls: Second visit: –53.3	<0.001*	Treatment effect due to significant baseline-placebo comparison.

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
				Errors: ADHD: ATMX:–2.2 Placebo: –2.4 ADHD+RD: ATMX: –3.2 Placebo: –3.2 RD: ATMX: –2.4 Placebo: –3.6 Controls: Second visit: +1.8	0.002*	Treatment effect due to significant baseline-placebo comparison.
			Lexical decision task	*Accuracy value (independent of response bias):* ADHD: ATMX: –0.1 Placebo: 0 ADHD+RD: ATMX: +0.1 Placebo: –0.1 RD: ATMX: –0.2 Placebo: –0.3 Controls: Second visit: 0	>0.05	
				Mean reaction time (valid words): ADHD: ATMX: –149.6 Placebo: –188.3 ADHD+RD: ATMX: +25.2 Placebo: +46.2 RD: ATMX: –137.6 Placebo: –108.5 Controls: Second visit: –81.6	>0.05	
				Mean reaction time (pseudowords): ADHD: ATMX: –162.3 Placebo: –46.0 ADHD+RD: ATMX: +27.5 Placebo: –1.9 RD: ATMX: –156.6 Placebo: –110.7 Controls: Second visit: –117.1	>0.05	

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
Dell'Agnello et al[70]	Non-responders to parent training randomized: ATMX: 1.10 ± 0.13 (range: 0.85–1.33) Placebo	8 weeks	SNAP-IV	*ADHD subscale:* ATMX: –8.1 ± 9.2 Placebo: –2.0 ± 4.7	<0.001*	ATMX response rate > Placebo
				ODD subscale: ATMX: –2.7 ± 4.1 Placebo: –0.3 ± 2.6	0.001*	
			CGI-S	ATMX: –0.6 Placebo: +0.1	<0.001*	
			CPRS-R:S	*Oppositional subscale:* ATMX: –1.2 Placebo: +0.8	0.002*	
				Cognitive problems subscale: ATMX: –2.3 Placebo: –0.2	<0.001*	
				Hyperactivity subscale: AMTX: –2.2 Placebo: –0.7	0.022*	
				ADHD index: ATMX: –5.1 Placebo: –0.1	<0.001*	
			CTRS-R:S	*Oppositional subscale:* ATMX: –1.1 Placebo: 0.1	0.002*	
				Cognitive problems subscale: ATMX: +3.8 Placebo: 0.0	0.113	
				Hyperactivity subscale: ATMX: –2.1 Placebo: –1.1	0.051	
				ADHD index: ATMX: –3.5 Placebo: –1.5	0.061	
Dittman et al[31] and Wehmeier et al[33]	Target dose: 1.2 (mean or range nr)	9 weeks	SNAP-IV	*ODD scale:* Least square mean difference: ATMX v. Placebo: –3.2	<0.001*	ES: –0.69
				Least square mean scores at endpoint: ATMX-fast titration: 8.6		
				ATMX-slow titration: 9.0 Placebo: 12.0	0.003*	ES: –0.65

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
				ADHD scale: Least square mean difference: ATMX v. Placebo: –7.4	<0.001*	ES: –0.72
				Least square mean scores at endpoint: ATMX-fast titration: 22.9		
				ATMX-slow titration: 21.3	0.002*	No difference between ATMX groups.
				Placebo: 29.6		
			ADDB-Inv	*Disruptive behavior:* Least square mean difference: ATMX v. Placebo: –1.4	<0.001*	ES: –0.62. No difference between ATMX groups.
				ODD symptoms: ATMX improved > Placebo (data nr)	nr	
				ADHD symptoms: ATMX improved > Placebo (data nr)	nr	
			CGI-S	*ODD:* ATMX improved > Placebo: –0.8	<0.001*	ES: –0.22
				ADHD: ATMX improved > Placebo: –0.7	<0.001*	ES: –0.7
			Quality of life (German "KINDL-R" questionnaire)	*Total:* ATMX: +2.6 ± 16.4	Cf. Placebo 0.021*	
				Groups: ATMX fast titration: +2.0 ± 17.5	0.038*	No difference between ATMX groups.
				ATMX slow titration: +3.1 ± 15.4	0.053	
				Placebo: –1.6 ± 14.3		
				Physical well-being: ATMX: –6.6 ± 23.8	Cf. Placebo 0.017*	Scores sig. worse after ATMX than Placebo after treatment.
				Groups: ATMX fast titration: –9.7 ± 24.8	0.015*	
				ATMX slow titration: –3.6 ± 22.7	0.087	
				Placebo: –3.1 ± 16.9		
				Emotional well-being: ATMX: +0.1 ± 21.4	Cf. Placebo 0.05	
				Groups: ATMX fast titration: –0.4 ± 24.1	0.135	

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
				ATMX slow titration: +0.5 ± 18.6 Placebo: –3.7 ± 20.4	0.058	
				Self-esteem: ATMX: +5.3 ± 21.9 Groups: ATMX fast titration: +5.0 ± 23.2 ATMX slow titration: +5.5 ± 20.8 Placebo: –3.0 ± 20.4	Cf. Placebo <0.001* <0.001* 0.006*	ES: 0.590 No sig. difference between ATMX groups.
				Family: ATMX: +5.0 ± 26.4 Groups: ATMX fast titration: +5.7 ± 24.9 ATMX slow titration: +4.2 ± 28.0 Placebo: +1.9 ± 21.8	Cf. Placebo 0.015* 0.02* 0.062	No sig. difference between ATMX groups.
				Friends: ATMX: +7.5 ± 22.9 Groups: ATMX fast titration: +9.0 ± 21.0 ATMX slow titration: +6.0 ± 24.6 Placebo: +0.3 ± 21.6	Cf. Placebo 0.018* 0.006* 0.187	No sig. difference between ATMX groups.
				School: ATMX: +4.6 ± 21.7 Groups: ATMX fast titration: +2.4 ± 21.4 ATMX slow titration: +6.8 ± 22.0 Placebo: –1.8 ± 19.4	Cf. Placebo 0.138 Not sig. Not sig.	
			Impact on Family Scale (German)	*Total score:* nr (no sig. change)	>0.05	
				General negative impact: nr (no sig. change)	>0.05	
				Disruption of social relations: nr (no sig. change)	>0.05	
				Impact on siblings: ATMX: nr (improved) Groups: ATMX fast titration: nr (improved)	Cf. Placebo 0.005* 0.047*	

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
				ATMX slow titration: nr (improved) Placebo: nr	0.005*	
				Financial impact: nr (no sig. change)	>0.05	
				Problems in coping: nr (no sig. change)	>0.05	
Dittman et al[14]	Mean: 1.17–1.19 (range: 0.4–1.4)	8 weeks + optional 16 week extension period (same treatment)	GIPD: Patient	*Total group:* Week 2: –2.0 Week 8:–2.9 Week 24: –2.6	<0.05* <0.05* <0.05*	
				Combined subtype: Week 2: –1.9 Week 8: –2.5 Week 24: –2.6	<0.05* <0.05* <0.05*	
				Predominantly inattentive subtype: Week 2: –2.4 Week 8: –3.5 Week 24: –2.9	<0.05* <0.05* <0.05*	
			GIPD: Parent	*Total group:* Week 2: –4.6 Week 8: –5.8 Week 24: –5.5	<0.05* <0.05* <0.05*	
				Combined subtype: Week 2: –4.4 Week 8: –5.9 Week 24: –5.9	<0.05* <0.05* <0.05*	
				Predominantly inattentive subtype: Week 2: –4.7 Week 8: –5.7 Week 24: –5.0	<0.05* <0.05* <0.05*	
			GIPD: Physician	*Total group:* Week 2: –6.2 Week 8: –7.8 Week 24: –6.7	<0.05* <0.05* <0.05*	
				Combined subtype: Week 2: –5.8 Week 8: –7.2 Week 24: –6.7	<0.05* <0.05* <0.05*	
				Predominantly inattentive subtype: Week 2: –6.6 Week 8: –8.3 Week 24: –6.7	<0.05* <0.05* <0.05*	
			CGI-S	*Total group:* Week 8: –1.4 Week 24: –0.1	(sig. based on 95%CIs)	
			ADHD-RS: Parent	*Total group:* Week 2: –11.7 Week 8: –27.2 Week 24: –15.1	(sig. based on 95%CIs)	

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
				Combined subtype had significantly higher scores at all time-points than predominantly inattentive subtype.		
Escobar[74]	Max target dose: 1.2 (Mean or range nr)	12 weeks	CHIP: Parent	*Satisfaction:* ATMX: (value nr) Placebo: (value nr)	0.810	
				Comfort: ATMX: (value nr) Placebo: (value nr)	0.243	
				Resilience: ATMX: (value nr) Placebo: (value nr)	0.419	
				Risk avoidance: ATMX: +7.89 ± 17.5 Placebo: –0.64 ± 15.1	<0.001*	
				Achievement: ATMX: +4.94 ± 12.6 Placebo: +1.55 ± 11.1	0.042*	
			CHIP: Patient	*Satisfaction:* ATMX: (value nr) Placebo: (value nr)	0.323	
				Comfort: ATMX: (value nr) Placebo: (value nr)	0.452	
				Resilience: ATMX: (value nr) Placebo: (value nr)	0.910	
				Risk avoidance: ATMX: +3.60 ± 9.6 Placebo: +0.003 ± 8.8	0.006*	
				Achievement: ATMX: (value nr) Placebo: (value nr)	0.541	
			ADHD-RS: Parent	*Total score:* ATMX: –12.75 Placebo: –4.7	<0.001*	IA and HI scores also decreased significantly in ATMX group at week 12 (data nr).
Gau and Shang[75]	Mean: 1.20 ± 0.07	Measures at 4 and 12 weeks	CANTAB (Z scores)	*Intra-/extra-dimensional shifts:* Week 4: – Extra-dimensional shift errors: –0.58	0.0039*	ES: –0.49
				– Pre-extra-dimensional shift errors: –0.68	0.0018*	ES: –0.56

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
				– Completed stages: +0.62	0.077	ES: 0.44
				– Total errors (adjusted): –0.75	0.022*	ES: –0.63
				– Total trials (adjusted): –0.75	0.018*	ES: –0.57
				Week 12:		
				– Extra-dimensional shift errors: –0.34	0.005*	ES: –0.58
				– Pre-extra-dimensional shift errors: +0.452	0.452	ES: –0.16
				– Completed stages: +0.33	0.098	ES: 0.39
				– Total errors (adjusted): –0.31	0.054	ES: –0.59
				– Total trials (adjusted): –0.29	0.081	ES: –0.39
				Rapid visual information processing:		
				Week 4:		
				– Probability of hits: +0.59	0.005*	ES: 0.51
				– Probability of false alarms: +0.07	0.870	ES: 0.03
				– Sensitivity to errors: +0.65	0.002*	ES: 0.38
				– Strength of trace required to elicit a response: +0.26	0.352	ES: 0.20
				– Mean latency: –0.66	0.010*	ES: –0.42
				Week 12:		
				– Probability of hits: +0.29	0.011*	ES: 0.42
				– Probability of false alarms: –0.35	0.050	ES: –0.41
				– Sensitivity to errors: +0.43	0.001*	ES: 0.50
				– Strength of trace required to elicit a response: +0.42	0.015*	ES: 0.50
				– Mean latency: –0.59	<0.001*	ES: –0.80
				Spatial span:		
				Week 4:		
				– Span length: +0.36	0.109	ES: 0.34
				– Total errors: +0.07	0.768	ES: 0.07
				– Total usage errors: –0.46	0.016*	ES: –0.40

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
				Week 12:		
				– Span length: +0.34	0.001*	ES: 0.64
				– Total errors: –0.01	0.935	ES: –0.02
				– Total usage errors: –0.41	0.002*	ES: –0.69
				Spatial working memory:		
				Week 4:		
				– Total errors:–0.15	0.539	ES: –0.10
				– Strategy utilization: –0.38	0.118	ES: –0.29
				Week 12:		
				– Total errors: –0.22	0.033*	ES: –0.33
				– Strategy utilization: –0.30	0.004*	ES: –0.47
				Stockings of Cambridge:		
				Week 4:		
				– Problems solved in minimum moves: +0.03	0.899	ES: 0.03
				– Mean moves: –0.29	0.244	ES: –0.30
				– Mean initial thinking time: –0.30	0.082	ES: –0.34
				– Mean subsequent thinking time: –0.81	0.005*	ES: –0.74
				Week 12:		
				– Problems solved in minimum moves: +0.31	0.006*	ES: 0.64
				– Mean moves: –0.28	0.017*	ES: –0.60
				– Mean initial thinking time: –0.16	0.041*	ES: –0.35
				– Mean subsequent thinking time: –0.53	<0.001*	ES: –1.12
			CGI-S: Physician	Change from Baseline:		
				Week 4: –2.13	<0.001*	ES: –2.61
				Week 12: –1.37	<0.001*	ES: –3.41
			SNAP-IV (Chinese version): Parent	*Inattentive:*		
				Week 4: –1.16	<0.001*	ES: –0.9
				Week 12: –0.82	<0.001*	ES: –1.15
				Hyperactive-impulsive:		
				Week 4: –1.03	<0.001*	ES: –0.51
				Week 12: –0.72	<0.001*	ES: –0.80

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
			CPRS-R:S (Z scores)	*Oppositional:* Week 4: –0.28 Week 12: –0.28 *Inattentive/ cognitive problems:* Week 4: –0.84 Week 12: –0.62 *Hyperactivity/ impulsivity:* Week 4: –1.45 Week 12: –0.84 *Oppositional:* Week 4: –0.38 Week 12: –0.25	 0.176 0.020* 0.002* <0.001* <0.001* <0.001* 0.189 0.041*	 ES: –0.25 ES: –0.45 ES: –0.63 ES: –0.93 ES: –0.71 ES: –0.82 ES: –0.29 ES: –0.37
Ghuman et al[76]	Mean: 1.59 ± 0.31	Mean: 8.24 ± 2.99 weeks (range: 2–12 weeks)	SNAP-IV: Parent	HI: –10.16 ± 7.3 IA: –7.00 ± 5.41 Total ADHD composite: –16.17 ± 12.16 ODD: –5.75 ± 6.48	0.0005* 0.0009* 0.0008* 0.0108*	ES: 1.54 ES: 1.34 ES: 1.70 ES: 0.83
			SNAP-IV: Teacher	HI: –3.43 ± 10.94 IA: –3.71 ± 6.45 Total ADHD composite: –7.14 ± 16.12 ODD: –3.15 ± 4.91	0.439 0.1783 0.2855 0.1420	
			Parent early childhood inventory-4 scale	Communication developmental milestones: +0.56 ± 2.24 Elimination disorders: –0.89 ± 1.97 Anxiety disorders: –5.33 ± 5.45 Depressive disorders: +1.00 ± 5.43 Peer conflict scale: –7.45 ± 7.84 Sleep problems: –1.58 ± 1.94	0.479 0.212 0.019* 0.5958 0.022* 0.043*	ES: 0.75 ES: 0.99 ES: 0.44
			CGI-S: Parent	–1.70 ± 1.34	0.003*	ES: 1.28
			CGI-S: Physician	–1.17 ± 1.11	0.004*	ES: 1.64
			Children's Global Assessment Scale: Physician	+10.08 ± 9.71	0.0042*	ES: 1.47

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
Hammerness et al[77]	Mean: 1.26 ± 0.22	6 weeks	ADHD-RS	*Total score:* –15.0 (exact value nr)	<0.05*	
				Inattention score: –8.1 ± 1.3	<0.001*	
				Hyperactivity/ impulsivity score: –5.7 ± 1.0	<0.001*	
			Responders to treatment	*CGI + 30% reduction in ADHD-RS:* Responders: 56% Remissions: 32%		
Hammerness et al[17] and Wilens et al[78]	Mean ATMX: 1.1 Mean MPH: 1.0	3 weeks (prior 4 weeks ATMX only, then partial responders completed subsequent 3 week adjunct MPH phase)	ADHD-RS	*ATMX-only phase:* –25.1	<0.0001*	
				ATMX+MPH phase (change from end of previous ATMX-only phase): –8.34	<0.0001*	
			CGI-S	*ATMX-only phase:* –1.0	nr	Cf. Baseline
				ATMX+MPH phase (change from end of previous ATMX-only phase): –0.8	<0.0001*	
			BRIEF: Inhibition	*ATMX-only phase:* –3.0	<0.05*	Cf. Baseline
				ATMX+MPH phase (change from end of previous ATMX-only phase): –5.0	<0.05*	Cf. ATMX-only phase
			BRIEF: Shifting	*ATMX-only phase:* –3.0	<0.05*	Cf. Baseline
				ATMX+MPH phase (change from end of previous ATMX-only phase): –3.0	<0.05*	Cf. ATMX-only phase
			BRIEF: Initiation	*ATMX-only phase:* –7.0	<0.05*	Cf. Baseline
				ATMX+MPH phase (change from end of previous ATMX-only phase): –6.0	<0.001*	Cf. ATMX-only phase

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
			BRIEF: Working memory	*ATMX-only phase:* –7.0	<0.05*	Cf. Baseline
				ATMX+MPH phase (change from end of previous ATMX-only phase): –7.0	<0.001*	Cf. ATMX-only phase
			BRIEF: Emotional control	*ATMX-only phase:* –2.0	<0.05*	Cf. Baseline
				ATMX+MPH phase (change from end of previous ATMX-only phase): –1.0	>0.05	
			BRIEF: Plan/ organize	*ATMX-only phase:* –4.0	<0.05*	Cf. Baseline
				ATMX+MPH phase (change from end of previous ATMX-only phase): –7.0	<0.001*	Cf. ATMX-only phase
			BRIEF: Organization of material	*ATMX-only phase:* –4.0	<0.05*	Cf. Baseline
				ATMX+MPH phase (change from end of previous ATMX-only phase): –4.0	<0.01*	Cf. ATMX-only phase
			BRIEF: Monitor	*ATMX-only phase:* –3.0	<0.05*	Cf. Baseline
				ATMX+MPH phase (change from end of previous ATMX-only phase): –6.0	<0.001*	Cf. ATMX-only phase
Kratz et al[79]	Mean dose: ATMX: 34.95 ± 7.80 mg MPH: 27.9 ± 7.87 mg	8 weeks	CGI-I: Physician	Mean score after each treatment: ATMX: 2.16 ± 1.12 MPH: 1.84 ± 1.01	nr	
			FBB-HKS (German)	*Total score (cf. Baseline):* ATMX: –0.91 (–56.23 ± 28.79%)	≤0.001*	
				MPH: –0.8 (–50.24 ± 36.90%)	≤0.001*	
				Inattention score (cf. Baseline): ATMX: –0.98	≤0.001*	
				MPH: –0.90	≤0.001*	
				Hyperactivity/ impulsivity score (cf. Baseline): ATMX: –0.85	≤0.001*	
				MPH: –0.71	≤0.001*	

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
			Responders to treatment	*40% reduction in FBB-HKS total score:* ATMX: n = 13 (68.4%) MPH: n = 12 (63.2%)	nr	
			Attention network test	*Number of hits (out of 192; cf. Baseline):* ATMX: +14.0 MPH: +18.6	≤0.001* ≤0.001*	No sig. difference between ATMX and MPH.
				Median reaction time (cf. Baseline): ATMX: –62.2 ms MPH: –82.9 ms	≤0.001* ≤0.001*	No sig. difference between ATMX and MPH.
				Median reaction time variability (cf. Baseline): ATMX: –31.8 ms MPH: –50.6 ms	≤0.001* ≤0.001*	MPH < ATMX ($p \leq 0.05$)
				Alerting score (reaction time for no-cue trials – reaction time for neutral-cue trials; cf. Baseline): ATMX: –5.6 ms MPH: –10.6 ms	>0.05 >0.05	No sig. difference between ATMX and MPH.
				Orienting score (reaction time for neutral-cue trials – reaction time for spatial-cue trials; cf. Baseline): ATMX: –4.4 ms MPH: –5.5 ms	>0.05 >0.05	No sig. difference between ATMX and MPH.
				Conflict score (reaction time for incongruent trials – reaction time for congruent trials; cf. Baseline): ATMX: –25.3 ms MPH: –22.7 ms	≤0.01* ≤0.05*	No sig. difference between ATMX and MPH.
				Median reaction time no-cue (cf. Baseline): ATMX: –61.3 ms MPH: –86.1 ms	nr nr	

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
				Median reaction time neutral cue (cf. Baseline):		
				ATMX: –58.2 ms	nr	
				MPH: –81.9 ms	nr	
				Median reaction time spatial cue	nr	
				(cf. Baseline):	nr	
				ATMX: –53.8 ms		
				MPH: –76.4 ms		
				Median reaction time congruent	nr	
				(cf. Baseline):	nr	
				ATMX: –56.8 ms		
				MPH: –78.6 ms		
				Median reaction time incongruent	nr	
				(cf. Baseline):	nr	
				ATMX: –82.1 ms		
				MPH: –101.3 ms		
Martenyi et al[36]	Mean ATMX: 1.4 ± 0.4	6 weeks	ADHD-RS: Parent	*Total score:*	0.013*	Improvement from ATMX > Placebo
				ATMX: –15.8 ± 0.9		
				Placebo: –11.4 ± 1.4		
				HI score:	0.002*	Improvement from ATMX > Placebo
				ATMX: –7.6 ± 0.5		
				Placebo: –4.8 ± 0.7		
				IA score:	0.030*	Improvement from ATMX > Placebo
				ATMX: –8.7 ± 0.5		
				Placebo: –6.5 ± 0.8		
			CGI-S	nr	0.035*	Improvement from ATMX > Placebo
			CPRS-R:S	*Oppositional:*	0.326	
				ATMX: –1.3 ± 0.4		
				Placebo: –0.6 ± 0.6		
				Cognitive:	0.065	
				ATMX: –4.8 ± 0.4		
				Placebo: –3.3 ± 0.6		
				Hyperactivity:	0.014*	Improvement from ATMX > Placebo
				ATMX: –5.1 ± 0.4		
				Placebo: –3.2 ± 0.6		
				ADHD index:	0.028*	Improvement from ATMX > Placebo
				ATMX: –10.7		
				Placebo: –7.5		
				Clinical global impressions-ADHD-Severity:	0.035*	Improvement from ATMX > Placebo
				ATMX: –1.5 ± 0.1		
				Placebo: –1.1 ± 0.2		
			Treatment response	>*25% reduction in ADHD-RS total score:*	0.022*	
				ATMX: n = 52 (72.2%)		

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
				Placebo: n = 16 (48.5%)		
				≥ 50% *reduction in ADHD-RS total score:* ATMX: n = 28 (38.9%)	<0.001*	
				Placebo: n = 3 (9.1%)		
Maziade et al[80]	Maximum dose: 1.4 mg/kg or 100 mg (whichever was less; mean nr)	6 months	NEPSY	*Memory and learning (cf. Baseline):* ADHD: 10.6 ± 13.3	0.010*	No sig. difference between ADHD and controls.
				Controls: 10.5 ± 13.3	0.011*	
				Attention/ executive functions (cf. Baseline): ADHD: 3.3 ± 17.0	0.397	No sig. difference between ADHD and controls.
				Controls: 0.8 ± 14.8	0.588	
				Language: ADHD: 1.9 ± 12.9	0.715	No sig. difference between ADHD and controls.
				Controls: 4.9 ± 8.1	0.039*	
				Visual-spatial processing (cf. Baseline): ADHD: 2.2 ± 13.6	0.309	No sig. difference between ADHD and controls.
				Controls: 1.1 ± 11.6	0.880	
				Sensorimotor (cf. Baseline): ADHD: 1.3 ± 16.7	0.910	No sig. difference between ADHD and controls.
				Controls: –2.1 ± 11.9	0.682	
			BRIEF: (T scores; ADHD only)	*Global executive composite:* Parent: –12.8 ± 9.77	<0.001*	
				Teacher: –5.6 ± 9.18	<0.05*	
				Behavioral regulation: Parent: –9.8 ± 6.57	<0.001*	
				Teacher: –2.1 ± 8.63	>0.05	
				– *Inhibit:* Parent: –10.3 ± 7.14	<0.001*	
				Teacher: –2.7 ± 8.43	>0.05	
				– *Shift:* Parent: –7.3 ± 7.56	<0.01*	

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
				Teacher: 0.0 ± 10.33	>0.05	
				– *Emotional control:* Parent: –7.6 ± 8.66	<0.01*	
				Teacher: –2.8 ± 7.25	>0.05	
				Metacognition: Parent: –12.9 ± 12.31	<0.001*	
				Teacher: –6.3 ± 9.78	<0.05*	
				– *Initiate:* Parent: –9.6 ± 10.89	<0.01*	
				Teacher: –2.5 ± 8.00	>0.05	
				– *Working memory:* Parent: –14.2 ± 9.14	<0.001*	
				Teacher: –6.6 ± 11.53	<0.05*	
				– *Plan and organize:* Parent: –13.3 ± 14.58	<0.01*	
				Teacher: –7.6 ± 10.20	<0.05*	
				– *Organization of materials:* Parent: –7.3 ± 10.41	<0.05*	
				Teacher: –8.1 ± 11.23	<0.05*	
				– *Monitor:* Parent: –12.4 ± 11.18	<0.001*	
				Teacher: –6.6 ± 9.54	<0.05*	
			ADHD-RS (ADHD only)	Cf. Baseline: 2 months:		
				Parent: –11.8	<0.05*	
				Teacher: –7.2	<0.05*	
				6 months: Parent: –20.0	<0.05*	
				Teacher: –13.8	<0.05*	
			Test of everyday attention (ADHD only)	*Selective attention: Sky search time per target:* –1.8	<0.001*	
				Sky search attention score: –1.6	0.004*	
				Sky search targets found: approx. –1.2	>0.05	

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
				Attentional control:		
				Creature counting accuracy: +1.1	0.021*	
				Creature counting time scores: –2.4	0.048*	
				Sustained attention:		
				Walk, don't run: +3.1	0.024*	
				Score!: approx. +0.5	>0.05	
			CGI-S	Cf. Baseline:		
				3 weeks: –0.03	<0.05*	
				5 weeks: –0.60	<0.05*	
				2 months: –0.70	<0.05*	
				4 months: –1.70	<0.05*	
				6 months: –2.10	<0.05*	
			Weiss functional impairment rating scale: Parent (ADHD only)	*Overall score:*		
				2 months: –0.22 ± 0.27	0.002*	
				6 months: –0.26 ± 0.31	0.002*	
				Family score:		
				2 months: –0.30 ± 0.40	0.029*	
				6 months: –0.25 ± 0.35	0.014*	
				Learning and school score:		
				2 months: –0.24 ± 0.46	1.00	
				6 months: –0.46 ± 0.46	0.002*	
				Life skills score:		
				2 months: –0.34 ± 0.45	0.007*	
				6 months: –0.36 ± 0.55	0.025*	
				Child self-concept:		
				2 months: +0.04 ± 0.69	1.00	
				6 months: –0.33 ± 0.40	0.006*	
				Social activities:		
				2 months: –0.25 ± 0.43	0.063	
				6 months: –0.13 ± 0.45	0.266	
				Risky activities:		
				2 months: –0.03 ± 0.25	0.886	
				6 months: –0.06 ± 0.23	0.418	

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
Mendez et al[81]	Mean: 1.2 ± 0.12	24 weeks	ADHD-RS	*Total score:* –18.8 ± 9.27	<0.001*	
			CGI-S	–2.1 ± 1.25	<0.001*	
			CGI-I	+2.3 ± 1.05	nr	
			CPRS-R:S	*Hyperactivity:* –4.5 ± 4.24	<0.001*	
				Inattention: –4.4 ± 4.60	<0.001*	
				Oppositional: –2.6 ± 4.43	<0.001*	
				Total: –9.8 ± 7.94	<0.001*	
			School grade	*Language:* +3.9 ± 13.35	<0.001*	
				Mathematics: +4.1 ± 16.58	<0.001*	
				Science: +6.1 ± 14.98	<0.001*	
				School grade average: +4.7 ± 10.68	<0.001*	
Montoya et al[82]	Target dose: 1.2 (mean actual nr)	12 weeks	ADHD-RS (Total score)	ATMX: –14.6 Placebo: –4.7	Sig. (nr)* Not sig.	
			CGI-S	ATMX: nr Placebo: nr	Sig. (nr)* Not sig.	
			CPRS-R:S (Total score)	ATMX: nr Placebo: nr	Sig. (nr)* Not sig.	
Montoya et al[83]	Range: 0.8–1.4	12 weeks	ADHD-RS	*Total score:* ATMX: –12.8 ± 9.3 Placebo: –4.7 ± 7.4	0.013* Not sig.	Improvement in ATMX > Placebo ($p < 0.001$*); improvement in No comorbidity sig. > With comorbidities
				Inattention: ATMX: –7.0 Placebo: –2.6	0.018* Not sig.	Improvement in ATMX > Placebo ($p < 0.001$*)
				Hyperactivity-impulsivity: ATMX: –5.7 Placebo: –2.1	0.068 Not sig.	Improvement in ATMX > Placebo ($p < 0.001$*)
			CPRS-R:S	*Total:* ATMX: –16.8 Placebo: –6.2	nr nr	Improvement in ATMX > Placebo (95%CI: –15.1––6.2*)
				Oppositional: ATMX: –1.7 Placebo: +0.1	nr nr	Difference between ATMX & Placebo not sig. (95%CI: –2.3–0.2)

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
				Cognitive problems: ATMX: –5.1 Placebo: –2.4	 nr nr	Improvement in ATMX > Placebo (95%CI: –4.2 – –1.3*)
				Hyperactivity: ATMX: –3.8 Placebo: –1.5	 nr nr	Improvement in ATMX > Placebo (95%CI: –3.4– –1.0*)
				ADHD index: ATMX: –9.3 Placebo: –3.4	 nr nr	Improvement in ATMX > Placebo (95%CI: –8.1– –3.6*)
			CGI-S	(Values nr): Improvement in ATMX sig. > Placebo	nr	
			Responders	≥ *25% reduction in ADHD-RS:* ATMX: 65% Placebo: 22%	sig. difference	
				≥ *30% reduction in ADHD-RS:* ATMX: 60% Placebo: 16%	sig. difference	
				≥ *40% reduction in ADHD-RS:* ATMX: 50% Placebo: 14%	sig. difference	
Svanborg[30]	Mean final dose: 1.1 ± 0.2 Range: 0.6–1.4	10 weeks	ADHD-RS (Swedish)	*Total (least square mean change):* ATMX: –19.0 ± 10.5 Placebo: –6.3 ± 10.6	<0.001* (between groups)	
				IA (least square mean change): ATMX: –10.3 ± 5.6 Placebo: –3.8 ± 4.9	<0.001* (between groups)	
				HI (least square mean change): ATMX: –8.7 ± 5.6 Placebo: –2.5 ± 5.7	<0.001* (between groups)	
			CGI-S	Least square mean change: ATMX: –1.8 ± 0.7 Placebo: –0.3 ± 0.7	<0.001* (between groups)	
			CGI-I	Least square mean change: ATMX: +2.3 ± 1.4 Placebo: +3.7 ± 1.4	<0.001* (between groups)	

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
				[lower score reflects greater improvement]		
Saylor et al[26] and Wietecha et al[27]	*8 week phase:* Target dose: 1.2 *40 week maintenance:* Target doses: 0.8 or 1.4 [mean actual and range nr]	8 weeks acute, then 40 weeks maintenance	ADHD-RS	*Total:*		
				8 week phase:		No sig. differences between groups.
				Slow titration: −17.3 ± 9.0	<0.001*	
				Fast titration: −16.48 ± 8.9	<0.001*	
				40 week maintenance (cf. end of 8 week phase):		
				0.8 mg/kg/d: +3.8 ± 9.6	<0.001*	
				1.4 mg/kg/d: +1.93 ± 9.6	0.068	
				HI score:		
				8 week phase:		No sig. differences between groups.
				Slow titration: −6.8 ± 4.4	<0.001*	
				Fast titration: −6.8 ± 4.3	<0.001*	
				40 week maintenance (cf. end of 8 week phase):		
				0.8 mg/kg/d: +1.2 ± 4.6	0.025*	
				1.4 mg/kg/d: +0.51 ± 4.6	0.314	
				IA score:		
				8 week phase:		No sig. differences between groups.
				Slow titration: −10.5 ± 5.7	<0.001*	
				Fast titration: −9.7 ± 5.6	<0.001*	
				40 week maintenance (cf. end of 8 week phase):		
				0.8 mg/kg/d: +2.6 ± 5.9	<0.001*	
				1.4 mg/kg/d: +1.4 ± 5.9	0.034*	
			CGI-S	8 week phase:		No sig. difference between groups.
				Slow titration: −1.5 ± 0.09	<0.001*	
				Fast titration: −1.45 ± 0.09	<0.001*	
				40 week maintenance (cf. end of 8 week phase):		
				0.8 mg/kg/d: +0.5 ± 0.1	<0.001*	Loss of benefit in 1.4 < 0.8 ($p = 0.008$*).
				1.4 mg/kg/d: +0.04 ± 0.1	0.699	

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
			Life participation scale for ADHD: Parent	8 week phase:		No sig. difference between groups.
				Slow titration: +11.0 ± 1.0	<0.001*	
				Fast titration: +9.7 ± 1.1	<0.001*	
				40 week maintenance (cf. end of 8 week phase):		
				0.8 mg/kg/d: –4.1 ± 1.5	0.009*	
				1.4 mg/kg/d: –2.1 ± 1.4	0.138	
				Change from Baseline to end of 40 week maintenance:		
				0.8 mg/kg/d: +7.7 ± 1.4	<0.001*	
				1.4 mg/kg/d: +10.5 ± 1.3	<0.001*	
				High risk group (cf. Baseline):		
				8 weeks: 7.9 ± 12.1	<0.001*	
				40 weeks: 9.3 ± 12.5	<0.001*	
			Family assessment measure version III: Patient (T score)	8 week phase:		No sig. difference between groups.
				Slow titration: –1.3 ± 0.3	0.009*	
				Fast titration: –0.8 ± 0.3	<0.001*	
				40 week maintenance (cf. end of 8 week phase):		
				0.8 mg/kg/d: nr	Not sig.	
				1.4 mg/kg/d: nr	Not sig.	
			Woodcock-Johnson III tests of achievement form	*Total score:*		No sig. difference between groups.
				8 week phase:		
				Slow titration: approx. +7.9	<0.001*	
				Fast titration: approx. +7.4	<0.001*	
				40 week maintenance (cf. end of 8 week phase):		
				0.8 mg/kg/d: approx. –4.5	<0.231	
				1.4 mg/kg/d: approx. –3.7	<0.254	
				High risk group (cf. Baseline):		
				8 weeks: +6.3 ± 14.6	0.004*	
				40 weeks: +8.8 ± 13.2	0.004*	

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
				Broad reading standard score:		No sig. difference between groups.
				8 week phase:		
				Slow titration: approx. +3.9	<0.001*	
				Fast titration: approx. +2.9	<0.001*	
				40 week maintenance (cf. end of 8 week phase):		
				0.8 mg/kg/d: approx. −2.1	<0.132	
				1.4 mg/kg/d: approx. +0.9	<0.471	
				High risk group (cf. Baseline):		
				8 weeks: +4.1 ± 10.9	0.011*	
				40 weeks: +4.4 ± 6.2	0.002*	
				Broad math standard score:		No sig. difference between groups.
				8 week phase:		
				Slow titration: approx. +0.4	0.177	
				Fast titration: approx. +1.0	0.543	
				40 week maintenance (cf. end of 8 week phase):		
				0.8 mg/kg/d: approx. −2.3	0.105	
				1.4 mg/kg/d: approx. −2.7	0.040*	
				High risk group (cf. Baseline):		
				8 weeks: −0.4 ± 5.2	0.551	
				40 weeks: 0.8 ± 7.2	0.610	
				Broad written language standard score:		No sig. difference between groups.
				8 week phase:		
				Slow titration: approx. +3.4	<0.001*	
				Fast titration: approx. +3.7	<0.001*	
				40 week maintenance (cf. end of 8 week phase):		
				0.8 mg/kg/d: approx. −0.2	0.880	

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
				1.4 mg/kg/d: approx. −1.8	0.197	
				High risk group (cf. Baseline):		
				8 weeks: +2.5 ± 5.4	0.002*	
				40 weeks: +3.9 ± 6.3	0.007*	
			Youth risk behavior survey	*Tobacco use:*		No sig. difference between groups.
				8 week phase:		
				Slow titration: nr	Not sig.	
				Fast titration: nr	Not sig.	
				40 week maintenance (cf. end of 8 week phase):		
				0.8 mg/kg/d: nr	Not sig.	
				1.4 mg/kg/d:nr	Not sig.	
				High risk group (cf. Baseline):		
				8 weeks: −1.4 ± 4.8	0.046*	
				40 weeks: −1.1 ± 5.7	0.317	
				Unhealthy dietary behaviors:		No sig. difference between groups.
				8 week phase:		
				Slow titration: nr	Not sig.	
				Fast titration: nr	Not sig.	
				40 week maintenance (cf. end of 8 week phase):		
				0.8 mg/kg/d: nr	Not sig.	
				1.4 mg/kg/d:nr	Not sig.	
				High risk group (cf. Baseline):		
				8 weeks: −3.2 ± 6.0	<0.001*	
				40 weeks: −4.1 ± 4.9	<0.001*	
				Inadequate physical activity:		No sig. difference between groups.
				8 week phase:		
				Slow titration: nr	Not sig.	
				Fast titration: nr	Not sig.	
				40 week maintenance (cf. end of 8 week phase):		
				0.8 mg/kg/d: nr	Not sig.	
				1.4 mg/kg/d:nr	Not sig.	
				High risk group (cf. Baseline):		
				8 weeks: −3.8 ± 7.6	<0.001*	
				40 weeks: −5.8 ± 6.7	<0.001*	

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
				Alcohol and other drug use:		No sig. difference between groups.
				8 week phase:		
				Slow titration: nr	Not sig.	
				Fast titration: nr	Not sig.	
				40 week maintenance (cf. end of 8 week phase):		
				0.8 mg/kg/d: nr	Not sig.	
				1.4 mg/kg/d:nr	Not sig.	
				High risk group (cf. Baseline):		
				8 weeks: -0.7 ± 4.4	0.168	
				40 weeks: $+0.6 \pm 5.4$	0.488	
				Sexual behaviors leading to unintended pregnancy and/or sexually transmitted diseases:		No sig. difference between groups.
				8 week phase:		
				Slow titration: nr	Not sig.	
				Fast titration: nr	Not sig.	
				40 week maintenance (cf. end of 8 week phase):		
				0.8 mg/kg/d: nr	Not sig.	
				1.4 mg/kg/d:nr	Not sig.	
				High risk group (cf. Baseline):		
				8 weeks: $+1.3 \pm 4.12$	0.053	
				40 weeks: $+0.8 \pm 2.5$	0.158	
				Behaviors contributing to unintentional injuries and violence:		
				8 week phase:		No sig.
				Slow titration: nr (improved)	<0.001*	difference between
				Fast titration: nr (improved)	<0.001*	groups.
				40 week maintenance (cf. end of 8 week phase):		
				0.8 mg/kg/d: nr	Not sig.	Improvement in $1.4 > 0.8$ ($p = 0.032$*).
				1.4 mg/kg/d:nr (improved)	0.036*	

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
				High risk group (cf. Baseline):		
				8 weeks: –4.0 ± 4.3	<0.001*	
				40 weeks: –4.5 ± 4.8	<0.001*	
			Grade point average	*English (Least squares means; cf. Baseline):*		No sig. difference between groups.
				40 week maintenance:		
				0.8 mg/kg/d: +0.2 ± 1.6	0.561	ES: 0.303
				1.4 mg/kg/d: +0.3 ± 1.6	0.136	ES: 0.279
				High risk group (cf. Baseline):		
				40 weeks: +0.4 ± 1.4	0.211	
				Math (Least squares means; cf. Baseline):		No sig. difference between groups.
				40 week maintenance:		
				0.8 mg/kg/d: +0.7 ± 2.0	0.032*	ES: 0.398
				1.4 mg/kg/d: +0.3 ± 2.0	0.394	ES: 0.485
				High risk group (cf. Baseline):		
				40 weeks: +0.5 ± 1.7	0.156	
				Science(Least squares means; cf. Baseline):		No sig. difference between groups.
				40 week maintenance:		
				0.8 mg/kg/d: –0.1 ± 2.0	0.810	ES: 0.319
				1.4 mg/kg/d: 0.0 ± 2.1	0.989	ES: 0.036
				High risk group (cf. Baseline):		
				40 weeks: –0.02 ± 1.5	0.949	
				Social studies (Least squares means; cf. Baseline):		No sig. difference between groups.
				40 week maintenance:		
				0.8 mg/kg/d: +0.6 ± 2.0	0.086	ES: 0.364
				1.4 mg/kg/d: +0.2 ± 1.9	0.427	ES: 0.263

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
				High risk group (cf. Baseline): 40 weeks: +0.4 ± 1.6	0.262	
			Kaufman brief intelligence test	*Composite score (Least squares means; cf. Baseline):*		No sig. difference between groups.
				40 week maintenance:		
				0.8 mg/kg/d: +3.8 ± 15.1	0.101	ES: 0.262
				1.4 mg/kg/d: +3.1 ± 14.2	0.150	ES: 0.249
				High risk group (cf. Baseline): 40 weeks: +1.3 ± 8.1	0.461	
Sumner et al[34]	Mean: 1.29	Approx. 16 weeks	ADHD-RS	*Total:*		
				ADHD: −20.2 ± 2.8	<0.001*	No sig. differences between groups.
				ADHD + dyslexia: −17.7 ± 2.5	<0.001*	
				IA:		
				ADHD: −11.0 ± 1.6	<0.001*	No sig. differences between groups.
				ADHD + dyslexia: −10.4 ± 1.4	<0.001*	
				HI:		
				ADHD: −8.5 ± 1.4	<0.001*	No sig. differences between groups.
				ADHD + dyslexia: −7.7 ± 1.2	<0.001*	
			Life participation scale for ADHD: Parent	ADHD: nr (improved)	<0.05*	No sig. differences between groups.
				ADHD + dyslexia: nr (improved)	<0.05*	
			Kaufman test of educational achievement	*Reading decoding standard:*		
				ADHD: +3.9 ± 9.4%	Not sig.	No sig. differences between groups.
				ADHD + dyslexia: +5.6 ± 10.8	≤0.05*	
				Reading decoding age equivalent (months):		
				ADHD: +17.8 ± 23.7	≤0.05*	No sig. differences between groups.
				ADHD + dyslexia: +16.9 ± 34.2	≤0.05*	
				Spelling standard:		
				ADHD: +3.2 ± 4.9	≤0.05*	No sig. differences between groups.
				ADHD + dyslexia: +1.5 ± 6.0	Not sig.	

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
				Spelling age equivalent (months):		
				ADHD: +9.7 ± 10.7	≤0.05*	No sig. differences between groups.
				ADHD + dyslexia: +8.7 ± 13.2	≤0.05*	
				Reading comprehension standard:		
				ADHD: +5.6 ± 8.9	≤0.05*	No sig. differences between groups.
				ADHD + dyslexia: +9.8 ± 10.2	≤0.05*	
				Reading comprehension age equivalent (months):		
				ADHD: +17.0 ± 25.5	≤0.05*	No sig. differences between groups.
				ADHD + dyslexia: +26.0 ± 31.2	≤0.05*	
				Reading composite standard:		
				ADHD: +4.5 ± 8.0	≤0.05*	No sig. differences between groups.
				ADHD + dyslexia: +8.1 ± 9.6	≤0.05*	
				Reading composite age equivalent (months):		
				ADHD: +17.2 ± 19.7	≤0.05*	No sig. differences between groups.
				ADHD + dyslexia: +23.5 ± 25.8	≤0.05*	
			Working memory test battery for children	*Phonological loop:*		
				Component score:		
				ADHD: +1.5 ± 14.3	Not sig.	
				ADHD + dyslexia: +4.8 ± 18.0	Not sig.	
				Standard score:		
				ADHD: +5.2 ± 43.4	Not sig.	
				ADHD + dyslexia: +20.2 ± 53.4	≤0.05*	
				Central executive:		
				Component score:		
				ADHD: +8.4 ± 17.0	≤0.05*	
				ADHD + dyslexia: +4.9 ± 19.8	Not sig.	
				Standard score:		
				ADHD: +24.3 ± 43.8	≤0.05*	Improvement in ADHD > ADHD + dyslexia ($p = 0.012$*)
				ADHD + dyslexia: +5.9 ± 54.6	Not sig.	
				Visuo-spatial sketchpad:		
				Component score:		
				ADHD: +0.6 ± 19.2	Not sig.	
				ADHD + dyslexia: +6.9 ± 24.6	Not sig.	

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
				Standard score: ADHD: +6.2 ± 40.7 ADHD + dyslexia: +16.0 ± 51.0	Not sig. Not sig.	
Takahashi et al[25]	Target doses: 0.5 or 1.2 or 1.8 (mean actual nr)	8 weeks	ADHD-RS (Japanese version)	*Total:* 0.5 mg/kg/d: –9.6 ± 9.1 1.2 mg/kg/d: –10.8 ± 6.8 1.8 mg/kg/d: –11.6 ± 8.8 Placebo: –8.1 ± 7.1 *IA:* 0.5 mg/kg/d: –5.7 ± 5.8 1.2 mg/kg/d: –6.3 ± 4.9 1.8 mg/kg/d: –6.8 ± 5.8 Placebo: –4.7 ± 4.7 *HI:* 0.5 mg/kg/d: –3.9 ± 4.7 1.2 mg/kg/d: –4.5 ± 4.0 1.8 mg/kg/d: –4.8 ± 4.4 Placebo: –3.4 ± 3.3	Not sig. 0.037* 0.010* Not sig. Not sig. 0.059 0.019* Not sig. Not sig. Not sig. 0.033* Not sig.	
Thurstone et al[29]	For those <70 kg: ATMX + MI/CBT: 1.2 ± 0.2 mg/kg (0–1.81 mg/kg) Placebo + MI/CBT: 1.3 ± 0.2 mg/kg (1.1–1.6 mg/kg) For those ≥ 70 kg: ATMX + MI/CBT: 88.8 ± 15.0 mg (62.5–100 mg) Placebo + MI/CBT: 86.7 ± 16.0 mg (50–100 mg)	12 weeks	ADHD checklist score	*Participant-rated:* ATMX + MI/CBT: –18.2 Placebo + MI/CBT: –19.0 *Parent-rated:* ATMX + MI/CBT: –13.8 Placebo + MI/CBT: –8.8	0.00005* 0.00005* 0.00005* 0.0018*	No sig. difference between groups.
			CGI-I	N with score <3 ("very much improved" or "much improved"): ATMX + MI/CBT: 17 (53.1%) Placebo + MI/CBT: 20 (60.6%)	0.543	

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
			Non-tobacco substance use over past 28 days (n days)	ATMX + MI/CBT: −5.8 Placebo + MI/CBT: −2.2	0.0013* 0.1956	No sig. difference between groups.
			Negative urine drug screens	Means: ATMX + MI/CBT: 1.0 Placebo + MI/CBT: 1.1	0.972	
Waxmonsky et al[15,16]	Mean: 1.4 ± 0.3 (1.1–2.0) Groups: ATMX: 1.47 ATMX + BT: 1.40 Subsample: 1 daily dose: 1.33 2 daily doses: 1.56	8 weeks	Student behavior teacher response observation code	*Observed classroom rule violations:* ATMX: −4.46 ATMX + BT: −4.99 Subsample: 1 daily dose: −6.16 2 daily doses: −2.36	Medication/ time effect: <0.05* <0.0001* 0.2789	
			Disruptive behavior disorders rating scale	*ADHD-inattentive:* Teacher-rated: ATMX: −0.47 ATMX + BT: −0.67 Parent-rated: ATMX: −0.48 ATMX + BT: −0.83	Medication/ time effect: <0.05* <0.0340*	
				ADHD-hyperactive/ impulsive: Teacher-rated: ATMX: −0.4 ATMX + BT: −0.53 Parent-rated: ATMX: −0.53 ATMX + BT: −0.69	Medication/ time effect: <0.05* <0.05*	
				ODD: Teacher-rated: ATMX: −0.18 ATMX + BT: −0.61 Parent-rated: ATMX: −0.1 ATMX + BT: −0.42	Medication/ time effect: <0.05* <0.05*	Improvement in ATMX + BT > ATMX ($p = 0.059$).
				Conduct disorder: Teacher-rated: ATMX: −0.15 ATMX + BT: −0.11 Parent-rated: ATMX: −0.03 ATMX + BT: −0.11	Medication/ time effect: <0.05* >0.10	
			Social skills rating scale	*Social skills:* Teacher-rated: ATMX: +4.02 ATMX + BT: +5.05 Parent-rated: ATMX: +2.96 ATMX + BT: +2.93	Medication/ time effect: <0.05* <0.05*	

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
				Problem behavior: Teacher-rated: ATMX: −2.49 ATMX + BT: −3.14 Parent-rated: ATMX: +0.14 ATMX + BT: −4.6	Medication/ time effect: <0.05* >0.05 0.0002*	Improvement in ATMX + BT > ATMX ($p < 0.0001$*)
				Academic competence (teacher-rated only): ATMX: +0.93 ATMX + BT: +2.067	Medication/ time effect: ≤0.10	
			Academic performance rating scale: Teacher	*Academic success:* ATMX: +0.17 ATMX + BT: +0.35	Medication/ time effect: <0.05*	
				Academic productivity: ATMX: +0.34 ATMX + BT: +0.39	Medication/ time effect: <0.05*	
				Impulse control: ATMX: +0.05 ATMX + BT: +0.51	<0.05* 0.0441*	Improvement in ATMX + BT > ATMX ($p = 0.047$*).
			Impairment rating scale	*Peer relationships:* Teacher-rated: ATMX: −1.39 ATMX + BT: −1.54 Parent-rated: ATMX: −0.57 ATMX + BT: −0.95	Medication/ time effect: <0.05* <0.05*	
				Teacher relationships: Teacher-rated: ATMX: −1.03 ATMX + BT: −1.51	Medication/ time effect: <0.05*	
				Sibling relationships: Parent-rated: ATMX: −1.75 ATMX + BT: −1.92	Medication/ time effect: <0.05*	
				Parent relationships: Parent-rated: ATMX: −0.68 ATMX + BT: −1.32	Medication/ time effect: <0.05*	
				Academic performance: Teacher-rated: ATMX: −1.76 ATMX + BT: −1.74 Parent-rated: ATMX: −1.78 ATMX + BT: −2.23	Medication/ time effect: <0.05* <0.05*	

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
				Classroom behavior:		
				Teacher-rated:	Medication/ time effect:	
				ATMX: −1.86	<0.05*	
				ATMX + BT: −1.94		
				Parent-rated:		
				ATMX: −1.24	<0.05*	
				ATMX + BT: −2.25		
				Family relationships:		
				Parent-rated:	Medication/ time effect:	
				ATMX: −1.29	<0.05*	
				ATMX + BT: −1.53		
				Overall impairment:		
				Teacher-rated:	Medication/ time effect:	
				ATMX: −1.85	<0.05*	
				ATMX + BT: −1.7		
				Subgroups:		
				1 daily dose: −1.4	<0.05*	Improvements in 1 dose > 2 doses.
				2 daily doses: −0.7	Not sig.	
				Parent-rated:		
				ATMX: −1.26	<0.05*	ATMX + BT had less impairment after treatment than ATMX ($p = 0.0489$*).
				ATMX + BT: −1.76	nr	
				Subgroups:		
				1 daily dose: −1.5	<0.05*	
				2 daily doses: −1.0	Not sig.	
			CDRS-revised	*Suicidal ideation:*	Medication/ time effect:	
				ATMX: −0.23	<0.0340*	
				ATMX + BT: −0.26		
				Subsample:		
				1 daily dose: −0.14	>0.30	
				2 daily doses: −0.27	>0.30	
				Total score:		Improvement in ATMX + BT > ATMX ($p = 0.0349$*)
				ATMX: −0.17	nr	
				ATMX + BT: −3.7	<0.05*	
				Subsample:		
				1 daily dose: −1.97	>0.30	
				2 daily doses: −1.95	>0.30	
			Daily report card/ Individual target behavior evaluation	ATMX: +6.1	Medication/ time effect:	
				ATMX + BT: +10.2	0.0036*	
				Subsample:		
				1 daily dose: +9.0	<0.05*	Improvement in 1 dose > 2 doses.
				2 daily doses: +2.2	Not sig.	
			CGI-I	N with score <3 ("very much improved" or "much improved"):	NA	No sig. difference between groups.
				ATMX: 14 (51.9%)		
				ATMX + BT: 16 (55.2%)		
			CGI-S	ATMX: −0.81	Medication/ time effect:	
				ATMX + BT: −0.79	<0.05*	

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
			IOWA Conners rating scale	Subsample: Teacher ratings *Inattentive-impulsive-overactive:* 1 daily dose: –1.4 2 daily doses: –0.7 *Oppositional-defiant:* 1 daily dose: –1.9 2 daily doses: –0.3 Subsample: Parent ratings *Overall impairment:* 1 daily dose: –1.5 2 daily doses: –1.0 *Inattentive-impulsive-overactive:* 1 daily dose: –2.5 2 daily doses: –3.1 *Oppositional-defiant:* 1 daily dose: –2.2 2 daily doses: –1.8	<0.05* <0.05* <0.05* <0.05* <0.05* <0.05* <0.05* <0.05* <0.05	Improvements in 1 dose > 2 doses. Improvements commenced from start of treatment with 1 dose, and mid-way through for 2 doses.
Wehmeier et al[32]	Target: 1.2 (actual mean nr)	8 weeks		Least squares mean difference between groups at endpoint are presented for this paper:		
			ADHD-RS	*Total score:* 11.6	<0.001*	ES: 1.3
				IA: 5.12	<0.001*	ES: 1.07
				HI: 6.55	<0.001*	ES: 1.37
			CGI-S	1.11	<0.001*	ES: 1.11
			WREMB-R	*Total score:* 5.74	<0.001*	ES: 1.0
				Morning subscore: 1.18	0.002*	ES: 0.59
				Late noon and evening subscore: 3.96	<0.001*	ES: 1.02
				Difficulty falling asleep: 0.62	<0.001*	ES: 0.62
	[2]		Computer-based cognitive performance test with infrared motion-tracking device	*Hyperactivity variables:* ATMX improvement superior to Placebo in all measures (change nr): Time active Distance	<0.05*	ES: 0.32–1.31

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
				Area Microevents Motion simplicity *Inattention variables:* ATMX improvement superior to Placebo in all measures (change nr): Reaction time variation Omission error rate Reaction time Normalized reaction time variation *Impulsivity variables:* Commission error rate: ATMX improvement superior to Placebo (change nr). Anticipatory: no difference between groups (change nr). *Further variables:* Error rate: ATMX improvement superior to Placebo (change nr). Multiresponse: no difference between groups (change nr).	<0.05* <0.05* >0.05 <0.001* >0.05	ES: 0.31–0.74 ES: 0.37–0.61 ES: 0.10–0.21 ES: 0.91–1.00 ES: –0.03–0.24
Wilens et al[21] (Study 1 only)	Target doses (actual mean nr): ATMX: 1.2 ABT-089 doses: 0.085 0.260 0.520 0.700 Placebo: NA	8 weeks	ADHD-RS	*Total score:* ATMX: –15.9 ± 1.7 ABT-089(0.085): –9.0 ± 1.8 ABT-089(0.26): –8.6 ± 1.8 ABT-089(0.52): –10.1 ± 1.8 ABT-089(0.7): –9.7 ± 1.9 Placebo: –7.8 ± 1.8 *IA:* nr. No effect of ABT-089, ATMX effective on "almost all other secondary outcomes" – specific outcomes nr. *HI:* nr. No effect of ABT-089, ATMX effective on "almost all other secondary outcomes" – specific outcomes nr.	Cf. Placebo <0.001* 0.31 0.374 0.177 0.231 nr	

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
			CGI-S	ATMX: −1.2 ± 0.2 ABT-089(0.085): −0.6 ± 0.2 ABT-089(0.26): −0.5 ± 0.2 ABT-089(0.52): −0.7 ± 0.2 ABT-089(0.7): −0.8 ± 0.2 Placebo: −0.6 ± 0.2	0.003* 0.400 0.633 0.257 0.198	
			CGI-I	nr. No effect of ABT-089, ATMX effective on "almost all other secondary outcomes" – specific outcomes nr.	nr	
			BRIEF: Parent	nr. No effect of ABT-089, ATMX effective on "almost all other secondary outcomes" – specific outcomes nr.	nr	
			Child's sleep habits questionnaire	nr. No effect of ABT-089, ATMX effective on "almost all other secondary outcomes" – specific outcomes nr.	nr	
			ADHD impact module: Patient	nr. No effect of ABT-089, ATMX effective on "almost all other secondary outcomes" – specific outcomes nr.	nr	
			Child health questionnaire	nr. No effect of ABT-089, ATMX effective on "almost all other secondary outcomes" – specific outcomes nr.	nr	
			ADHD-RS: school version	nr. No effect of ABT-089, ATMX effective on "almost all other secondary outcomes" – specific outcomes nr.	nr	
Yang et al[19]	Permitted doses depending on participant response (actual means/ranges nr): ATMX: 0.5–1.4 (or 100 mg maximum) MPH: 18–54	Titration up to 5 weeks, then maintenance for 4–6 weeks	ADHD-RS (Chinese)	nr	nr	
			CGI-S	nr	nr	

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
			Stroop color-word interference task	*Color interference (s):*		
				ATMX: –2.81	Not sig.	No sig. difference between groups.
				MPH: +0.58	Not sig.	
				Controls: +1.8	Not sig.	
				Word interference (s):		
				ATMX: –6.04	>0.05*	Improvement with ATMX and MPH > Controls.
				MPH: –5.56	>0.01*	
				Controls: –2.04	>0.05*	
			Rey complex figure test	*Immediate structure:*		
				ATMX: +0.76	>0.001*	No sig. difference between groups.
				MPH: +1.43	>0.001*	
				Controls: +0.32	>0.05*	
				Immediate detail:		
				ATMX: +3.96	>0.001*	No sig. difference between groups.
				MPH: +6.11	>0.001*	
				Controls: +3.47	>0.001*	
				Recall structure:		
				ATMX: +0.78	>0.001*	No sig. difference between groups.
				MPH: +1.29	>0.001*	
				Controls: +0.35	>0.05*	
				Recall detail:		
				ATMX:+5.06	>0.001*	No sig. difference between groups.
				MPH: +6.04	>0.001*	
				Controls: +3.39	>0.001*	
			Digit span	*Order digit span:*		
				ATMX: –0.54	>0.01*	No sig. difference between groups.
				MPH: –0.15	Not sig.	
				Controls: –0.20	Not sig.	
				Reverse digit span:		
				ATMX: +0.13	>0.05*	No sig. difference between groups.
				MPH: +0.31	>0.01*	
				Controls: –0.47	>0.05*	
			Tower of Hanoi	*Completion (%):*		
				ATMX: +5.3	>0.05*	Improvement in MPH > ATMX.
				MPH: +28.2	>0.05*	
				Controls: +6.6	Not sig.	
				Total steps:		
				ATMX: +4.67	nr	
				MPH: –2.46	nr	
				Controls: –1.05	nr	
			Trail-making test	*Shifting time (s):*		
				ATMX: –19.15	Not sig.	Improvement in MPH > Controls.
				MPH: –23.70	0.005*	
				Controls: –15.28	Not sig.	

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
			Verbal fluency test	*Correct responses:* ATMX: +0.4 MPH: +1.1 Controls: +0.24	 Not sig. >0.05* Not sig.	 No sig. difference between groups.
			BRIEF	*Inhibition:* Parent-rated: ATMX: –2.68 MPH: –3.43 Teacher-rated: ATMX: –4.57 MPH: –4.83	 >0.001* >0.001* >0.001* >0.001*	No sig. difference between groups.
				Shift: Parent-rated: ATMX: –0.93 MPH: –1.17 Teacher-rated: ATMX: –2.82 MPH: –2.26	 >0.05* >0.001* >0.01* >0.001*	No sig. difference between groups.
				Shift: Emotional control: Parent-rated: ATMX: –1.6 MPH: –2.06 Teacher-rated: ATMX: –3.21 MPH: –2.45	 >0.001* >0.001* >0.01* >0.001*	No sig. difference between groups.
				Shift: Initiate: Parent-rated: ATMX: –0.81 MPH: –1.47 Teacher-rated: ATMX: –1.75 MPH: –2.93	 Not sig. >0.001* >0.001* >0.001*	No sig. difference between groups.
				Working memory: Parent-rated: ATMX: –3.23 MPH: –4.0 Teacher-rated: ATMX: –3.9 MPH: –4.64	 >0.001* >0.001* >0.001* >0.001*	No sig. difference between groups.
				Plan: Parent-rated: ATMX: –3.63 MPH: –4.35 Teacher-rated: ATMX: –3.14 MPH: –4.07	 >0.001* >0.001* >0.001* >0.001*	No sig. difference between groups.
				Organize: Parent-rated: ATMX: –2.15 MPH: –2.05	 >0.001* >0.001*	No sig. difference between groups.

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
				Teacher-rated: ATMX: –2.82 MPH: –3.4	 >0.001* >0.001*	
				Monitor: Parent-rated: ATMX: –2.52 MPH: –3.36 Teacher-rated: ATMX: –3.61 MPH: –4.3	 >0.001* >0.001* >0.001* >0.001*	No sig. difference between groups.
				Behavior regulation index: Parent-rated: ATMX: –5.34 MPH: –6.66 Teacher-rated: ATMX: –10.6 MPH: –9.53	 >0.001* >0.001* >0.001* >0.001*	No sig. difference between groups.
				Metacognition index: Parent-rated: ATMX: –12.44 MPH: –15.24 Teacher-rated: ATMX: –15.21 MPH: –19.34	 >0.001* >0.001* >0.001* >0.001*	No sig. difference between groups.
Yildiz et al[20]	ATMX: 1.28 (range: 18–60 mg/d) MPH: 1.07 (range: 18–54 mg/d)	12 weeks	CGI-I	*Slightly-markedly improved (n):* ATMX: 10 (71.4%) MPH: 11 (91.7%)	NA	No sig. difference between groups.
			T-DSM-IV-	*IA scores:* Parent-rated: ATMX: –2.82 MPH: –7.91 Teacher-rated: ATMX: –2.55 MPH: –6.27	 0.153 0.005* 0.04* 0.023*	
				HI scores: Parent-rated: ATMX: –5.79 MPH: –7.09 Teacher-rated: ATMX: –2.45 MPH: –4.36	 0.056 0.017* 0.136 0.119	
				Opposition-defiance scores: Parent-rated: ATMX: –0.73 MPH: –6.9 Teacher-rated: ATMX: –0.09 MPH: –5.55	 0.474 0.011* 0.944 0.016*	

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
				Conduct disorder scores:		
				Parent-rated:		
				ATMX: 0	0.833	
				MPH: –2.09	0.015*	
				Teacher-rated:		
				ATMX: +0.64	0.715	
				MPH: –2.37	0.027*	
				Total scores:		
				Parent-rated:		
				ATMX: –9.91	0.033*	
				MPH: –24.0	0.010*	
				Teacher-rated:		
				ATMX: –6.27	0.05*	
				MPH: –18.36	0.041*	
			Responders	*40% decrease in T-DSM-IV-S score:*	0.076	
				ATMX: 4 (36.4%)		
				MPH: 7 (63.6%)		
			Stroop test (Turkish)	*Words (s):*		
				Test 1:		
				ATMX: –3.45	0.009*	
				MPH: –0.67	0.721	
				Test 2:		
				ATMX: –3.53	0.139	
				MPH: –0.59	0.507	
				Colors (s):		
				Test 3:		
				ATMX: –5.96	0.013*	
				MPH: –3.48	0.041*	
				Test 4:		
				ATMX: –3.76	0.047*	
				MPH: –12.08	0.007*	
				Test 5:		
				ATMX: –8.14	0.059	
				MPH: –20.78	0.009*	
				Test 5 error:		
				ATMX: –0.27	0.334	
				MPH: –0.33	0.414	
				Test 5 correction:		
				ATMX: +0.46	0.863	
				MPH: –1.09	0.046*	
			Visual memory span (Turkish)	*Forward:*		
				ATMX: +0.55	0.379	
				MPH: +0.83	0.572	
				Backward:		
				ATMX: +1.24	0.058	
				MPH: –0.45	0.107	
				Total:		
				ATMX: +1.22	0.120	
				MPH: +0.47	0.864	

(*Continued*)

Table 2. (*Continued*)

Study	Dose (mg/kg/d)	Treatment duration	Outcomes	Outcome (mean difference from Baseline)	*P* value	Comment
			Wisconsin card sorting test (Turkish)	*Pervasive error (%):*		
				ATMX: –2.9	0.074	
				MPH: –20.15	0.005*	
				Conceptual level responses (%):		
				ATMX: +12.66	0.028*	
				MPH: +24.37	0.017*	
				Failure to maintain set:		
				ATMX: +0.21	0.078	
				MPH: +0.18	0.726	
				Number of categories:		
				ATMX: +1.58	0.041*	
				MPH: +1.81	0.046*	

Dose refers to mean endpoint dose unless otherwise specified.
Abbreviations: ADHD-RS, Attention deficit hyperactivity disorder – Rating scale IV; HALFS, Health and life functioning scale; CSI, Child symptom inventory; GAF, Global assessment of functioning; HI, Hyperactive-impulsive; IA, Inattentive; CGI, Clinical global impressions; CGI-I, Clinical global impressions-Improvement; CGI-S, Clinical global impressions-Severity; CDRS, Children's depression rating scale-revised; YMRS, Young mania ratings scale; SNAP-IV, Swanson, Nolan and Pelham rating scale-revised; CPRS-R:S, Conners' parent rated scale-revised: short form; CTRS-R:S, Conners' teacher rated scale-revised: short form; GIPD, Global impression of perceived difficulties; ODD, Oppositional defiant disorder; ADDB-Inv, Attention-deficit and disruptive behavior disorders instrument; CHIP, Child health and illness profile; CANTAB, Cambridge neuropsychological test automated battery; BRIEF, Behavioral rating inventory of executive functioning; FBB-HKS, German ADHD rating scale; NEPSY, A developmental neuropsychological assessment; WREMB-R, Weekly ratings of morning and evening behavior-revised; T-DSM-IV-S, Turgay DSM-IV-based child and adolescent behavior disorders screening and rating scale; Parent, Parent-rated; Teacher, Teacher-rated; Psychiatrist, Psychiatrist-rated; Patient, Patient/child-rated; Physician, Physician/investigator-rated; NA, Not applicable; nr, Not reported/ specified; MPH, Methylphenidate; MI, Motivational interviewing; CBT, Cognitive behavior therapy; ABT-089, a novel alpha-sub 4 beta sub 2 neuronal nicotinic receptor partial agonist (numbers in parentheses indicate dosage in mg/kg); *, indicates a statistically significant difference at the level set by the authors of each paper; ES, Effect size; 95%CI, 95% confidence interval.

results from Yang et al[23] and Yildiz et al[24] suggest that although there are similar benefits with atomoxetine and methylphenidate, the magnitude and consistency of improvement from methylphenidate may be marginally superior to atomoxetine (Table 2). Across both studies, methylphenidate demonstrated improvements in a larger number of measures than atomoxetine and also yielded improvements that were significantly greater than those from atomoxetine (on the Tower of Hanoi test) and greater than changes observed in control participants (on the Trail-making test, Table 2). It should be noted, however, that there were differences between the cohorts enrolled in the Bastiaens et al study compared with those in the studies by Yang et al and Yildiz et al: the cohort in Bastiaens et al's study included those with comorbid internalizing disorders, whereas the participants from the latter two studies only had externalizing disorders (conduct disorder and ODD) (Table 1). This may in part explain the differences observed in response to atomoxetine and methylphenidate/stimulant medication.

Atomoxetine was also compared with placebo, where both treatment arms were combined with four sessions of psychoeducation for parents[34] or motivational interviewing plus cognitive behavior therapy.[33] Atomoxetine was superior to placebo when both groups also received four sessions of psychoeducation for parents in improving ADHD symptom and improvement ratings,[34] while there was no difference between the improvements seen in ADHD symptom ratings after atomoxetine and placebo when participants also received motivational interviewing plus cognitive behavior therapy.[33] In Thurstone et al's older cohort, the group receiving atomoxetine had a significant reduction in non-tobacco substance use over the prior 28 days, but the change was not significantly different to the placebo group.[33] No other changes were observed (Table 2).

There were no significant differences in improvements seen when participants were administered a fast versus slow titration schedule, and improvements were seen with both titration schedules in ADHD

symptom ratings and some quality of life measures (Table 2).[35,37] Interestingly, physical well-being scores worsened significantly more after atomoxetine treatment than placebo, while most other quality of life measures improved after atomoxetine treatment compared with placebo.

Only one trial was undertaken (reported in two papers) comparing a low dose to a high dose after a 40-week maintenance period.[30,31] As mentioned in the short-term treatment section above, atomoxetine was very effective in improving outcome measures during the initial eight-week acute treatment phase and was effective at both 0.8 and 1.4 mg/kg/d doses in maintaining improvements (compared with baseline) in parent-rated life participation scores. However, life participation scores were significantly poorer after the 40-week maintenance phase in comparison with scores achieved after the previous eight-week acute treatment phase in the low-dose (0.8 mg/kg/d) group, suggesting that a higher dose is required to maintain these benefits. The same was observed in ADHD symptom ratings, whereby the lower dose was unable to sustain improvements in total, inattentive, and hyperactive-impulsive symptom scores after the 40-week maintenance phase. The higher dose (1.4 mg/kg/d) was also unable to sustain the improvement in symptom ratings only in the inattentive symptoms score. In a subgroup of participants classified as having high risk-taking behavior, improvements to academic functioning and risky behaviors were maintained at 40-weeks (Table 2).

Within the long-term studies included in this review, one approximately 16-week long study looked at the effects of atomoxetine on ADHD compared with ADHD with a specific comorbidity. Specifically, Sumner et al studied ADHD compared with ADHD with dyslexia and found that atomoxetine improved ADHD symptom ratings, life participation scores, and educational achievement in both ADHD groups with no differences between those with ADHD alone compared with those with comorbid dyslexia.[38] A working memory test battery for children was also used in this study, where those with comorbid dyslexia showed an improvement in phonological loop standard score (from tests including digit recall, word list matching, word list recall, and non-word list recall), while those with ADHD alone had significant improvements (which were also significantly greater than in those with dyslexia) in central executive measures from tests including backward digit recall, listening recall, and counting recall (Table 2).

There is clearly still a paucity of long-term atomoxetine literature available, particularly in regards to the effects of different dosing schedules and comorbidities, so it is difficult to draw conclusions from what is currently available. However, these latest papers indicate that atomoxetine may be effective at higher doses in longer-term control of symptoms, functioning, symptoms, and behavior. Regular follow-ups of patients to continuously reassess symptom levels is currently indicated to maximize the likelihood that initial benefits from treatment are maintained.

Tolerability and safety

General tolerability

Atomoxetine is generally well tolerated in healthy children and adolescents, with typically only mild adverse effects, which seldom lead to discontinuation of medication.[4] Adverse events include headache, abdominal pain, nausea, decreased appetite, weight loss, vomiting, and somnolence. There is a very low incidence of serious adverse events. A full list of the nature and frequency of side effects in treatment with atomoxetine (and comparator) groups is provided in Table 3. The importance of methodology to permit determination of risk of adverse events and tolerability is emphasized in the outcomes of these papers and is included in the discussion below.

Kratochvil et al[1,39] reported that atomoxetine was well tolerated by both younger and older children with ADHD. Rates of adverse events were similar in both age groups, although the types of adverse events experienced differed between the groups. Atomoxetine treatment in the 6- to 7-year-olds resulted in higher rates of upper abdominal pain, decreased appetite, vomiting, and somnolence compared with placebo, while 8- to 12-year-olds experienced higher rates of decreased appetite, somnolence, irritability, and fatigue. Statistically significant increases in pulse and decreases in weight for both younger and older children on atomoxetine treatment were noted compared with placebo in the 2008 study only.[1] Increases in systolic and diastolic blood pressures in the older children and decreased weight in the younger children, although statistically significant, were not judged as

clinically significant. Of the 33 studies since 2009, 11 reported side effects in a comparator group, 8 of which included a placebo group (Table 3). While the nature and frequency of side effects were comparable with earlier studies and greater than in the placebo groups, participants did not discontinue treatment more often in the treatment groups compared with participants receiving placebo (Table 3).

Several recent papers reported on the impact of dosage on side effects. These titration studies reported on side effects with dosing between 0.2 and 1.8 mg/kg.[28,29,31,37] The occurrence of gastrointestinal side effects were equivalent to placebo at doses of 0.5 mg/kg or less. Where weight loss was reported, there were no statistically significant differences between the atomoxetine-treated group compared with the placebo group in a double-blind study of 93 participants by Kratchovil et al.[39] In another double-blind study of 105 participants, Martenyi et al[40] reported a statistically significant higher rate of weight loss in the atomoxetine treated group compared with the placebo group (9.7% versus 6.1%).

Some subpopulations may vary in tolerability of atomoxetine. Tolerability of atomoxetine may be reduced in children and adolescents with an autistic spectrum disorder. In the study by Troost et al,[41] 5 participants (42%) discontinued because of side effects including gastrointestinal symptoms, irritability, sleep problems, and fatigue, though this was a young population.[42] Tolerability was greater and side effects were fewer in a recent cohort of 24 participants reported by Fernandez-Jaen et al. Adverse side effects occurred in 5 participants (21%), 2 of whom discontinued medication as a result.[42]

Rarely, atomoxetine may be associated with serious liver injury.[43] Reports of liver injury related to atomoxetine were reviewed by Bang et al in 2008 and are discussed further in regard to safety below.[44] No new or unexpected safety concerns have been reported over longer-term treatment.[45]

The frequency of adverse events with atomoxetine treatment is impacted by the method of drug initiation. Participants rapidly titrating to a full treatment dose within the first week of treatment and those receiving daily rather than twice-daily dosing are more likely to experience side effects. Optimal ways to initiate therapy with atomoxetine were studied by Grennhill et al.[46] Some children may tolerate a divided dose well during initiation of treatment and are then able to switch over to a once-daily dosing schedule for maintenance. Side effects were also more commonly noted in association with faster titration schedules in studies from 2009.[30,35]

Growth

It has been postulated that growth delay may be intrinsic in the ADHD condition rather than being drug-induced,[47] and studies have not found evidence that unmedicated children and adolescents with ADHD are smaller than expected.[48,49] While weight loss of about 1 kg over a period of 2 to 3 months is reported to occur in 5% to 10% of patients treated with atomoxetine, recent studies of greater than 12 weeks duration have not included measurements of growth.

Several earlier open-label studies of atomoxetine administered for 2 years or longer have been conducted, and two meta-analyses have recently reported on growth outcomes.

Kratochvil et al[50] included data from 13 studies of 6- to 7-year-old children who were treated with atomoxetine up to a mean dose of 1.47 mg/kg/d. At the end at the 24-month treatment, weight was on average 2.5 kg less and height on average 2.7 cm less than expected based on baseline percentile. In another meta-analysis, Spencer et al[51] pooled data from both children and adolescents aged 6 to 16 years. After 24 months of treatment, there was a decrease of 2.7 percentile points for weight (corresponding to a mean 0.87 kg less than expected) and a decrease of 2.2 percentile points for height (0.44 cm less than expected). These differences between observed and estimated growth in both these studies were statistically significant. The slowing in growth velocity was most evident after 18 months of treatment and tended to attenuate afterwards.

The clinical significance of this effect has been considered negligible at the group mean level but may be important at the individual patient level with extended treatment beyond two years. The mechanism of the effect is speculated to be through a decrease in caloric intake. Caloric supplementation has been suggested as a possible remedy, but its efficacy has not been tested. Because the therapeutic effect of atomoxetine requires continuous dosing, drug holidays are not an option during the academic year, but may be

Table 3. Safety.

Study	Discontinued from AE (n, %)	AEs: ATMX (n, %)
Bastiaens et al[32]	nr	nr
Kratochvil et al[39]	ATMX: 0 (0%) Placebo: 3 (3.2%)	**Decreased appetite** (13, 30.0%), **gastrointestinal upset** (17, 39.0%), **sedation** (13, 30.0%), aches/pains (6, 14.0%), affective flattening/blunting (2, 4.0%), allergy (1, 2.0%), anxiety (1, 2.0%), attention/hyperactivity events (3, 7.0%), auditory events (2, 5.0%), dermatological (6, 14.0%), disruptive behaviours (3, 7.0%), insomnia (1, 2.0%), mood lability (18, 41.0%), respiratory (5, 11.0%), self-harm (1, 2.0%), weight loss (2, 5.0%), other (6, 14.0%).
Chang et al[76]	2 (16.7%)	Hypomanic symptoms* (1, 8.3%), suicidal ideation* (1, 8.3%), tiredness (3, 25.0%), stomach ache (3, 25.0%), agitation (2, 16.0%), nausea (1, 8.0%), dizziness (1, 8.0%), anticholinergic reaction (1, 8.0%).
Cho et al[77]	Group: 0.2 mg/kg/d: 2 (3.9%) 0.5 mg/kg/d: 3 (5.9%) 1.2 mg/kg/d: 3 (5.9%)	*0.2 mg/kg/d:* Upper abdominal pain (0, 0%), anorexia (2, 3.9%), decreased appetite (1, 2.0%), dizziness (1, 2.0%), irritability (2, 3.9%), nasopharyngitis (3, 5.9%), nausea (2, 3.9%), sleep disturbance (4, 7.8%). *0.5 mg/kg/d:* Upper abdominal pain (5, 9.3%), anorexia (2, 3.7%), decreased appetite (4, 7.4%), dizziness (3, 5.6%), irritability (2, 3.7%), nasopharyngitis (4, 7.41%), nausea (3, 5.6%), somnolence (1, 1.85%). *1.2 mg/kg/d:* Upper abdominal pain (4, 8.3%), anorexia (6, 12.5%), decreased appetite (6, 12.5%), irritability (4, 8.3%), nasopharyngitis (2, 4.2%), nausea (2, 4.2%), sleep disturbance (1, 2.1%), somnolence (4, 8.3%).
de Jong et al[78]	1 (1.2%, group nr)	nr
Dell'Agnello et al[79]	3 (2.2%, group nr)	**Anorexia** (36, 33.6%), **somnolence** (32, 29.9%), headache (23, 21.5%), **nausea** (22, 20.6%), abdominal pain (16, 15.0%), vomiting (15,14.0%), abdominal pain upper (11, 10.3%), decreased appetite (10, 9.3%), influenza (9, 8.4%), nervousness (7, 6.5%), weight decreased (6, 5.6%), insomnia (5, 4.7%), diarrhea (4, 3.7%).
Dittman et al[35] and Wehmeier et al[37]	ATMX-fast titration: 6 (10%) ATMX-slow titration: 2 (3.3%) Placebo: 1 (1.7%)	*Fast titration:* **Fatigue*** (21, 35.0%), **upper abdominal pain** (9, 15.0%), **anorexia** (9, 15.0%), aggression* (1, 1.7%), **nausea*** (13, 21.7%), **vomiting** (9, 15.0%), headache* (15, 25.0%), tachycardia* (1, 1.7%), severe stomach cramps (1, 1.7%). [**Nausea or related symptoms** (21, 35.0%), **fatigue or related symptoms** (19, 31.7%), **gastrointestinal complaints** (12, 60%)]. *Slow titration:* Fatigue (13, 21.3%), upper abdominal pain (8, 13.1%), anorexia (7, 11.5%), nausea (12, 19.7%), vomiting (11, 18.0%), headache (9, 14.8%), suicidal ideation* (1, 1.6%). [**Nausea or related symptoms** (18, 29.5%), fatigue or related symptoms (14, 23.0%), gastrointestinal complaints (8, 13.1%)].
Dittman et al[80]	7 (4.4%)	Fatigue* (42, 26.2%), nausea (22, 13.8%), headache (15, 9.4%), upper abdominal pain (11, 6.9%), decreased appetite* (11, 6.9%), dizziness (9, 5.7%), vomiting (9, 5.7%), severe vomiting (1, 0.6%), abdominal pain + dissociation + disturbance in attention + dizziness + fatigue + peripheral vasoconstriction + dark, marbled skin* (1, 0.6%), alopecia* (1, 0.6%), vertigo* (1, 0.6%).
Escobar et al[81]	0	**Decreased appetite** (27, 27.0%), **somnolence** (24, 24.0%), **headache** (18, 18.0%), **abdominal pain** (13, 13.0%), vomiting (9, 9.0%), irritability, (11, 11.0%), fatigue (9, 9.0%), nausea (6, 6.0%).
Gau and Shang[82]	nr	nr

AEs: comparison group (n, %)	Comments
na Decreased appetite (4, 8.0%), gastrointestinal upset (8, 16.0%), sedation (5, 10.0%), aches/pains (7, 14.0%), affective flattening/blunting (2, 5.0%), allergy (1, 2.0%), anxiety (1, 2.0%), attention/hyperactivity events (6, 12.0%), auditory events (2, 4.0%), dermatological (5, 10.0%), disruptive behaviours (4, 9.0%), insomnia (3, 6.0%), mood lability (11, 22.0%), respiratory (4, 8.0%), self-harm (1, 2.0%), weight loss (2, 4.0%), other (10, 20.0%), constipation (1, 2.0%).	
na	
nr Anorexia (3, 9.4%), somnolence (2, 6.3%), headache (4, 12.5%), abdominal pain (2, 6.3%), vomiting (1, 3.1%), abdominal pain upper (4, 12.5%), nervousness (2, 6.3%), weight decreased (1, 3.1%), insomnia (2, 6.3%), diarrhea (2, 6.3%).	
Placebo: Fatigue (6, 10.2%), anorexia (1, 1.7%), nausea (3, 5.1%), vomiting (3, 5.1%), headache (9, 15.3%). [Nausea or related symptoms (5, 8.5%), fatigue or related symptoms (6, 10.2%), gastrointestinal complaints (2, 3.4%)].	ATMX groups stayed on treatment longer than Placebo (hazard ratio: 3.57, $P = 0.007$*).
na	
Decreased appetite (4, 7.8%), somnolence (2, 3.9%), headache (3, 5.9%), abdominal pain (1, 2.0%), vomiting (2, 3.9%), irritability, (3, 5.9%), fatigue (2, 3.9%), nausea (1, 2.0%).	
na	

(*Continued*)

Table 3. (*Continued*)

Study	Discontinued from AE (n, %)	AEs: ATMX (n, %)
Ghuman et al[83]	1 (8.3%)	(Spontaneously reported AEs): Irritability, defiance, aggression (5, 41.7%), stomach upset (4, 33.3%), reduced appetite (3, 25.9%), vomiting (2, 16.7%), constipation/diarrhea (2, 16.7%), trouble falling asleep (3, 25.9%), sleepy, tired (2, 16.7%), headache (2, 16.7%), increased thirst (1, 8.3%), chest ache* (1, 8.3%).
Hammerness et al[84]	3 (8.8%)	Gastrointestinal (9, 26.5%), colds/allergies/infections (5, 14.7%), headache (4, 11.8%), sedation (4, 11.8%), decreased energy (3, 8.8%), insomnia (2, 5.9%), dizziness (1, 2.9%), tics (1, 2.9%), genitourinary (1, 2.9%), decreased appetite* (1, 2.9%), insomnia* (1, 2.9%), agitation/irritability* (2, 5.9%), dermatological: redness under eyes* (1, 2.9%).
Hammerness et al[21] and Wilens et al[85]	8 (16.0%)	*ATMX-only phase:* **Fatigue** (17, 34.0%), gastrointestinal (18, 36.0%), headache (12, 24.0%), insomnia (7, 14.0%), irritable (8, 16.0%), loss of appetite (7, 14.0%), rhinitis (10, 20.0%), other (7, 14.0%). *ATMX+MPH phase:* Fatigue (5, 10.0%), gastrointestinal* (20, 40.0%), headache (11, 22.0%), **insomnia*** (26, 52.0%), **irritable** (16, 32.0%), **loss of appetite*** (22, 44.0%), rhinitis (11, 22.0%), **other** (15, 30.0%), **weight loss**.
Kratz et al[86]	ATMX: 0 MPH: 0	nr
Martenyi et al[40]	ATMX: 1 (1.4%) Placebo: 0	Anorexia (13, 18.1%), somnolence (11, 15.3%), abdominal pain (9, 12.5%), nausea (8, 11.1%), weight loss (6, 8.3%), headache (5, 6.9%), mild skin itch and eruptions* (1, 1.4%), **clinically-significant weight loss** (7, 9.7%), **increased blood glucose** (mean: +0.3 ± 0.6 mmol/L ATMX cf. 0.0 ± 0.7 mmol/L Placebo).
Maziade et al[87]	ADHD: 2 (9.5%) Controls: 0	Abdominal pain (8, 38.0%), somnolence (8, 38.0%), headache (7, 33.0%), decreased appetite (5, 24.0%).
Mendez et al[88]	13 (5.7%)	≥1 ATMX-related AE (175, 76.0%), decreased appetite (74, 32.5%), anorexia (55, 24.1%), nausea (49, 21.5%), somnolence (46, 20.2%), dizziness (31, 13.6%), headache (29, 12.7%), vomiting (26, 11.4%), fatigue (25, 11.0%), irritability (20, 8.8%), decreased weight (16, 7.0%), upper abdominal pain (15, 6.6%), nasopharyngitis (15, 6.6%), hyperthyroidism (1, 0.4%).
Montoya et al[89]	0	nr
Montoya et al[90]	ATMX: 0 Placebo: 0	**Decreased appetite** (27, 27.0%), **somnolence** (24, 24.0%), **headache** (18, 18.0%), **abdominal pain** (13, 13.0%), vomiting (9, 9.0%), irritability (11, 11.0%), fatigue (9, 9.0%), nausea (6, 6.0%).
Svanborg[34]	ATMX: 0 Placebo: 0	**Headache** (19, 38.8%), **upper abdominal pain** (20, 40.8%), fatigue (16, 32.7%), **anorexia** (17, 34.7%), **nausea** (14, 28.6%), vomiting (6, 12.2%), irritability (6, 12.2%), depressive symptom (5, 10.2%), upper respiratory tract infection (5, 10.2%), pyrexia (2, 4.1%), abdominal pain (3, 6.1%), decreased appetite (3, 6.1%).
Saylor et al[30] and Wietecha et al[91]	8 week phase: Slow titration: 8 Fast titration: 13 40 week maintenance: 0.8 mg/kg/d: 12 1.4 mg/kg/d: 11	8 week phase: *Slow release:* Nausea (23, 17.2%), decreased appetite (20, 14.9%), fatigue (25, 18.7%), somnolence (26, 19.4%), headache (14, 10.5%), dizziness (8, 6.0%), upper abdominal pain (12, 9.0%), vomiting (17, 12.7%), irritability (12, 9.0%), nasal congestion (9, 6.7%), upper respiratory tract infection (9, 6.7%), weight decrease (8, 6.0%), anorexia (7, 5.2%), nasopharyngitis (7, 5.2%), dysmenorrhoea (2, 4.4%), arthralgia (1, 0.8%).

AEs: comparison group (n, %)	Comments
na	7 participants withdrawn from study or dropped out. ie, 5 participants completed the study.
na	
nr	
Anorexia (2, 6.1%), somnolence (3, 9.1%), abdominal pain (1, 3.0%), nausea (1, 3.0%), headache (2, 6.1%), clinically-significant weight loss (2, 6.1%).	Other significant tolerability observations: **Potassium change** (–0.1 ± 0.5 ATMX cf. +0.1 ± 0.5 Placebo); **systolic blood pressure change** (–1.4 ± 10.4 mmHg ATMX cf. +2.2 ± 8.8 mmHg Placebo).
na	
na	
na	
Decreased appetite (4, 7.8%), somnolence (2, 3.9%), headache (3, 5.9%), abdominal pain (1, 2.0%), vomiting (2, 3.9%), irritability (3, 5.9%), fatigue (2, 3.9%), nausea (1, 2.0%). Headache (9, 18.0%), upper abdominal pain (7, 14.0%), fatigue (9, 18.0%), nausea (2, 4.0%), vomiting (4, 8.0%), irritability (2, 4.0%), depressive symptom (2, 4.0%), upper respiratory tract infection (2, 4.0%), pyrexia (3, 6.0%), abdominal pain (1, 2.0%), nasopharyngitis (3, 6.0%).	Weight loss in AMTX sig. > Placebo.
na	

(*Continued*)

Table 3. (*Continued*)

Study	Discontinued from AE (n, %)	AEs: ATMX (n, %)
		Fast release: Nausea (29, 22.5%), decreased appetite (27, 20.9%), fatigue (24, 18.6%), somnolence (21, 16.3%), headache (20, 15.5%), dizziness (11, 8.5%), upper abdominal pain (10, 7.8%), vomiting (10, 7.8%), irritability (6, 4.7%), nasal congestion (3, 2.3%), upper respiratory tract infection (6, 4.7%), weight decrease (4, 3.1%), anorexia (5, 3.9%), nasopharyngitis (2, 1.6%), dysmenorrhoea (3, 6.1%), arthralgia (3, 2.3%). 40 week maintenance: *0.8 mg/kg/d:* Nausea (7, 8.1%), decreased appetite (2, 2.3%), fatigue (3, 3.5%), somnolence (4, 4.6%), headache (2, 2.3%), **dizziness** (5, 5.8%), upper abdominal pain (2, 2.3%), vomiting (3, 3.5%), irritability (2, 2.3%), nasal congestion (1, 1.2%), upper respiratory tract infection (4, 4.6%), nasopharyngitis (3, 3.5%), arthralgia (1, 1.2%). *1.4 mg/kg/d:* Nausea (9, 10.0%), decreased appetite (3, 3.3%), fatigue (4, 4.4%), somnolence (2, 2.2%), headache (3, 3.3%), **dizziness** (0, 0%), vomiting (4, 4.4%), irritability (2, 2.2%), nasal congestion (4, 4.4%), upper respiratory tract infection (3, 3.3%), nasopharyngitis (7, 7.8%), arthralgia (5, 5.6%).
Sumner et al[38]	ADHD: 1 (5.0%) ADHD+dyslexia: 3 (8.3%)	Somnolence (19, 33.9%), nausea (17, 30.4%), decreased appetite (12, 21.4%), headache (11, 19.6%), nasopharyngitis (7, 12.5%), upper abdominal pain (11, 19.6%), vomiting (9, 16.1%), cough (4, 7.1%), upper respiratory tract infection (3, 5.4%), constipation (3, 5.4%), irritability (5, 8.9%), psychomotor hyperactivity (3, 5.4%), fatigue (6, 10.7%), abdominal pain (3, 5.4%).
Takahashi et al[92]	0.5 mg/kg/d: 0 1.2 mg/kg/d: 1 (1.7%) 1.8 mg/kg/d: 1 (1.6%) Placebo: 0	*0.5 mg/kg/d:* Nasopharyngitis (11, 17.7%), headache (7, 11.3%), decreased appetite (3, 4.8%), somnolence (4, 6.5%), nausea (4, 6.5%), vomiting (3, 4.8%), abdominal pain (5, 8.1%), diarrhea (1, 1.6%). *1.2 mg/kg/d:* Nasopharyngitis (7, 11.7%), headache (10, 16.7%), decreased appetite (6, 10.0%), somnolence (6, 10.0%), nausea (6, 10.0%), vomiting (7, 11.7%), abdominal pain (4, 6.7%), diarrhea (6, 10.0%). *1.8 mg/kg/d:* Nasopharyngitis (11, 18.0%), headache (9, 14.8%), **decreased appetite** (13, 21.3%), somnolence (8, 13.1%), nausea (6, 9.8%), **vomiting** (5, 8.2%), abdominal pain (2, 3.3%), diarrhea (4, 6.6%). Affect lability*, headache* (dose group nr).
Thurstone et al[33]	ATMX+MI/CBT: 1 Placebo+MI/CBT: 0	Difficulty concentrating (23, 66%), decreased appetite (21, 60%), difficulty falling asleep (21, 60%), nasal congestion (21, 60%), abdominal pain (20, 57%), difficulty staying asleep (18, 51%), drowsiness (18, 51%), **vomiting** (18, 51%), difficulty arising in morning (17, 49%), irritability (17, 49%), dizziness when standing up (16, 46%), appetite increase (15, 43%), nausea (15/12, 43/34%)[1], dizziness (10, 29%), dry mouth (9, 26%), sweating (8, 23%), depression* (7, 20%), blurry vision (6, 17%), heartburn (6, 17%), joint aches (6, 17%), motor tics (6, 17%), **muscle cramps** (6, 17%), **sadness** (6, 17%), slurred speech (6, 17%), tachycardia (6, 17%), excitement (5, 14%), tremor (5, 14%), frequent urination (4, 11%), fever (3, 9%), itching (3, 9%), pallor (2, 6%), monotonous speech (2, 6%), seizure (after overdose of bupropion in order to hallucinate; 1, 3%), transient suicidal ideation (4, 11%).

AEs: comparison group (n, %)	Comments
nr	
Placebo: Nasopharyngitis (10, 16.1%), headache (4, 6.5%), decreased appetite (2, 3.2%), somnolence (4, 6.5%), nausea (3, 4.8%), abdominal pain (5, 8.1%), diarrhea (2, 3.2%).	
Difficulty concentrating (16, 46%), decreased appetite (13, 37%), difficulty falling asleep (25, 71%), nasal congestion (18, 51%), abdominal pain (16, 46%), difficulty staying asleep (21, 60%), drowsiness (15, 43%), vomiting (1, 20%), difficulty arising in morning (18, 51%), irritability (17, 49%), dizziness when standing up (14, 40%), appetite increase (10, 29%), nausea (11/14, 31/40%)[1], dizziness (10, 29%), dry mouth (10, 29%), sweating (10, 29%), depression (13, 37%), blurry vision (5, 14%), heartburn (3, 9%), joint aches (5, 14%), motor tics (5, 14%), muscle cramps (14, 40%), sadness (14, 40%), slurred speech (3, 9%), tachycardia (4, 11%), excitement (5, 14%), tremor (3, 9%), frequent urination (3, 9%), fever (5, 14%), itching (4, 11%), monotonous speech (1, 3%), suicide attempt (1, 3%), transient suicidal ideation (7, 20%).	

(*Continued*)

Table 3. (*Continued*)

Study	Discontinued from AE (n, %)	AEs: ATMX (n, %)
Waxmonsky et al[19,20]	1 (group nr)	(From Pittsburgh side effects rating scale: parent-rated): Stomach aches (12%), tiredness (10%), irritability (14%), anxiousness (14%), increased emotional lability (nr), nausea (nr). Subsample: Parent ratings Improvement in "Crabby/irritable" score for 2 doses > 1 dose; improvement in appetite for 1 dose > 2 doses.
Wehmeier et al[36]	ATMX: 2 (3.2%) Placebo: 3 (4.8%)	Abdominal pain (7, 11.1%), nausea (6, 9.5%), fatigue (4, 6.3%), upper respiratory tract infection (4, 6.3%), pharyngolaryngeal pain (4, 6.3%), headache (3, 4.8%), aggression (0%).
Wilens et al[25] (study 1 only)	ATMX: 2 (4.0%) ABT-089 (all doses): 6 (3.4%) Placebo: 1 (2.2%)	Cough (1, 2.0%), fatigue* (8, 16.0%), headache* (5, 10.0%), insomnia (0), nausea (5, 10.0%), upper abdominal pain* (3, 6.0%), hepatic enzyme increased and Epstein-Barr virus infection* (1, 2.0%).
Yang et al[23]	ATMX: 27 (20.8%) MPH: 15 (11.4%) Controls: nr	nr
Yildiz et al[24]	ATMX: 3 (21.4%) MPH: 1 (9.0%)	Anorexia (12, 85.7%), nausea* (10, 71.4%), nervousness (10, 71.4%), weight loss (8, 57.1%), abdominal pain (8, 57.1%), somnolence (5, 35.7%), headache (5, 35.7%), insomnia (5, 35.7%), vertigo (5, 35.7%), vomiting* (2, 14.3%), depression (2, 14.3%). Sig. change in blood pressure ($P = 0.039$), and sig. decrease in weight.

considered for selected patients during non-academic periods.

In a 5-year safety of treatment study, Spencer et al[52] reported on the impact of atomoxetine on growth in a large sample of children and adolescent participants. Maximum decrement of weight loss was observed at 15 months (–9.9%, $P < 0.001$); however, by the 5-year time point, participants had slightly overshot their starting weight percentile.

Similarly, maximum decrement from expected height was observed at 18 months (–6.6 percentage points, $P < 0.001$). At present, continuous atomoxetine treatment does not appear to have a significant effect on juvenile growth and final stature for most patients.

Suicidality

McCarthy et al[53] used the United Kingdom General Practice Research Database to assess 5351 patients aged 2 to 21 years from January 1, 1993, to June 30, 2006, who had taken medication to treat ADHD. In over 18,000 patient years, there were seven acute deaths, three of which were attributed to suicide. No deaths occurred among those taking atomoxetine, though an increased standard mortality rate was reported for those taking medication for ADHD.

Several authors have published case reports describing acute suicidality and aggression commencing shortly after initiating treatment with atomoxetine, and, in 2008, a boxed warning was placed into the package insert for atomoxetine. These symptoms have been managed successfully by ceasing atomoxetine or adding a further medication.[54,55] The FDA recommends that prior to prescribing atomoxetine to a patient, clinicians should consider psychiatric comorbidities, obtain personal and family histories of mood disorders and suicidality, and monitor for any

AEs: comparison group (n, %)	Comments
nr	
Abdominal pain (2, 3.2%), nausea (2, 3.2%), fatigue (4, 6.3%), upper respiratory tract infection (0%), pharyngolaryngeal pain (0%), headache (5, 8.1%), aggression (4, 6.5%). *ABT-089 (all doses):* Cough (9, 5.1%), fatigue (6, 3.4%), headache (11, 6.2%), insomnia (4, 2.2%), nausea (11, 6.2%), upper abdominal pain* (10, 5.6%), emotional disorder* (1, 0.6%), iron deficiency anemia* (1, 0.6%), dysphoria* (1, 0.6%), vomiting* (1, 0.6%), negativism* (1, 0.6%). *Placebo:* Cough (2, 4.3%), fatigue (2, 4.3%), headache* (6, 13.0%), insomnia (0), nausea (2, 4.3%), upper abdominal pain (2, 4.3%).	No serious AEs
nr	Discontinuation from AE higher in ATMX than MPH (*p* nr).
Anorexia (9, 75.0%), nausea (5, 41.7%), nervousness (9, 75.0%), weight loss (5, 41.7%), abdominal pain (3, 25.0%), somnolence (1, 8.3%), headache (3, 25.0%), insomnia (7, 58.3%), vertigo (3, 25.0%), tics (2, 16.7%), vomiting (1, 8.3%), depression (3, 25.0%), chest pains and palpitations*. Sig. decrease in weight.	

Notes: AEs listed in **bold** indicate adverse events which were significantly more likely in ATMX group than in non-ATMX or comparison group(s) with $P < 0.05$. *indicates adverse events which led to study discontinuation (where reported); [1]in the original publication, nausea was reported twice within the same table with different values so both have been presented; ABT-089 = a novel alpha-sub 4 beta sub 2 neuronal nicotinic receptor partial agonist.
Abbreviations: AE, adverse event; na, not applicable; nr, not reported/specified.

negative changes in mood after the commencement of atomoxetine treatment.[17] In a group of 70 participants with ADHD and comorbid substance use, Thurlstone et al[33] noted lower rates of suicidal ideation (11%) in the group randomized to receive atomoxetine compared with the group receiving placebo (20%), further illustrating the importance of randomization and adequate comparator groups in evaluating tolerability and side effects from medication in clinical outcome studies.

Psychosis

Psychotic adverse events have been reported in association with stimulant medications and atomoxetine. The FDA review of ADHD drug randomized controlled trials reported the highest psychosis adverse event rate (13.2/100 person-years) with methylphenidate (in the form of transdermal patches) followed by dexamphetamine (2.0/100 person-years) and atomoxetine (0.8/100 person-years). As per the current FDA medication guide, clinicians should inquire about personal or family histories of mood disorders and psychosis prior to initiation of atomoxetine.[56]

Hepatic injury

By 2005, there had been 7962 pediatric and adult case reports of hepatic injury associated with atomoxetine, of which 41 were identified as requiring further analysis.[43] Most of these events were mild increases in hepatic transaminase levels. During the 4 years after the market launch of atomoxetine, 351 cases of liver injury reported in relation to the drug treatment for ADHD. Of those 351 cases, 69 had explanations unrelated to the use of the drug, 146 presented insufficient information to assess the cause, 133 contained confounding factors and were labelled as possibly related

Table 4. Withdrawal from lack of efficacy.

Study	Discontinued from lack of efficacy (n, %)
Bastiaens et al[32]	nr
Kratochvil et al[39]	ATMX: 1 (1.1%) Placebo: 4 (4.3%)
Chang et al[76]	0
Cho et al[77]	nr
de Jong et al[78]	0
Dell'Agnello et al[79]	0
Dittman et al[35] and Wehmeier et al[37]	ATMX-fast titration: 7 (11.7%) ATMX-slow titration: 4 (6.6%) Placebo: 17 (28.8%)
Dittman et al[80]	Before week 8: 2 (1.3%) Before week 24: 8 (5.0%)
Escobar et al[81]	nr
Gau and Shang[82]	nr
Ghuman et al[83]	nr
Hammerness et al[84]	2 (5.9%)
Hammerness et al[21] and Wilens et al[85]	ATMX-only phase: 3 (20%) ATMX+MPH phase: 0
Kratz et al[86]	0
Martenyi et al[40]	0
Maziade et al[87]	ADHD: 3 (14.3%)
Mendez et al[88]	5 (2.2%)
Montoya et al[89]	0
Montoya et al[90]	nr ("Parents decision": specific reason(s) nr)
Svanborg[34]	0
Saylor et al[30] and Wietecha et al[91]	*8 week phase:* Slow titration: 3 (2.3%) Fast titration: 6 (4.9%) *40 week maintenance:* 0.8 mg/kg/d: 18 (21.7%) 1.4 mg/kg/d: 11 (13.3%)
Sumner et al[38]	ADHD: 1 (5.0%) ADHD+dyslexia: 2 (5.5%)
Takahashi et al[92]	0.5 mg/kg/d: 1 (1.6%) 1.2 mg/kg/d: 0 1.8 mg/kg/d: 0 Placebo: 0
Thurstone et al[33]	nr ("Lost to follow up": specific reason(s) nr)
Waxmonsky et al[19,20]	4 (7.1%)
Wehmeier et al[36]	ATMX: 5 (7.9%) Placebo: 7 (11.2%)
Wilens et al[25] (study 1 only)	ATMX: 1 (2.0%) ABT-089 (all doses): 6 (3.4%) Placebo: 1 (2.2%)
Yang et al[23]	ATMX: 9 (6.9%) MPH: 2 (1.5%)
Yildiz et al[24]	nr

Note: ABT-089 = a novel alpha-sub 4 beta sub 2 neuronal nicotinic receptor partial agonist.
Abbreviations: ATMX, atomoxetine; MPH, methylphenidate; nr, not reported/specified.

to drug use, and the remaining 3 cases reported liver injury probably related to atomoxetine use.[43] The etiology of drug-induced liver injury with atomoxetine is uncertain. There have been no cases of liver failure. Cases of liver injury have resolved following cessation of medication.[57]

Given the rare nature of these reports, it is not currently recommended for clinicians to do routine monitoring of liver function during treatment.

Cardiovascular effects

Concern about the cardiovascular safety of atomoxetine falls into two main areas: concern about acute dynamic effects of this medication on heart rate and blood pressure and concern that these changes may confer increased risk of major cardiac or neurovascular events.

It is well documented that atomoxetine may increase heart rate in both younger and older children. A statistically significant treatment-group difference in systolic blood pressure and diastolic blood pressure has been observed for older children but not for younger children.[1]

A small minority of children and adolescents taking atomoxetine (2.5% in pediatric placebo controlled trials) have been identified, with larger heart rate increases of 25 beats per minute (bpm), whereby 1.1% have increases in heart rate of this magnitude on more than one occasion.[43] These observations underpin the recommendation for pulse and blood pressure to be measured at baseline and periodically while on therapy to enable children and adolescents at heightened risk to be identified.

In a large cohort of over 440,000 adults aged 25 to 64 years, including over 150,000 users of ADHD medications, evidence was not found of an increased risk of heart attack or stroke associated with current ADHD medication use.[58] Similarly, this study did not find evidence to support an increased risk of cardiovascular complications for current use of any of the specific medications examined (ie, methylphenidate, amphetamines, or atomoxetine) or for an increase in risk with increasing duration of current use of ADHD medications. Furthermore, results were similar when restricted to new users or to those with or without ADHD. Results also were similar when the cohort was restricted to those with or without evidence of prior

cardiovascular disease or to those with or without evidence of prior non-ADHD psychiatric conditions. Authors of this large longitudinal study recognized several limitations.[58] Use of ADHD medications was based on electronic records of filled prescriptions. Use of ADHD documented on these records may not fully correspond with actual medication taken; however, electronic pharmacy databases have been found to be excellent unbiased sources of information on drug use, and it seems unlikely that any misclassification of use would be differential with respect to the endpoints of interest. While diagnosis of myocardial infarct is also reliably recorded and occurred at an expected rate in the non-treated population, the recording of other vascular events is less well validated.[59]

The findings of no increased risk of serious coronary heart disease in young or middle-aged adults associated with use of ADHD medications are consistent with some but not all previous reports.[60] A cohort study conducted among adults over 18 years of age compared risk of cerebrovascular accidents (CVA) and transient ischemic attacks (TIA) among those prescribed atomoxetine and those prescribed stimulant ADHD medications with risk or CVA and TIA among adults in the general population.[61] Higher rates of CVA and lower rates of TIA were observed in current users of atomoxetine compared with users of stimulants, although the number of events was small and risk ratios were not statistically significant. Compared with rates in the general population, users of ADHD medications had higher rates of TIAs and lower rates of CVA, although the latter was not statistically significant.

Non-clinical cohort studies have examined the cardiovascular effects of atomoxetine in conjunction with examining the effects of other medications used to treat ADHD. Gould et al used a case-control design to examine the association between ADHD medications and risk of sudden death in children and youths aged 7 to 19 years of age.[62] This study found an elevated odds ratio of 7.4 (95% CI 1.4–74.9) of sudden death associated with use of medication (stimulants or atomoxetine) to treat ADHD. In contrast, no increase in sudden cardiac deaths among children, adolescents, and young adults using ADHD medications (methylphenidate, dexamphetamines, or atomoxetine) was observed in a cohort study conducted in the General Practice Research Database in the United Kingdom by McCarthy et al.[53]

Findings from the report by Habel et al[58] are reassuring with respect to the cardiac safety of relatively short-term use of ADHD medication use in young and middle-aged adults. As stated in an earlier review by Perrin et al, current evidence does not suggest that treatment with therapeutic doses of ADHD pharmacotherapies in healthy children causes serious cardiovascular effects or sudden death.[63] However, sudden death has been reported in association with atomoxetine treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, the National Institute for Health and Clinical Excellence NICE guidelines recommend that atomoxetine generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, and serious heart rhythm.[64]

Children who are being considered for treatment with atomoxetine should have a careful clinical history (including assessment for a family history of early sudden death) and physical exam to assess whether cardiac disease is present as well as to inquire about possible cardiac symptoms including chest pain and syncope. Electrocardiogram is not a mandatory component of cardiovascular assessment and monitoring before or during ADHD treatment with atomoxetine.[63,65]

Neurological effects

ADHD patients have been shown to have incidence rates of unprovoked seizures and epilepsy as many as two to three times greater than non-ADHD children.[66]

The incidence of seizures has not been found to differ between subjects on atomoxetine and placebo for current versus non-use (relative risk 1.1).[67] The rate of seizures as an adverse event with atomoxetine use has been estimated at between 0.1% and 0.2%. In post-market reports of seizure, the rate of seizures among children and adolescents prescribed atomoxetine was within the normal population occurrences.[68]

Overdose

Based upon poison centre reports,[69–71] adverse drug reactions do not correlate with atomoxetine dose,[69]

though serious outcomes have been more commonly found with greater maximum dose. No major outcomes or fatalities have been reported.

Gastrointestinal symptoms and lethargy are typically reported with overdose of atomoxetine.[69–71] Seizures were reported in two patients, including one adolescent female who ingested 2840 mg of atomoxetine in a suicide attempt.[72]

While subacute effects of atomoxetine seem negligible under therapeutically relevant concentrations, abnormalities in cardiac conduction should be considered in cases of atomoxetine overdose and when administering atomoxetine to patients at increased risk for long QT syndrome.[73] Sinus tachycardia and increased blood pressure have also been noted.[69–71]

Adverse effects of overdose with atomoxetine also include mood symptoms and agitation.[69] In one study, 17% of patients had acute agitation when treated with benzodiazepines.[71]

Sleep

In a randomized, double-blind, cross-over study comparing the effect of methylphenidate (given thrice daily) and atomoxetine (given twice daily) on the sleep of children with ADHD, methylphenidate increased sleep-onset latency significantly more than atomoxetine.[74] Moreover, both children's diaries and parent reports indicated a better quality of sleep (in terms of "getting ready in the morning," "getting ready for bed," and "falling asleep") with atomoxetine compared with methylphenidate. Both medications decreased nighttime awakenings, but the decrease was greater for methylphenidate. Clearly, these results from a single study need to be replicated.

In studies from 2009, insomnia and disturbances in sleep were reported to occur with frequencies ranging between 10% and 60%. Importantly, the occurrence of disturbances in sleep were not significantly different in studies in which there was a placebo group.[33,39,75]

Summary

Atomoxetine is a highly selective noradrenaline reuptake inhibitor. It is both clinically effective and cost effective in the treatment of children and adolescents with ADHD.

Treatment doses of less than 0.5 mg/kg/day are unlikely to be effective. Higher doses of 1.8 mg/kg/day may also enable greater ADHD symptom control as well as management of comorbid externalizing disorders, though may result in increased side effects. Twice-daily dosing assists in ameliorating these effects and is a useful strategy when prescribing atomoxetine at doses greater than 1.2 mg/kg/day.

Atomoxetine decreases comorbid anxiety at usual treatment doses for ADHD.

Approximately 10% of patients are poor metabolizers of atomoxetine (CPY2D6) and will have blood levels four to five times that of patients who are efficient metabolizers for a given dose. The dose of atomoxetine also needs to be decreased in those with liver or renal disease and when prescribed with other medications impairing metabolism in the cytochrome P450 system. Atomoxetine should be withheld for at least two weeks after discontinuing MAOIs.

Atomoxetine is well tolerated. Gastrointestinal symptoms and lethargy are the main reason for discontinuation of atomoxetine, which is recorded at around 5% in many studies. Atomoxetine does not adversely affect seizure threshold or tics. Around 1% of patients prescribed atomoxetine have been noted to have large increases in resting heart rate (>25 bpm) on more than one occasion. Statistically significant but not clinically significant increases in blood pressure are observed only in older patients taking atomoxetine.

The safety profile of atomoxetine is also well established, both in terms of clinical prescription and overdosage. Overdose effects include lethargy, liver injury, and cardiac conduction changes. As indicated by the black box warning, atomoxetine is associated with increased suicidal ideation, though it has not been associated with death from suicide. The etiology of drug-induced liver injury with atomoxetine is uncertain. There have been no cases of liver failure with atomoxetine. Seizures have been reported twice. All medication-related effects attributed to atomoxetine have resolved either with cessation of medication or addition of a further medication.

The medication guide for atomoxetine can be found at http://www.fda.gov/cder/Offices/MG/AtomoxetineMG/pdf.

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Author Contributions

Conceived and designed the experiments: MRK. Analysed the data: MRK, TWT. Wrote the first draft of the manuscript: MRK. Contributed to the writing of the manuscript: MRK, TWT, SDC. Agree with manuscript results and conclusions: MRK, TWT, SDC. Jointly developed the structure and arguments for the paper: MRK, TWT. Made critical revisions and approved final version: MRK, TWT, SDC. All authors reviewed and approved of the final manuscript.

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