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A Review of Atomoxetine Effects in Young People with Developmental Disabilities

Michael G. Aman[a], **Tristram Smith**[b], **L. Eugene Arnold**[a], **Patricia Corbett-Dick**[b], **Rameshwari.Tumuluru**[c], **Jill A. Hollway**[a], **Susan L. Hyman**[b], **Marissa Mendoza-Burchamm**[c], **Xueliang Pan**[d], **Daniel W. Mruzek**[b], **Luc Lecavalier**[a], **Lynne Levato**[b], **Laura B. Silverman**[b], and **Benjamin Handen**[c]

[a]The Nisonger Center UCEDD, Ohio State University, McCampbell Hall, 1581 Dodd Dr., Columbus, OH, 43210

[b] Division of Neurodevelopmental and Behavioral Pediatrics at the University of Rochester, Box 671, 601 Elmwood Ave., Rochester, NY, 14642

[c] Department of Psychiatry at the Western Psychiatric Institute and Clinic, Thomas Detre Hall, 3811 O'Hara St., Pittsburgh, PA, 15213

[d] Center for Biostatistics, Ohio State University, 2012 Kenny Rd., Columbus, OH, 43221

Abstract

This review summarizes the pharmacokinetic characteristics, pharmacodynamic properties, common side effects, and clinical advantages and disadvantages associated with atomoxetine (ATX) treatment in typically developing children and adults with ADHD. Then the clinical research to date in developmental disabilities (DD), including autism spectrum disorders (ASD), is summarized and reviewed. Of the 11 relevant reports available, only two were placebo-controlled randomized clinical trials, and both focused on a single DD population (ASD). All trials but one indicated clinical improvement in ADHD symptoms with ATX, although it was difficult to judge the magnitude and validity of reported improvement in the absence of placebo controls. Effects of ATX on co-occurring behavioral and cognitive symptoms were much less consistent. Appetite decrease, nausea, and irritability were the most common adverse events reported among children with DD; clinicians should be aware that, as with stimulants, irritability appears to occur much

Conflict of Interest

Dr. Aman has received research contracts, consulted with, or served on advisory boards of Biomarin Pharmaceuticals, Bristol-Myers Squibb, Confluence Pharmaceutica, Coronado Bioscience, Forest Research, Hoffman LaRoche, Johnson & Johnson, MedAvante Inc., Novartis, Pfizer, and Supernus Pharmaceutica.

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more commonly in persons with DD than in typically developing individuals. Splitting the dose initially, starting below the recommended starting dose, and titrating slowly may prevent or ameliorate side effects. Patience is needed for the slow build-up of benefit. Conclusions: ATX holds promise for managing ADHD symptoms in DD, but properly controlled, randomized clinical trials of atomoxetine in intellectual disability and ASD are sorely needed. Clinicians and researchers should be vigilant for emergence of irritability with ATX treatment. Effects of ATX on cognition in DD are virtually unstudied.

Keywords

Atomoxetine (Strattera); Review; Developmental Disabilities; Autism Spectrum Disorders

1. Introduction

Overactivity and inattention are among the most common behavioral concerns for individuals with developmental disabilities (DD; Emerson, 2003). The prevalence of attention-deficit hyperactivity disorder (ADHD) in this population has been estimated at 9-16% (Emerson, 2003; Strømme & Diseth, 2000), substantially exceeding the rate of ADHD in typically developing (TD) individuals. Stimulants such as methylphenidate are the most extensively studied treatment for ADHD in individuals with DD (Handen & Gilchrist, 2006). Findings indicate that individuals with DD are less likely to show therapeutic benefit and more likely to experience negative side effects from stimulants than are TD individuals (Aman, Farmer, Hollway, & Arnold, 2008; Handen & Gilchrist, 2006; Research Units on Pediatric Psychopharmacology Autism Treatment Network [RUPP], 2005). Thus, there remains a need to identify additional treatment options for this common and impairing set of symptoms in individuals with DD.

Atomoxetine (ATX; Strattera) is a nonstimulant medication of considerable interest. Although ATX only received Food and Drug Administration approval in 2002 for treatment of ADHD, there is a large literature base on effectiveness in TD children, adolescents, and adults (Cheng, Chen, Ko, & Ng, 2007; King et al., 2006; Kratochvil, Milton, Vaughan, & Greenhill, 2008). Not surprisingly, because of the difficulties in recruiting and testing individuals with DD, the research on any therapeutic agent tends to lag behind that of the TD population. Comparatively speaking, the literature on ATX in people with DD is very small. Moreover, as illustrated by the research on methylphenidate (Research Units on Pediatric Psychopharmacology Autism Treatment Network [RUPP], 2005), medication effects for individuals with DD may differ from effects seen in TD individuals. It is essential that, to the extent possible, clinical decision making is based on findings on the population with DD. We conducted this review in an effort to summarize the available findings in patients with DD and to compare some of these findings relative to TD patients (e.g., data on adverse events [AEs]). Our aims in this paper were to: (a) provide a general context for assessing ATX in individuals with DD by first providing pharmacological data (pharmacodynamics, pharmacokinetics, side effects) from the general/TD population, (b) comment on general advantages and disadvantages of ATX relative to other ADHD medicines, (c) critically review the existing literature on ATX therapeutic effects in DD, (d)

characterize the side effects observed in DD samples to determine if they differ from those seen in the TD population, and (e) provide an overall summary and conclusion about the status quo of ATX research in the field of DD. To the best of our knowledge, there is no similar published review to date.

1.1 Atomoxetine Pharmacodynamics

ATX enhances norepinephrine (NE) activity by selectively and potently blocking its reuptake through transporter inhibition and increasing presynaptic concentrations in noradrenergic pathways (Hammerness, 2009). In the rat, ATX increases NE in regions such as the occipital cortex, lateral hypothalamus, dorsal hippocampus, and cerebellum (Swanson, 2006). Increased NE neurotransmission in the prefrontal cortex (PFC) is associated with enhanced attention and higher cognitive processes (Bymaster, 2002). ATX increases DA in the PFC because, in contrast to other areas of the brain, DA is taken up by NE transporters in that location. Dopamine is increased in the PFC in animals and is attributed to a common regional uptake inhibition of monoamines (Hammerness, 2009; ATX has relatively low affinity for other dopamine and serotonin uptake sites. ATX does not increase the dopamine levels in the nucleus accumbens and associated reward pathways or in the striatum. As a result, it has limited abuse potential and is not associated with tics (Garnock-Jones & Keating, 2009).

1.2 Atomoxetine Pharmacokinetics

Pharmacokinetics are well established in TD children and adults, have been found to be similar after adjusting for body weight, and are linear after 6 years of age, yielding plasma levels predictably proportional to mg/kg dose (Sauer et al., 2005; Witcher et al., 2003). ATX is highly water soluble with high membrane permeability; hence it is rapidly and well absorbed after oral administration. The extent of absorption is unaffected by food, and the manufacturer recommendation is that it may be taken with or without food (Sauer et al., 2005).

Atomoxetine clearance is achieved through three metabolic pathways: aromatic ring-hydroxylation, benzylic hydroxylation and N-demethylation (Hammerness et al., 2009). Primary metabolism occurs via CYP450-2D6, with extensive first-pass liver metabolism via oxidative processes to equipotent primary metabolite 4-hydroxyATX. Further transformation occurs via glucoronidation, resulting in 4-hydroxyATX-O-glucoronide (Sauer et al., 2005). ATX is metabolized to a much lesser degree via CYP2C19 to N-desmethylATX, an active metabolite which exerts minimal pharmacologic activity. Differences in ATX pharmacokinetics are noted between genetically determined CYP2D6 extensive metabolizers (EMs) (over 90% of the population) and CYP2D6 slow metabolizers (SMs) (approximately 7% of population) (Sauer et al., 2005). Plasma clearance of ATX in both EMs and SMs occurs primarily via oxidative pathways, though this occurs at a much slower rate in SMs, yielding higher peak plasma concentrations for the slower metabolizing subgroup (Sauer et al., 2005). Individuals with slow metabolism are at risk for higher serum ATX levels even at lower drug doses, though these pharmacokinetic differences have not been found to be clinically relevant, and dose recommendations are consistent across CYP2D6 genetic subtypes (Sauer et al., 2004), Bioavailability ranges from 63% in EMs and

94% in SMs. Peak plasma levels are typically achieved in 1-2 hours in EMs and in 3-4 hours in SMs. A high-fat meal reduces the peak plasma concentration, and delays the time it takes to reach peak plasma concentration by 3 hours, but does not affect the extent of absorption (Sauer et al., 2005). The volume of distribution into total body water is 0.85 L/kg after an IV dose, and it is well distributed in both EMs and SMs (Sauer et al., 2005). In EMs, twice-daily dosing was not associated with elevated peak plasma concentrations (Witcher, et al, 2003). ATX is 98% bound to plasma proteins, primarily to albumin, and does not affect the protein binding of other highly plasma-bound drugs (e.g., warfarin, acetylsalicylic acid, phenytoin, diazepam) to albumin, nor do these drugs affect the protein binding of ATX to albumin (Sauer et al., 2005). Since ATX is highly protein-bound, systemic clearance may be reduced in hepatic insufficiency, and dosage adjustments are advised (Hammerness, 2009).

Mean plasma elimination half-lives vary considerably between EMs and SMs. Half-lives of ATX and its metabolites, in EMs, are: (a) ATX, 5.2 hours; (b) 4-hydroxyATX, 6-8 hours; and (c) N-desmethylATX 6-8 hours. Half-lives of ATX and its metabolites in SMs are: (a) ATX, 21 hours; (b) 4-hydroxyATX, 19 hours and (c) N-desmethylATX 34-40 hours. (Sauer et al., 2003). While the primary ATX metabolism is similar in both EMs and SMs, specific metabolite amounts, and rates of formation vary between the subgroups (Sauer et al., 2005).

Excretion of ATX occurs primarily in the urine, with less than 3% of an oral dose excreted unchanged and 80% as 4-hydroxyATX-O-glucoronide; the remaining 17% is excreted in feces (Sauer et al., 2005). ATX does not significantly account for inhibition or induction of metabolism of *other* CYP-2D6 medications, though drugs that inhibit CYP-2D6, such as paroxetine and fluoxetine, cause slower elimination and increases in peak plasma concentrations (Hammerness et al, 2009).

1.3 Side Effects, Typically Developing Patients

Clinical Trials sponsored by Eli Lilly indicated that , serious potential side effects of ATX may include suicidal thoughts, hepatotoxicity, sedation, and weight loss or slowed growth. Common side effects in TD children include upset stomach, decreased appetite, nausea or vomiting, dizziness, tiredness, and mood swings. This was further confirmed by later reviews in the literature Cheng et al. (2007) and Schwartz and Correll (2013). A more detailed review of the literature is reported as follows.Though there was no incidence of completed suicide, the incidence of suicidal ideation was 5/1337 (.0037) compared to 0% taking placebo (Bangs et al., 2008). Patients with DD were not included in the review of Bangs et al.. The review did not report incidents of QTc changes or hepatotoxicity. According to Wernicke et al. (2003), ATX caused no QT interval prolongation and minimal changes in diastolic blood pressure in TD children and a minimal increase in pulse rate. Kratchovil et al. (2006) reported a notable change in growth early in treatment, which increased after 18 months indicating that, though there is an early decrease in growth, there was no significant change at 2-year follow-up. Many common side effects reported could be explained as common childhood illnesses (Kratchovil et al., 2006). Wilens et al. (2006) monitored TD children and adolescents and reported that children experienced higher rates of somnolence and headaches than adolescents. There also appears to be a difference in side

effects experienced based on titration method. Greenhill et al. (2007) reported that TD children who were titrated slowly experienced headaches as a common side effect, whereas those who were titrated quickly reported a decrease in appetite and somnolence. This may be pertinent for children with autism spectrum disorder ASD (and perhaps other children with DD) who are notoriously picky eaters. Appetite suppression is often a concern for parents of these children.

1.4 Potential Advantages and Disadvantages of ATX

Until now, the focus of this paper has been on ATX effects in TD patients; henceforth, we consider individuals with DD (including ASD) as well. Although further research is obviously needed to elucidate the role of ATX in management of ADHD symptoms in the presence of DD, we have enough information for tentative conclusions about its advantages and disadvantages relative to other FDA-approved options. Some of these are based on clinical experience and knowledge of the pharmacological properties of ATX (e.g., pharmacokinetics), whereas others have literature bearing on the issue.

1.4.1 Advantages of ATX—These include the following: (a) ATX may reduce anxiety, an important issue in children with ASD and potentially other DD (Gabriel & Violato, 2011; Dell'Agnello et al., 2009; Ravindran, Kim, Letamendi, & Stein, 2009). (This advantage is shared with alpha-2 agonists such as guanfacine.) (b) ATX may have some benefit for depression, although one trial with neurotypical adults was negative (Young, Sarkis, Qiao, Wietecha, 2011). (c) ATX's longer duration of action provides a smoother effect over time, without the ups and downs of stimulants. (d) Timing of ATX doses is not as critical as with other ADHD medications. (e) ATX appears to have less “rebound irritability” (i.e., disruptive behavior occurring at the end of the day, when the effects of many stimulants wear off) than stimulants. (f) ATX does not interfere with sleep as do stimulants, often important in ASD and other DD (Hollway & Aman, 2011). (g) ATX does not induce or exacerbate tics. (h) There may be less limitation by side effects for ATX than for stimulants if titration proceeds slowly and if doses are split initially. (i) ATX is not a Schedule II drug, allowing refills and phone prescriptions. (j) ATX has little or no abuse potential.

1.4.2 Disadvantages of ATX—These include the following: (a) ATX takes longer than stimulants to reach an effective level; maximal benefit may be delayed a month or two. (b) The ATX response rate may be lower than for stimulants, at least in TD children. (c) If there are limiting side effects, they may take longer to wash out given the longer half-life of ATX compared with stimulants. (d) Initial split doses to prevent side effects can be inconvenient. (e) Side effects of fatigue or sedation, shared with alpha-2 agonists but not stimulants, can be unacceptable. (f) ATX may pose more gastrointestinal side effects than ADHD alternatives. (g) The risk of reversible liver toxicity exists, although it is rare. (h) ATX may pose sensitivity to metabolic aberrations or enzyme induction or suppression by other drugs. (i) Whereas ATX probably is responsible for less growth inhibition than stimulants, it occurs more frequently than with alpha-2 agonists. (j) In adults, ATX may cause dry mouth, urinary retention, and sexual dysfunction. (k) ATX is irritating to skin and eyes if capsules are opened.

2. Review Method

We used PsychInfo, PubMed, and Google Scholar to search for the following terms in combination with *atomoxetine* and *Strattera:* "mental retardation," "intellectual disability," "developmental disability," "autism spectrum disorder," "autistic disorder," "autism," "pervasive developmental disorder," "PDD," and "Asperger's disorder." These searches turned up numerous papers, but the majority simply referred in passing to children with some form of DD and treatment of ADHD symptoms. Ultimately, our search turned up 11 relevant papers. Data from these articles were extracted by the authors and checked by the first author for accuracy.

The findings were analyzed by subjects, design, and results. Under "Subjects," we reported the number of participants, clinical condition or disorder, functional level (IQ), and gender breakdown. Within "Design," we reported type of design (case report, open-label [OL], crossover, or parallel groups); duration of the trial; and whether the study used a randomized controlled design. Finally, under "Results," we reported types of outcome measure, baseline (BL) and end-point (EP) scores for standardized scales, effect sizes (ES), and adverse events (AEs).

Most studies used standardized scales to assess behavior problems (including subscales intended to measure ADHD); periodically studies also reported measures of ASD symptoms, adaptive behavior, and cognitive functioning. The most commonly used scales were the Aberrant Behavior Checklist (ABC; Aman, Singh, Stewart, & Field, 1985), the ADHD Rating Scale (see Aman & Pearson, 1999), variations of Conners' Parent and Conners' Teacher Rating scales (Aman & Pearson, 1999), and the Swanson, Nolan, and Pelham SNAP) Rating Scale (https://www.omh.ny.gov/omhweb/ebt/resources/snap_instructions.html). The ABC was developed for assessing treatment effects and has five subscales, as follows: (a) Irritability (15 items), (b) Social Withdrawal (16 items), (c) Stereotypic Behavior (7 items), (d) Hyperactivity/Noncompliance (16 items), and Inappropriate Speech (4 items). The ADHD Rating Scale was based on the 18 DSM-IV symptoms for ADHD, and can be completed by parents, teachers, or professionals. The Conners' Scales come in numerous versions for completion by parents or teachers, and often include some mix of the following subscales, with variable numbers of items: (a) Oppositional, (b) Cognitive Problems, (c) Hyperactivity, (d) Anxious-Shy, (e) Perfectionism, (f) Social Problems), (g) ADHD Index, (h) Conners' Global Index, and DSM-IV Symptoms (Aman & Pearson, 1999). Earlier versions of the Conners' Scales also included a Conduct Problem and an Inattention subscale. Finally, the SNAP is based on DSM symptoms and most frequently involves parent or teacher ratings of DSM symptoms relevant to ADHD (ADHD Inattention [9 items]; ADHD Hyperactive/Impulsive [9 items]); and oppositional defiant disorder (8 items).

3. Results

All 11 studies of ATX effects in children with DD are summarized in detail in Table 1. The studies are arranged chronologically and are referenced by numeral (1-11) here. Only two were randomized clinical trials (RCT) with placebo controls; seven were OL prospective,

one was an OL retrospective study, and one was a case report. In general, we reference the two RCTs (#2 & 10) in **bold** font, whereas the remainder are in regular font. In this narrative summary, we focus mainly on primary outcome variables and commonly used outcomes. When applicable, a "T" is used to signify that a rating scale was completed by a teacher or "D" for doctor (as opposed to the default, parent-completed reports, which were most common).

3.1. ADHD, Disruptive Behavior, and Adverse Events

The following scales were used multiple times across studies: various versions of Conners' Rating Scale (#**2**, 4, 6, 9, **10**), the Aberrant Behavior Checklist (ABC; #**2**, 3, 4, 7), and the two DSMIV-derived scales (the ADHD Rating Scale and the SNAP scale; #**2**, 4, 6, 9, **10,** 11D). The following general findings were supported with these scales. *All* Conners'-derived Hyperactivity subscales (1, 4, 6, 6T, **10**) showed a significant reduction in scores with ATX. Likewise, the Conners' Inattention subscale scores were reduced in every instance they were assessed (#1, 6, **6T**, 9, 9T). The Conners' ADHD Index scores declined each time they were employed as outcomes (#4, **10**). Conners' Conduct or Oppositional subscales were sensitive to ATX treatment several times (#1, 6, 6T, **10**), but not always (#4). Conners' Learning and Cognitive Problems were rated improved with ATX in three studies (#2, 4, **10**).

With the ABC, the outcomes were less optimistic. The Hyperactivity/Noncompliance subscale scores improved in two studies (#**2**, 3, 3T) but failed to improve in two others (#4, 7). Irritability scores improved in one instance (#3) but were unchanged in the remainder (#**2**, 3T, 4, 7). Social Withdrawal subscale scores improved in two instances (#**2**, 3) but not in three others (#3T, 4, 7). Stereotypic Behavior and Inappropriate Speech subscale scores generally did not change (#**2**, 3T, 4, 7) except for one set of comparisons (#3).

In terms of the DSM scales, the SNAP and ADHD Rating Scales provided positive, though not uniform, results. First, the Inattention subscales declined with ATX in *all* comparisons (#**2**, 4, 6, 6T, 9, 9T, **10D**). The Hyperactive/Impulsive subscale scores declined in all but one comparison (#**2**, 6, 6T, 9, **10D;** not 9T). In the only study to report SNAP Oppositional Behavior, it declined with ATX (#**2**). In the largest study done to date, the Clinical Global Impressions-Improvement (CGI-I) subscale did not distinguish statistically between ATX and placebo treatment [#**10**; Π^2 (2) = 5.37; with Yates' correction: $p = 0.068$]. In the open-label studies, the rates of clinical response (CGI-I = 1 or 2) were as follows: 42% (study #7), 47% (#8), 49% (#6), 50% (#9), 60% (#1), and 75% (#3). In the only study (#8) to evaluate the possible effect of IQ on CGI response (IQ ≥85 vs. <85), 77% of high-IQ subjects were responders as compared with 21% of low-IQ subjects ($p < 0.001$).

In the only study to include an extension phase (11D; 20-week ATX extension for both subjects initially assigned to PBO or ATX), additional improvements were seen in children initially assigned to ATX on ADHD-RS for the Inattention subscale ($p = .02$) but not the Hyperactivity/Impulsivity subscale ($p = .06$). Although not reported separately, changes for subjects originally assigned to PBO were almost certainly significant when they were treated

openly with ATX, as the change scores were substantially larger than for the ATX acute trial to ATX extension.

We computed effect sizes (ES, Cohen's d) for the primary outcomes and priority secondary variables, and these appear shaded in gray in Table 1. The ESs were generally large, ranging from 0.29 to 2.30, with a median of 1.05.

3.2. Other Scales and Cognitive Performance

Subjects were assessed using additional rating scales. No effects of ATX were found on the Repetitive Behavior Scale—Revised (#**2**). An open-label study found no ATX effect on the Vineland Adaptive Behavior Scales (#3). One RCT (#**2**) found no ATX effect on the following cognitive measures: (a) continuous performance task (measuring sustained attention), (b) the delayed match-to-sample task (memory), or (c) the analogue classroom task (motivation & sustained attention). Likewise, an open-label study (3) found no ATX effect on the continuous performance task. Thus, unlike the case with stimulants (Aman, 1980), there is no evidence that ATX significantly enhances cognitive function in children with developmental disabilities.

3.3 Adverse Events (AEs)

We made an effort to document the most commonly occurring AEs in Table 2. Study 11 is not included because its subjects overlapped with study 10. The number of subjects in each study appears near the column headers. The figures in parentheses indicate the percentage of subjects in that study to show the AE. The right-most column, with bolded numerals, indicates the total number of participants across all studies to show that AE. The first percentage in the right column is based on total sample only for cells where that adverse event was reported; the second percentage is based on all 241 subjects across all studies and assumes that investigators screened for that adverse event (unlikely to be true) in all studies. We regard the first percentage as likely to be more accurate, perhaps a bit on the high side.

The most commonly occurring AEs were decreased appetite (n=66; 29.1/27.4%) and nausea (n=44, 29.5/18.3%). Irritability (n=39; 30.0/16.2%) and sedation/sleepiness (n=29; 19.0/12.1%) were also prominent. Other AEs included fatigue, sleep difficulty, mood swings, gastrointestinal discomfort, and vomiting. It is important to be aware that some of these AEs are common ailments of childhood. For instance, 10% of subjects in one placebo group (#**10**) also experienced vomiting; and irritability was reported for 81% of subjects while receiving placebo in another study (#2). Suicidal ideation was not reported in these articles, but the total number of study participants was small.

Several of the studies summarized in Table 1 referenced AEs that led to study discontinuance. These more-serious AEs were as follows: (a) Study #1 (N=20), severe mood swings (n=1); (b) Study #2 (N=16) aggressive rage (n=1); (c) Study #3 (N=16) lost one subject because of irritability and another one because of irritability plus blunted affect plus nausea; (d) in Study #4 (N=12), five subjects discontinued because of anxiety (n=1), nausea (n=1), aggression (n=1), nausea/vomiting (n=1), and weight loss (n=1); (e) Study #6 lost 3 of 48 participants, all because of irritability; and (f) Study #10 (n=48 in ATX group) lost one

participant because of fatigue. Study #5 was a case report of a 13-year-old boy with intellectual disability and ADHD. When treated with ATX, titrated up to 60 mg/day, he became psychotic, hearing voices and worrying about being followed; symptoms remitted on withdrawal. Thus, of the reasons for discontinuance in the studies, mood swings were cited in one case and some aspect of irritability in five more cases; the remaining seven cases had various reasons given. If mood swings and irritability can be viewed as facets of the same AE, then irritability/mood issues appear to warrant particular monitoring when children with DD are being treated with ATX.

Finally, study #11 reported AEs after the first 8 weeks and later, after 12 or 20 additional weeks of ATX treatment. It is noteworthy that three AEs showed evidence of significant *decline* with time: (a) decreased appetite ($p = .10$), (b) fatigue ($p = .04$), and (c) nausea ($p = .003$). Thus some of the most common AEs seem to remit with continued exposure to ATX.

4. Discussion: State of the Research in the Developmental Disabilities

The clinical effects of ATX on ADHD were reportedly positive in all ten studies that were reviewed, although the effects on co-occurring behavioral and cognitive problems were much less consistent. This positive outcome for ADHD is very welcome, but we note that the large majority of these investigations were not double blind, placebo controlled, randomized clinical trials (RCTs). Thus the effects of publication bias and the extent of placebo response are unknown for much of this work. Our computations suggested very large ESs in these studies, with a median value of d=1.05. However, we are currently investigating ATX in a large multi-site, placebo-controlled investigation of children with ASD and ADHD symptoms. Based on clinical experience in this study, we believe these existing ES values to be inflated, perhaps due in part to the use of uncontrolled designs in so many previous studies.

Both RCTs used methodologically rigorous double-blind, placebo-controlled designs. One RCT also included a comprehensive battery of outcome measures but was limited by a small sample size (N = 16, Arnold et al., 2006). The other RCT recruited a much larger sample (N = 102) and incorporated a long-term follow-up, but relied solely on parent and clinician ratings as measures of outcome (Harfterkamp et al., 2012; Harfterkamp et al., 2013). Both RCTs restricted enrollment to children with ASD. Thus, RCTs of ATX in other DD populations are currently unavailable.

Clearly more RCTs with ATX in children with ASD and other DD are badly needed. Our group is currently completing a RCT trial of ATX; this study has included 128 children and may help to resolve some of the questions posed in this review. For instance, we have gathered data on ATX effects on a number of cognitive measures, and the trial includes parent management training (PMT) and a control condition. This will enable us to determine if there are clinically synergistic effects from the combination of ATX and PMT.

The median response rate of the reviewed studies was about 50%, which is lower than rates usually reported in TD children (Schwartz & Correll, in press). However, this somewhat muted response rate is consistent with what has been reported with psychostimulants in children with ASD (RUPP, 2005) and in children with intellectual disability (Aman, Buican,

& Arnold, 2003). Indeed as in Mazzone et al.'s (2011) study of ATX, Aman et al. (2003) found that lower IQ was associated with a poorer response rate to methylphenidate in children with ID and ADHD. It suggests that response rates to noradrenergic and dopaminergic ADHD medicines may be diminished in young people with IDD relative to responses of TD children with ADHD.

Somnolence and fatigue were among the most common AEs found in these studies. This is a double-edged sword in that it can be viewed as potentially harmful (interfering with learning in children, many of whom have cognitive handicaps) but potentially helpful in children with sleep onset insomnia (by timing dosing so that any somnolence enhances sleep). Mild to moderate initial side effects typically diminish over time as witnessed in the Harfterkaamp et al. (2013) study; however, careful side effect monitoring in this population is warranted. Splitting the daily dose initially, starting lower than recommended in the package insert, and escalating slowly may prevent or ameliorate side effects. As noted above, irritability and mood swings with ATX appear to be more common among children with DD than in TD children (Schwartz & Correll, in press). This is an important consideration for clinicians and families while choosing and monitoring treatment in children with DD.

5. Summary and Conclusions

Our conclusions are as follows. First, ATX holds promise for reducing ADHD symptoms in persons with DD, but only two RCTs have been published at the time of this writing. Second, only one study has been completed in children with ID without ASD, and this was only an open-label study. Clearly, studies are needed to determine the usefulness of ATX in children with ID but without ASD. Third, even in children with ASD, the overall strength of evidence is low. The evidence thus far suggests improvements in both inattentive and hyperactive/impulsive behavior, as well as possible reductions in oppositional behavior with ATX. Nevertheless, additional RCTs with ATX are needed. Fourth, we are aware of no RCTs, either within DD or among TD children, to show enhancement (or worsening) of cognitive functioning with ATX treatment. This is an area that needs further study. Given that many trials of psychostimulants have shown enhancement of cognitive functioning, both in TD children and those with DDs, this could be an important qualitative difference between the two treatments. Fifth, irritability appears to be a common AE that accompanies ATX treatment in DD (as it does with stimulants, although perhaps not as severely (RUPP, 2005). Both future researchers and clinicians should attend to cost-benefit analyses that take this possible AE into account.

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Highlights

- Ten published trials and one case study of atomoxetine in developmental disabilities
- Only two controlled clinical trials; and only one non-acute extension
- Individuals with intellectual disability especially neglected in studies
- Improved attention, impulsivity, overactivity, oppositional behavior often reported
- Common adverse events include anorexia, nausea, and irritability/mood

Table 1

Summary of Studies of Atomoxetine in Participants with Developmental Disabilities

Authors	Subjects	Design	Results
1. Jou et al., 2005	20 patients, including 16 M and 4 F (mean age = 11.5 years; SD = 3.5 years). 16 subjects (80%) with AD, 2 (10%) with ASP, and 2 (10%) with PDDNOS. 10 subjects (50%) had a diagnosis of intellectual disability (ID), 4 (20%) with mild ID, 4 (20%) with moderate ID, and 2 (10%) with severe ID. Most patients (80%) were taking at least 1 concomitant medication.	OL, case series. Retrospective case review. Review of outpatient clinic registry for individuals with PDDs. ATX initiated at 18 mg/day for 7 days. ATX then titrated up to target dose of 1.2 mg/kg/day. If no acceptable clinical response, dose was increased to a maximum of 1.4 mg/kg/day as tolerated. Subjects seen on average of once per month; phone calls were conducted on weekly basis during titration period. Duration mean= 19.5 weeks (SD = 10.5 weeks; Range, 1-36 weeks). Treatment response assessed using Improvement item of Clinical Global Impressions scale (CGI-I) based on the Conners' Parent Rating Scale (CPRS) completed by primary caretakers and other clinical information in the registry.	End-point (EP) dose was 43.3 mg on average (SD = 18.1 mg). a) 12 subjects (60%) judged to be responders, as defined by a score of 1 or 2 on the CGI-I. b)One patient discontinued ATX because of severe mood swings. Children's Psychiatric Rating Scale (CPRS): c)Conduct: BL= 10.5; EP= 8.1 (p = 0.01). d)Hyperactivity: BL= 17.1; EP= 13.0 (p = 0.001); ES=0.89. e)Inattention: BL= 7.5; EP= 5.8 (p = 0.01) f)Learning: (BL= 7.2 ; EP= 5.6 (p = 0.01). g)Psychosomatic: BL= 0.55; EP= 0.20 (p = 0.05)* h)Anxiety: BL= 3.7; EP= 3.2 (p = 0.09) **AEs:** Constipation (n=6), decreased appetite (n=6), ear ringing (n=6), mood swings (n=6), and sedation (n=6)were reported. One patient who discontinued ATX because of severe mood swings. Mean weight change was 0.36 ± 2.41 kg (range, −3.18 to 9.09 kg); 5 subjects experienced weight loss, 7 weight gain, and 8 no change.
2. Arnold et al, 2006	16 subjects (12M, 4F) age 5-15 (mean 9.3 yr), with ASD (7 AD, 8 PDDNOS) and DSM-IV ADHD syndrome. Diagnosed by DSM criteria and ADI-R. ABC Hyperactivity subscale score 25.0±12.07. ADHD symptom mean 1.91±0.54. 6 with concomitant meds, mostly antipsychotics	Double-blind, PBO-controlled, randomized-order crossover, 6 weeks each condition, 1-week washout between. Dose 20-100 mg/day, 1.0-1.4 mg/kg/day.	Aberrant Behavior Checklist (ABC): a)Hyperactivity (primary): ATX, BL=24.69, EP=19.31; PBO, BL=22.50, EP=22.37, p=0.04, ES=0.74 b)Irritability: ATX BL=16.00, EP=13.06; PBO BL=14.18, EP=14.13, p=0.12, ES=0.61 c)Social Withdrawal: ATX BL=8.69, EP=6.5; PBO BL=6.62, EP=7.43, p=0.01, ES=1.18 d)Stereotypic Behavior: ATX BL=7.37, EP=4.69; PBO BL=6.19, EP=6.63, p=0.08, ES=0.87 e)Inappropriate Speech: ATX BL=5.75, EP=4.87; PBO BL=4.68, EP=5.43, p=0.28, ES=0.52 *DSM-IV* (SNAP): f)Inattentive: ATX BL=16.06, EP=11.20; PBO BL=14.81, EP=13.63, p=0.053, ES=0.89 g)Hyperactive-Impulsive: ATX BL=17.31, EP=10.40; PBO BL=14.88, EP=14.50, p=0.005, ES=1.27 h)Oppositional defiant: ATX BL=8.81, EP=6.07; PBO BL=8.83, EP=7.25, p=0.59, ES=0.20 Repetitive Behavior Scale–R (RBS–R): i) Stereotypy: ATX BL=8.56, EP=5.37; PBO BL=7.00, EP=6.56, p=0.11, ES=0.19 j) Self-injury: ATX BL=1.25, EP=1.88 PBO BL=2.13, EP=2.38, p=0.29, ES=0.65 k) Compulsions: ATX BL=4.25, EP=3.19; PBO BL=3.93, EP=4.13, p=0.07, ES=1.10 l) Rituals: ATX BL=10.50, EP=7.88; PBO BL=9.43, EP=9.31, p=0.13, ES=0.23 m) Restrictive ATX BL=4.06, EP=4.25; PBO BL=3.81, EP=4.13, p=0.75, ES=0.04 n) Total score: ATX BL=53.12, EP=43.50; PBO BL=49.06, EP=45.00, p=0.57, ES=0.09 Responders (CGI-I of 1-2, plus 25% improv't on ABC-Hyperactivity): ATX, 57% vs. placebo, 25%. Mean EP ATX dose= 44.2 mg/day. AEs: Heart Rate: ATX BL=88.5, EP=92.4; PBO BL=92.4, EP=84.1, p=0.005, ES=0.83 AEs higher for ATX than PBO:

Authors	Subjects	Design	Results
			Nausea/vomiting/upset stomach (100% vs. 31%; *p*= .006); Fatigue (75% vs. 44%; *p*= .004) Racing heart (25% vs. 0%; *p*= .048) Appetite suppression (75% vs. 50%) Irritability (88% vs. 81%) One dropout on ATX; hospitalized for aggressive rage. Cognition: No effects on (a) Continuous Performance Task, (b) Match-To-Sample Task, or (c) Analogue Classroom Task.
3. Posey et al., 2006	17 enrolled, 16 analyzed; ages 6-14 years (mean=7.7±2.2); 7 AD, 7 ASP, 2 PDDNOS; 3 F, 13 M; non-verbal IQ 70-121 (M=93.9±18); no concomitant psychotropics during trial (2-4 weeks free prior to baseline); no medical conditions & no comorbid psychiatric disorders; ADI-R- & ADOS-confirmed diagnosis.	OL, uncontrolled; structured titration in first 3 wks. of 8-week trial (0.5 mg/kg/day-0.8 mg/kg/day to 1.2 mg/kg/day). If CGI-Improvement in week 4 <much improved, then dose to 1.4 mg/kg/day; flexibility to adjust dose down to decrease adverse effects (AEs). Outcomes: CGI, SNAP-IV & ABC 2-weekly; SRS, VABS, ADOS pre/post; CPT baseline, 4 & 8.	a)13 subjects completed 8 weeks, 12 (75%) considered responders. b)Weight decreased mean of 0.8 kg (*p* = 0.0006) c)CGI-Severity (CGI-S) BL= 5.1; EP= 3.9 (*p* = 0.0007) SNAP-IV Total d)Teachers BL= 29.6; EP= 12.8 (*p* <0.0001), ES=1.4 e)Parents BL= 44.4; EP= 22.6 (*p* <0.0001), ES=1.9 ABC Teachers f)Irritability: BL=8.8; EP= 2.4 (*p*=0.01, *ns*) g)Social Withdrawal: BL=10.3; EP= 5.3 (*p*=0.05, *ns*), ES=0.8 h)Stereotypic Behavior: BL= 6.5; EP= 4.3 (*p*=0.03, *ns*), ES=0.4 h)Hyperactivity: BL= 18.2; EP= 8.4 (*p*=0.004), ES=1.0 i)Inappropriate Speech: BL= 8.8; EP= 2.4 (*p*=0.01, *ns*), ES=0.9 Parents j) Irritability: BL= 14.3; EP= 8.5 (*p*=0.03, ns), ES=0.7 k) Social Withdrawal: BL= 13.0; EP= 8.6 (*p*=0.003), ES=0.8 l) Stereotypy: BL= 5.6; EP= 2.4 (*p* <0.0001), ES=1.1 m) Hyperactivity: BL= 28.4; EP= 14.2 (*p* <0.0001), ES=1.9 n) Inappropriate Speech: BL= 4.1; EP= 1.8 (*p* <0.0001), ES=1.0 SRS: 0) BL= 110.2; EP= 92.7 (*p*=0.005, *ns*), ES=0.9 VABS: p) Communication: BL= 67.7; EP= 66.4 (*p*=0.71, *ns*) q) Daily Living Skills: BL= 46.8; EP= 43.3 (*p*=0.70, ns) r) Motor Development: BL= 62.8; EP= 59.5 (*p*=0.76, *ns*) s) Adaptive Behavior Composite: BL= 54.4; EP= 5.3 (*p*=0.94, *ns*) t) Maladaptive Part 1: BL= 21.9; EP= 15.2 (*p*=0.0003), ES=1.0 u) Maladaptive Part 2: BL= 8.1; EP= 4.8 (*p*=0.003), ES=1.4 **AEs:** 1 subject withdrew (week 6) due to increased irritability, 1 after experiencing irritability, blunted affect, and nausea at lowest dose. No significant differences from BL to EP on CPT or ADOS raw scores.
4. Troost et al., 2006	12 children, ages 6-17 years (M=10.22, SD=2.82); with investigator-assigned diagnosis of ASD and high levels of parent-rated ADHD symptoms; 7 with autistic disorder, 4 with PDD-NOS, 1 with Asperger's Disorder; 4 with “average IQ,” 8 with “borderline IQ”	OL (10 weeks); semi-structured titration, with target dose of 1.2 mg/kg/day. Single daily dose in the morning or twice-daily divided dose.	Seven study completers, 10 with ≥ 6 weeks of participation. a)Primary: ADHD Rating Scale–Parent Rating (investigator completed): BL= 40.33; EP= 22.42; ES=2.3 Conners’ Parent Rating Scale–Revised: b)Oppositional: BL= 9.17; EP= 8.17 N.S. c)Cognitive Problems: BL= 12.42; EP= 9.33 (*p*= 0.05), ES= 0.66 d)Hyperactivity: BL= 9.83; EP= 6.67 (*p*= 0.05), ES= 0.65 e)ADHD Index: BL= 24.25; EP= 18.67 (*p*= 0.05), ES= 0.63 Aberrant Behavior Checklist f)Irritability: BL= 15.83; EP= 14.50 NS g)Social Withdrawal: BL= 8.92; EP= 7.17 NS h)Stereotypic Behavior: : BL= 3.42; EP= 2.58 NS i)Hyperactivity/Noncomp. : BL= 23.58; EP= 18.67 (*p*= 0.07), ES= 0.44

Authors	Subjects	Design	Results
			j) Inappropriate Speech: BL= 3.33; EP= 3.75 NS **AEs:** Five of the 12 subjects discontinued due to AEs: nausea (n=1), anxiety (n=1), aggression/agitation (n=1), nausea/vomiting (n=1), and loss of appetite/weight loss (3.3 kg) (n=1). Most common AEs were anorexia (*n* = 10), irritability (*n* = 9), sleeping problems (*n* = 7).
5. Tang et al., 2009	13-year-old boy, with ADHD Inattentive type; Wechsler Intelligence Scale for Children FS IQ= 66. No substance abuse.	N/A: Case report. Patient was initially treated with OROS methylphenidate, which was discontinued because of severe headache. Patient was slowly titrated up to 60 mg ATX over 4 weeks.	**AEs:** Patient became suspicious, complained of being followed by strangers, heard voices talking about him. After discontinuance of ATX, all psychotic symptoms remitted.
6. Fernández – Jaén et al., 2010	48 youth (32 boys, 16 girls), mean age = 8.8 years (range = 5 – 19 years). All subjects had ID (IQ < 62) and ADHD (DSM-IV-TR criteria). 4 subjects excluded due to nonadherence with protocol (2 because of missed appointments; 2 because they failed to "follow the methodology for monitoring treatment efficacy").	16-week, OL, prospective study. Approximate dose of 0.4 mg/kg/day during the Week 1, 0.8 mg/kg/day during Week 2, and 1.2 mg/kg/day at 3rd week (mean EP dose = 1.22; S.D. = 0.19 max. dose of 60 mg/day), single dose taken at breakfast. Assessed at BL and at 16 weeks on CGI-S, ADHD-RS-IV (Parents & Teachers); Conners' Rating scale (short version; Parents & Teachers), at Week 16 on CGI-I.	a) CGI-S: Mean scores statistically significant between BL and EP (BL = 5.31; EP= 4.13 ($p < 0.001$); ES=1.4 b) CGI-I: Of the 45 Ss who finished 16-week treatment period, 22 (49%) much improved or very much improved; 14 (31%) minimally improved; no change in 7 (16%); 1 (2%) minimally worse; 1 (2%) much worse. ADHD-RS-IV Parent ratings c)Inattention: BL= 19.50; EP= 13.4 (p <0.001) d)Hyperactivity-Impulsiveness: BL= 16.72; EP= 11.67 (p <0.001); ES=1.3 e)Total: BL= 36.22; EP= 25.07 (p <0.001) Teacher ratings f)Inattention: BL= 16.21; EP= 11.04 (<0.001) g)Hyperactivity-Impulsiveness: BL= 12.95; EP= 8.52 (p <0.001) h)Total: BL= 29.17; EP= 19.56 (p <0.001). Conners' Rating Scale Parent ratings i)Inattention: BL= 11.02; EP= 7.94 (p <0.001) j) Hyperactivity: BL= 9.52; EP= 6.63 (p <0.001); ES= 1.1 k) Conduct Problem: BL= 11.75; EP= 8.88 (p<0.001); l) Total : BL= 32.30; EP= 23.47 (p <0.001) Teacher ratings m) Inattention: BL= 10.25; EP= 6.95 (p <0.001) n) Hyperactivity: BL= 8.15; EP= 5.50 (p 0.001) o) Behavior Issues:† BL= 9.45; EP= 6.05 (p<0.001) p) Total: BL= 27.85; EP= 18.50 (p <0.001) q) No association of age, sex, history of neuroleptic use, or methylphenidate use with ATX response. AEs: 15/48 (31%) presented with AEs. three of 48 (6%) were unable to complete titration due to excessive irritability; 12 of 48 (25%) exhibited one or more of the following: sleepiness (n=6, 12%), irritability (n=4, 8%), GI discomfort (n=3, 7%), anorexia (n=1, 2%).
7. Charnsil, 2011	12 children, ages 7-17 years (M=10.67, SD=2.96); with diagnosis of ASD based on investigator-completed CARS and DSM-IV-TR criteria. Sample characterized as having severe autistic disorder. ADHD based upon parent completed ABC, but no minimum cutoff reported.	OL: dose titration to 1.2 mg/kg. (given in morning, starting at 0.25 mg/kg/day and increased every 4-5 days by .3-.4 mg/kg/day as tolerated. 10-week trial and 1-month follow-up safety check. Measures; ABC by parent at baseline, Week 6 and Week 10. CGI-I by nurse at Week 10. Safety measures of weekly vitals and weight. Definition of response: 25% decrease on ABC-Hyperactivity subscale and	Average daily dose= 0.98 mg/kg/day (0.8-1.2 mg//kg/day). Three S's could only tolerate 0.8 mg/kg/day. .Three S's withdrew due to adverse effects (abdominal discomfort, irritable mood) during the first 2 weeks. Nine S's completed the study. a)CGI-I by study nurse: Much/Very much improved, n=5; 3 Mimimally improved, n=3; No change, n=1. (However, authors "concluded that atomoxetine was inefficient in reducing attention deficit in hyperactive symptoms" in these subjects due to lack of statistically significant improvement on the ABC-I and ABC-H subscales.. ABC Parent ratings: b)Irritability BL=27.11; EP=24.33 (p= .33), ES= .095 c)Social Withdrawal BL=23.44; EP=24.56 (p= .82), ES= .044 d)Stereotypic Behavior BL=11.78; EP=13.11 (p= .76), ES= .097 e)Hyperactivity BL=33.89; EP=31.78 (p= .34), ES= .29 f)Inappropriate Speech BL=3.11; EP=2.78 (p= .22), ES= .032 AEs:

Authors	Subjects	Design	Results			
		CGI-I of 1 or 2. Eight of 12 subjects CGI-I of 1 or 2. Eight of 12 subjects CGI-I of 1 or 2. Eight of 12 subjects CGI-I of 1 or 2. Eight of 12 subjects CGI-I of 1 or 2. Eight of 12 subjects CGI-I of 1 or 2. Eight of 12 subjects	[illegible] taking risperidone [plus fluoxetine (n=1), valproate (n=2) or diphenhydramine (n=1)] prior to and during the study. taking risperidone [plus fluoxetine (n=1), valproate (n=2) or diphenhydramine (n=1)] prior to and during the study. taking risperidone [plus fluoxetine (n=1), valproate (n=2) or diphenhydramine (n=1)] prior to and during the study. taking risperidone [plus fluoxetine (n=1), valproate (n=2) or diphenhydramine (n=1)] prior to and during the study. taking risperidone [plus fluoxetine (n=1), valproate (n=2) or diphenhydramine (n=1)] prior to and during the study.			
8. Mazzone et al., 2011	55 youth (53 male; 2 female), ages 5-15 years (mean = 9.9; SD = 2.4) with ADHD symptoms. 53 (96%) were Combined Type, 2 (4%) were Hyperactive/ Impulsive Type based on DSM-IV-TR and ≥ 6 inattention and/or hyperactivity/impulsivity items rated "pretty much" on SNAP-IV. IQ ranged from 43-117 (mean = 80.6, SD = 18.6) (17 had ID). 49% of subjects had ODD. No comorbid ASD, anxiety or mood disorder. No prior history of medication	OL, retrospective case review, of variable duration, using medical records for all child/adolescent patients given ATX over 3½-year period. ATX initiated at 0.5 mg/kg/day, and increased based on response. Treatment duration was 1-168 weeks (mean = 57.3 weeks; SD = 39.45). Treatment outcome based on CGI–Improvement (CGI-I) and CGI–Severity (CGI-S). Final dose ranged from 0.32 to 1.76 mg/kg/day (mean= 1.28; SD = 0.39).	a)CGI-I was correlated with full IQ ($r = -0.68$, $p < 0.01$), Verbal IQ ($r = -0.61$, $p < 0.01$), and Performance IQ ($r = -0.69$, $p < 0.01$). b)CGI-I of 1 or 2 more likely in IQ≥85 group (20 of 26 subjects; 76.9%) than in IQ < 85 group (6 of 29 subjects; 20.7%), Fisher's exact test $p < 0.001$). c)Smaller response rate in ID (IQ < 70): only 1 in 17 responders; $\chi^2 = 14.59$; $p < 0.01$) compared to subjects with IQ >70. d)No difference between IQ subgroups in mean duration of treatment or dose. e)AEs: loss of appetite (n=13); abdominal pain (n=12); nausea (n=7); weight loss (n=4); vomiting (n=3); sleepiness (n=2); paraesthesia (n=1); and myadrasis (n=1). f)Discontinuance: 20 subjects stopped treatment due to no response or reservations about medication.			
9. Zeiner, Gjevik, & Weidle (2011)	14 subjects, ages 7-17 years (M=11.6 ± 3.5); with ASD and ADHD symptoms; 2 had AD, 8 had ASP; 4 PDDNOS; diagnosed with DSM-IV criteria alone.	OL; intent-to-treat (ITT) design; titration started at 0.5 mg/kg/day with upper limit of 1.4 mg/kg/ day; 10-week trial; assessments every 14 days; statistical analyses= Wilcoxon Signed Ranks test	Clinician-completed AD/HD-RS a)Inattention: BL= 21.00; EP= 14.79 ($p = 0.003$); ES=1.1 b)Hyp/Imp: BL= 16.43; EP= 10.36 ($p = 0.001$). Teacher-completed AD/HD-RS c)Inattention: BL= 16.00; EP= 12.80 ($p = 0.012$) d)Hyp/Imp: BL=10.46; EP= 6.90 (N.S.). Response rate e)Seven of 14 participants (50%) classified as clinical responders AEs f)Significant increase in heart rate from BL to EP 77.6±6.5 to 84.7± 7.3, p=0.03; nausea (n=5); headache (n=5); stomach ache (n=3); irritability (n=3); drowsiness (n=3); dizziness (n=2); compulsive behavior (n-1)			
10. Harfter-kamp et al., 2012	102 enrolled, 97 analyzed; ages 6-17(ATX-mean=9.9, SD=2.7, range=6-16; PBO-mean=10.0, SD=2.9, range=6-17); 58 AD, 5 ASP, 32 PDDNOS, 2 No ASD; 83 M, 14 F; IQ 61-138; diagnoses confirmed through clinical assessment and ADI-R; IQ≥60, comorbidity was allowed except for psychosis or bipolar, no	Double-blind, PBO-controlled design, structured titration in first 3 wks. of 8-week trial (0.5 mg/kg/day to 0.8 mg/kg/day to 1.2 mg/kg/day), ITT design.	ADHD-RS (LOCF ANOVA)** a)Total score: ATX, BL=40.7, EP=31.2; PBO, BL=38.6, EP=38.3 (p<.001); ES=.93 b)Inattention: ATX, BL=20.7, EP=17.0; PBO, BL=20.6, EP=19.9 (p=.002) c)Hyperactivity/impulsivity: ATX, BL=20.0, EP=14.2; PBO, BL=17.9, EP=18.4 (p=.001); ES=1.0 CTRS-R:S Scores (LOCF ANCOVA) a)Oppositional: ATX, BL=4.1, EP=3.2; PBO, BL=3.6, EP=3.7 (p=.37) b)Hyperactivity: †† ATX-BL=8.8, EP=6.8; PBO-BL=8.2, EP=8.8 (p=.024) c)Cognitive/Attention: ATX, BL=6.8, EP=5.1; PBO, BL=4.8, EP=5.8 (p=.18) d)ADHD: ATX, BL=18.5, EP=15.1; PBO, BL=18.1, EP=17.8 (p=.077) CGI Much/Very much improved: ATX: n=9, PBO: n=4; Minimally improved: ATX: n=12, PBO, n=6; No change/ Worse: ATX: n=22, PBO: n=36 AEs (Sig. differences listed first) ATX and PBO, respectively: Nausea: 14 vs. 4, p=.009			

Authors	Subjects	Design	Results			
	other psychoactive medications allowed other psychoactive medications allowed		Decreased appetite: 13 vs. 3, p=.006 Early morning awakening: 5 vs. 0, p=.027 Headache: 12 vs. 9, p=.47 Fatigue: 11 vs. 4, p=.053 AEs higher for ATX than PBO, respectively: Upper abdominal pain: 9 vs. 3, p=.55 Abdominal pain: 4 vs. 3, p=.72 Dizziness: 3 vs. 1, p=.36 Influenza: 3 vs. 0, p=.12 Myalgia: 3 vs. 0, p=.12			
11. Harfter-kamp et al., 2013	88 subjects, 6-17 years of age (mean= 10.0); 51 AD, 5 ASP, 30 PDDNOS, 2 No ASD; 76 M, 12 F; IQ 61-138 (mean= 93.1); diagnoses confirmed through clinical assessment and ADI-R; IQ≥60, comorbidity was allowed except for psychosis or bipolar, no other psychoactive medications allowed.	20-week, open-label, ITT extension, without breaking the double blind from the previous trial. Subjects were previously in an 8-week, controlled trial of ATX. 46 subjects previously received PBO, and 37 previously received ATX (see Harfterkamp et al., 2012). Titration was structured in first 3 wks. of 20-week trial (0.5 mg/kg/day [wk 1] to 0.8 mg/kg/day [wk 2] to 1.2 mg/kg/day [wk 3 and thereafter]). Subjects started on PBO in the blinded trial received a total of 20 weeks of ATX treatment; subjects assigned to ATX in blinded trial received a total of 28 weeks ATX treatment.	ADHD-RS (paired sample t-tests); *subjects originally assigned to ATX:* a)Total score: ATX, Wk 8=32.4, EP=24.9; (p<.02) b)Inattention: ATX, Wk 8=16.9, EP=13.0; (p<.01) c)Hyperactivity/impulsivity: ATX, Wk 8=15.5, EP=11.8; (p<.06) *Subjects originally assigned to PBO:* Results not presented, although almost certainly statistically significant reduction in ADHD scores. *Subjects originally assigned to both PBO and ATX:* All comparisons were significant for both subscales and for Total score. AEs, reported from wk 8 of ATX and from EP (Wk 12 or 20 of ATX treatment) (N=88):		
			AE	First 8 Wks	After 12/20 Wks	*P* level
			abdominal pain	6	2	N.S.
			abdom. pain upper	11	7	N.S.
			decreased appetite	16	8	<.10
			early awakening	5	1	N.S.
			fatigue	16	6	=.04
			headache	18	13	N.S.
			influenza	5	2	N.S.
			initial insomnia	6	6	N.S.
			nausea	12	1	.003
			vomiting	6	5	N.S.

Abbreviations: ABC= Aberrant Behavior Checklist, AD= autistic disorder, ADOS= Autism Diagnostic Observation Schedule, AEs= adverse events ASP= Asperger's disorder, BL= baseline, bpm = beats per minute, CGI= Clinical Global Impressions scale, CPRS= Conners' Parent Rating Scale, CPT= Continuous Performance Task, EP= end-point, F= female(s), ES= Cohen's d (effect size), ID= Intellectual disability, ITT= intent-to-treat, M= male(s), NS= non-significant/not significant, OL= open label, PDD= pervasive developmental disorder, PBO= placebo, PDDNOS= pervasive developmental disorder not otherwise specified, RBS-R= Repetitive Behavior Scale-Revised,

*Alpha set at .01 to minimize Type I Error; actual p value = .05, nominally significant.

**Results using LS Means, from mixed models for repeated measures (MMRM) not summarized, to enable consistent reporting of results; MMRM not reported in original paper for CTRS-R:S.

†There is apparently no "Behavior Issues" subscale in the English or Spanish versions of the Conners' scales, so it is unknown which items comprised this subscale. Also, although the researchers used a Spanish version, it is unclear what edition of Conners' scales was used for the teachers ratings.

††This appears to be the 7-item subscale on Conners' Teacher Rating Scale—Short version. If scored in the usual way (0-3 convention), scores between 8-9 at baseline would be relatively low for symptoms of ADHD.

Table 2

Summary of Adverse Events Reported Across All Studies.

Percentages (%) and Totals Showing Adverse Events Across Studies Percent of Study Sample Showing AE											
	Study:	**1**	**2**		**4**	**6**	**7**	**8**	**9**	**10**	**Total Subjects Across Studies**
Adverse Event	**Sample Size:**	**20**	**16**	**16**	**12**	**48**	**12**	**55**	**14**	**48**	
Decreased Appetite		(30)	(75)	(44)	(83)	(2)	(42)	(24)	–	(27)	66 **(29.1, 27.4%)**
Nausea		–	(100)	(13)	–	–	–	(13)	(36)	(29)	44 **(29.5, 18.3%)**
Irritability		–	(88)	(57)	(75)	(8)	(17)	–	(21)	–	39 **(30.0, 16.2%)**
Sedation/Sleepiness		(30)	–	(81)	–	(12)	–	(4)	(21)	–	29 **(19.0, 12.0%)**
Fatigue		–	(75)	–	–	–	–	–	–	(23)	23 **(35.9, 9.5%)**
Sleep problems		–	–	(19)	(58)	–	(25)	–	–	(10)	18**(20.5, 7.5%)**
Mood swings		(30)	–	(31)	–	–	(25)	–	–	–	14 **(23.0, 5.8%)**
GI discomfort		–	–	(19)	–	(7)	(8)	–	(21)	(8)	14 **(10.1, 5.8%)**
Vomiting		–	–	(19)	–	–	–	(5)	–	(15)	13 **(10.9, 5.4%)**

Note. First percentage in right column is based on total sample for cells where adverse event is reported; second percentage is based on all 241 subjects across all studies and *assumes that investigators screened for that adverse event in all studies.* Whereas neither percentage may be correct, we regard the first as more accurate, albeit possibly high.