

A review of the efficacy of atomoxetine in the treatment of attention-deficit hyperactivity disorder in children and adult patients with common comorbidities

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Abstract: Attention-deficit hyperactivity disorder (ADHD) is a common neuropsychiatric disorder that is often diagnosed during childhood, but has also increasingly been recognized to occur in adults. Importantly, up to 52% of children (including adolescents) and 87% of adults with ADHD also have a comorbid psychiatric disorder. The presence of a comorbid disorder has the potential to impact diagnosis and could affect treatment outcomes. Atomoxetine is a nonstimulant treatment for ADHD. Despite numerous published studies regarding efficacy of atomoxetine in the treatment of ADHD in patients with comorbid disorders, there is limited information about the impact of individual common comorbid disorders on the efficacy of atomoxetine for ADHD, especially with regard to adults. Moreover, a cumulative review and assessment of these studies has not been conducted. For this reason, we performed a literature review to find, identify, and cumulatively review clinical studies that examined the efficacy of atomoxetine in the treatment of patients with ADHD and comorbid psychiatric disorders. We found a total of 50 clinical studies (37 in children; 13 in adults) that examined the efficacy of atomoxetine in patients with ADHD and a comorbid disorder. The comorbidities that were studied in children or in adults included anxiety, depression, and substance use disorder. Overall, the presence of comorbidity did not adversely impact the efficacy of atomoxetine in treatment of ADHD symptoms in both patient populations. In the studies identified and assessed in this review, atomoxetine did not appear to exacerbate any of the comorbid conditions and could, therefore, be an important therapy choice for the treatment of ADHD in the presence of comorbid disorders.

Keywords: comorbid psychiatric disorders, ADHD in children or adolescents, adult attention-deficit hyperactivity disorder, ADHD

Introduction

Attention-deficit hyperactivity disorder (ADHD) is a common neuropsychiatric disorder in both children and adults.¹ The global incidence of ADHD in children (ie, less than 18 years of age) ranges between 5.9% and 7.1%, and in adults, it ranges between 3% and 5%.¹⁻³ A considerable proportion of individuals diagnosed with ADHD as children continue to need long-term therapy into adulthood^{4,5} and are at risk for continued difficulties with employment, social interactions, and education, and even have increased mortality risk.^{4,6,7}

Complicating the clinical picture of patients with ADHD is the realization that a majority of these patients are likely to have coexisting psychiatric disorders.⁸⁻¹¹

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A recent study of 14,825 patients in Danish psychiatric inpatient or outpatient clinics who were between the ages of 4 and 17 years and diagnosed with ADHD for the first time between 1995 and 2010 found that 52% had at least 1 comorbid disorder and 26% had 2 or more comorbid disorders.⁸ The incidence of comorbidities in children with ADHD is summarized in Table 1.

It appears that adults with ADHD may have a higher incidence of comorbid disorders than do children. In a large family study, it was found that 87% of adults with ADHD had at least 1 comorbid psychiatric disorder, and 56% had at least 2 disorders.²² In this study, the most common comorbidities were anxiety, depression, mood disorders, and substance use disorder (SUD). Of note, adult ADHD is under-treated;^{23–25} consequently, treatment paradigms for adults, especially in the presence of a comorbid condition, are not as well established as for children, emphasizing the importance of establishing reliable treatment paradigms in this population. The incidence of comorbidities in adults with ADHD is summarized in Table 2. Tables 1 and 2 provide detailed insight into the incidence of each type of comorbidity, and list the comorbidities for which no studies were identified in the literature search.

Table 1 Incidence of comorbidities with ADHD in children

Comorbidity	Incidence	References
Anxiety	18% 25%–35% 25%–50% 27%	Larson et al ¹⁰ Geller et al ¹² Sciberras et al ¹³ Bakken et al ¹⁴
Binge eating	12%	Reinblatt et al ¹⁵
Bipolar disorder	0%–20% 7%–22% 5%	Taurines et al ¹⁶ Singh et al ¹⁷ Bakken et al ¹⁴
Conduct disorder/ODD	30%–50% 40%–60% 24%	Dopheide and Pliszka ³ Biederman et al ¹⁸ Bakken et al ¹⁴
Depression	21% 16%–26%	Bakken et al ¹⁴ Gillberg et al ¹⁹
Learning and language disorders	23% 46%	Bakken et al ¹⁴ Larson et al ¹⁰
Obsessive compulsive disorder	2%	Jensen and Steinhausen ⁸
Pervasive developmental disorders/ASD	12% 30%–50%	Jensen and Steinhausen ⁸ Reichow et al ²⁰
Substance abuse disorders	22%	Kollins ²¹
Tic disorders/Tourette's syndrome	7% 20%–30%	Bakken et al ¹⁴ Taurines et al ¹⁶

Note: No data were found in the literature for ADHD and antisocial personality disorder in children (ie, <18 years of age).

Abbreviations: ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; ODD, oppositional defiant disorder.

Table 2 Incidence of comorbidities with ADHD in adults

Comorbidity	Incidence	Reference
Anxiety	25%–35%	Kessler et al ⁹
Bipolar disorder	5%–20% 47% 19%	Perugi and Vannucchi ²⁶ Wingo and Ghaemi ²⁷ Kessler et al ⁹
Depression	19% 30%–50%	Kessler et al ⁹ Kolar et al ²⁸
Substance use disorders	47% 30%	Kollins ²¹ Biederman ²⁹

Note: No data were found in the literature for the following comorbidities in adults (ie, ≥18 years of age): antisocial personality disorder, binge eating, conduct disorder/ODD, learning and language disorders, obsessive compulsive disorder, pervasive developmental disorders/ASD, and tic disorders/Tourette syndrome.

Abbreviations: ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; ODD, oppositional defiant disorder.

Although the stimulants, which include various formulations of methylphenidates and amphetamines, provide good efficacy in treating symptoms of ADHD, these drugs are often contraindicated in patients with comorbid disorders, including Tourette's syndrome and bipolar disorder, as well as in patients at risk for substance abuse.^{30–32} Further, some investigators advise caution in prescribing these products to patients with comorbid disorders that are not explicitly contraindicated, such as tic disorders³³ and anxiety.^{3,34} Suicidal ideation is a symptom that may be present in ADHD patients with comorbid psychiatric disorders, especially depression and bipolar disorder. The presence of suicidal ideation in ADHD patients is a contraindication for methylphenidate in the European Union (EU).³² The labeling of both the EU and the US has a warning regarding suicidal ideation in child ADHD patients taking atomoxetine.^{35–38}

The selective noradrenergic reuptake inhibitor atomoxetine is approved for the treatment of ADHD in children and adults.⁶ Moreover, it has no abuse potential, and consequently, atomoxetine is considered a first-line therapy for patients at risk for substance abuse disorders.^{28,39,40} In addition, atomoxetine is often preferred over stimulants for patients with ADHD and comorbid tic disorders or anxiety.^{28,33,40–42} Data from recent longer-term studies that incorporate current ADHD trial design concepts also show that there is equivalent efficacy for atomoxetine and methylphenidate, both in adults and children,^{43,44} including data from the most recent updated network meta-analysis. Reported effect sizes for atomoxetine in children with ADHD are consistent with those for the stimulants and range from 0.6 to 1.3.⁴⁵ Effect sizes for atomoxetine in adults were estimated to be 0.40 and 0.41, which are within the range reported for methylphenidate in adults as well.⁴⁵

Because of the high incidence of psychiatric comorbidities in patients with ADHD, an alternative to stimulants that may be contraindicated due to comorbidities could be warranted

in some cases. Therefore, understanding the effect of comorbidities on atomoxetine ADHD treatment is clinically relevant. Thus, the aim of this literature review was to provide insight into the effects of comorbid disorders on the efficacy of atomoxetine for the treatment of ADHD symptomology. To the best of our knowledge, there are no comprehensive reviews collectively covering the common ADHD comorbidities in relationship to ADHD treatment for children and adults. The current findings may aid physicians making treatment algorithm decisions that include atomoxetine for patients with ADHD and psychiatric comorbidities.

Methods

The strategy for the literature search was a thorough review conducted in PubMed. Searches were conducted for (atomoxetine [Title OR Abstract] AND [search term (Title OR Abstract)]). The search was repeated for every item on the list of search terms (Table 3). The searches were limited to articles in English and covering human clinical data (animal data were not included). Each output item was examined for document type (ie, original article, review,

case report), and any article that discussed the efficacy of atomoxetine in the treatment of ADHD in patients who also had 1 of the comorbidities was included in this review. Review articles that were discovered by the search were examined and included in the present review if they contained original research results that were not otherwise captured by the literature search. Moreover, only studies that employed validated ADHD rating scales, such as the Attention-Deficit/Hyperactivity Disorder Rating Scale or the Adult ADHD Self-Report Scale-v1.1, were included. Clinical reports representing results found with a single patient were not included in this review. The searches were not limited by time period. The search terms were selected to cover the common comorbidities, and associated search terms were employed to broaden the search. Further, the general term “anxiety” would return specific disorders such as “social anxiety”. Tables 1 and 2 indicate the comorbidities that were found to be common based on the literature search and practical clinical experience. Tables 1 and 2 also provide published estimates of the incidence of these comorbidities in children and adults with ADHD, respectively. It should be noted that, throughout this review, the terms “child” or “children” are used to describe all patients aged less than 18 years. Although some studies might refer to “adolescents”, the age ranges tended to vary, and data were not stratified to select age groups other than those aged less than 18 years and 18 years or more. Unless otherwise indicated, the terms “significant” or “significantly” refer to statistical significance.

Results

The search yielded a total of 50 studies that included ADHD and atomoxetine and at least 1 comorbid disorder. Of these, 37 were in reference to children, whereas 13 were studies performed with adults.

Of the studies performed with children, 23 were double-blind, placebo-controlled randomized clinical trials (RCTs). Among these 23, there were 3 meta-analyses of RCTs and 4 post hoc subgroup analyses of RCTs. One of the RCTs was preceded by an open-label phase, and another contained an open-label extension. In addition, there were 10 open-label studies, including 4 prospective open-label studies. We also found 2 retrospective chart reviews, 1 retrospective review of medical records, and 1 consecutive case series in this search. No results were returned for atomoxetine in ADHD and antisocial personality disorder, binge eating disorders, or obsessive compulsive disorder in children. The studies on atomoxetine use in children with ADHD and at least 1 comorbid disorder identified in our literature search are summarized in Table 4.

Table 3 Comorbidities and associated terms used in PubMed literature search

Antisocial personality disorder	Pervasive developmental disorder
Antisocial	Asperger
Personality	Autism
Anxiety	Autistic
Anxiety	Pervasive
Binge eating disorder	PDD
Binge	Rett
Bipolar disorder	Sleep disorder
Bipolar	Hypersomnia
Mania	Insomnia
Conduct disorder or oppositional defiance disorder	Sleep
Conduct	Sluggish cognitive tempo
Oppositional	Sluggish
Defiance	Tempo
ODD	SCT
Depression	Substance abuse disorder
Depression	Abuse
Learning disorder or language disorder	Dependence
Language	Substance
Learning	SUD
Dyslexia	Alcohol
Reading	Tic disorder
Obsessive compulsive disorder	Tic
Obsessive	Tourette
Compulsive	
OCD	

Notes: The search performed was for “atomoxetine” AND the “comorbidity term”; eg, (atomoxetine[Title/Abstract]) AND bipolar[Title/Abstract].

Abbreviations: OCD, obsessive compulsive disorder; ODD, oppositional defiant disorder; PDD, pervasive developmental disorder; SCT, sluggish cognitive tempo; SUD, substance use disorder.

Table 4 Search results for ADHD and comorbidities in children

References	Type of study	Age range	Main findings
Antisocial personality disorder			
–	–	–	–
Anxiety			
Kratochvil et al ^{46,†}	RCT	7–17 years	ATX plus PBO not significantly different from ATX and fluoxetine. Significant improvements in ADHD symptoms (ADHD-RS) and anxiety symptoms (MASC)
Geller et al ¹²	RCT	8–17 years	ATX significantly improved ADHD symptoms (ADHD-RS) and anxiety (PARS)* ATX did not exacerbate comorbid anxiety
Binge eating disorders			
–	–	–	–
Bipolar disorder			
Chang et al ⁴⁷	Open-label	6–17 years	ATX improved ADHD symptoms ATX did not change symptoms of depression (CDRS) or of mania (YMRS) in Pts with ADHD and bipolar disorder
Hah and Chang ⁴⁸	Consecutive case series		Pts with ADHD and bipolar disorder treated with ATX and mood stabilizers Six of 7 Pts showed significant improvement in ADHD symptoms No Pts had episodes of hypomania or mania
Conduct disorders and oppositional defiant disorder			
Newcorn et al ⁴⁹	RCT	8–18 years	ATX produced clinically meaningful improvements in ADHD (ADHD-RS) and ODD (CPRS-R:S) symptoms Pts with ADHD plus ODD required more ATX than ADHD alone Pts with ADHD plus ODD remained more severely affected
Bangs et al ⁵⁰	RCT	6–12 years	ATX superior to PBO for ODD at 2 and 5, but not 8 weeks (SNAP-IV ODD) ATX superior to PBO for ADHD (SNAP-IV ADHD ratings; CGI scales for severity, improvement, and for the parent version) at 8 weeks
Biederman et al ¹⁸	Meta-analysis of 3 RCTs	6–16 years	ATX improved ADHD symptoms in Pts with and without ODD (ADHD-RS; CGI-ADHD-S) ATX improved ODD (CPRS-R:S oppositional scores), and ODD improvement correlated with ADHD improvement
Dittmann et al ⁵¹	RCT	6–17 years	ATX was superior to PBO for ADHD and CD/ODD symptoms (SNAP-IV ADHD and ODD subscales) Path analysis suggests ATX has a specific effect on CD/ODD
Dell'Agnello et al ⁵²	RCT	6–15 years	ATX was significantly superior to PBO in improving ADHD (SNAP-IV ADHD subscale; CGI-ADHD-S) and ODD (SNAP-IV ODD subscale) symptoms
Garg et al ⁵³	RCT	6–14 years	ATX and methylphenidate improved ADHD and ODD symptoms (VADPRS) in Pts with ADHD and comorbid ODD
Cheng et al ^{54,†}	Meta-analysis of 7 RCTs	Not stated	ATX superior to PBO in reducing ADHD (ADHD-RS-IV; CGI-S; CTRS-R:S) and ODD symptoms (Oppositional Index of CTRS-R:S) ATX produced smaller changes in ADHD symptoms in Pts with ADHD and ODD; ATX improved quality of life (CHQ)
Wehmeier et al ⁵⁵	Post hoc subgroup analyses of RCT	6–17 years	ATX improved quality of life and self-esteem, in Pts with ADHD and ODD (KINDL-R)
Waxmonsky et al ⁵⁶	Open-label	6–12 years	Switching to bid ATX with a slight increase in dose improved ODD, but not ADHD, symptoms (IOWA Connors Rating Scale) in children with both disorders
van Wyk et al ⁵⁷	Meta-analysis of 7 RCTs	6–16 years	ATX and methylphenidate produced similar results in Pts with ADHD and either with or without ODD
Wehmeier et al ⁵⁸	Post hoc subgroup analyses of RCT	6–12 years	ATX reduced severity of ADHD symptoms in Pts with or without ODD/CD (cb-CPT/MT); ATX had more pronounced effect on hyperactivity in Pts with comorbid ODD/CD
Ercan et al ⁵⁹	Retrospective chart review	Mean: 9.97±1.87 years	ATX improved symptoms of ADHD, but not ODD, in Pts with both (CGI)
Kaplan et al ⁶⁰	Post hoc subgroup analyses of RCT	7–13 years	ATX improved ADHD scores (ADHD-RS-IV; CGI-ADHD-S; CPRS-R:S) but not ODD scores (CPRS-R:S Oppositional subscore) in Pts with both ADHD and ODD
Hazell et al ⁶¹	Open-label	6–15 years	ODD did not change relapse rate or latency in Pts with ADHD after ATX treatment end

(Continued)

Table 4 (Continued)

References	Type of study	Age range	Main findings
Depression			
Cheng et al ^{54, #}	Meta-analyses of 7 RCTs	Not stated	ATX superior to PBO in reducing ADHD (ADHD-RS-IV; CGI-S; CTRS-R:S) NNTs were similar for ATX in Pts with and without comorbid depression
Scott et al ⁶²	Retrospective chart review	5–17 years	No significant differences in treatment success or treatment failure with ATX with ADHD and comorbid depression
Bangs et al ⁶³	RCT	12–18 years	ATX superior to PBO in improving ADHD symptoms (ADHD-RS) ATX not different from PBO for symptoms of depression (CDRS-R) in Pts with ADHD comorbid MDD
Kratochvil et al ^{46, #}	RCT	7–17 years	Marked improvement in ADHD symptoms (ADHD-RS) and depression symptoms (CDRS-R) No difference between ATX + PBO and ATX + fluoxetine
Bakken et al ^{14, #}	Prospective, observational, longitudinal, open-label	6–17 years	ATX improved ADHD symptoms (PGI-ADHD-S) in Pts with ADHD with or without depression Depressive symptoms improved in 55% of these Pts
Learning and language disorders			
Wietecha et al ^{64, #}	RCT with open-label extension	10–16 years	ATX significantly better than PBO in improving ADHD symptoms (ADHD-RS) in Pts with ADHD and ADHD with comorbid dyslexia No difference between groups for ADHD symptoms ATX improved Phonological Loop and Central Executive components of WMTB-C
de Jong et al ⁶⁵	RCT	8–12 years	ATX was similarly effective against ADHD symptoms (ADHD-RS) in Pts with ADHD alone or ADHD and RD ATX improved visuospatial working memory (CBTT) and inhibition (SSRT) in Pts with ADHD and RD, but not with ADHD or RD alone Note age and IQ differences among groups
Sumner et al ⁶⁶	Open-label	10–16 years	ATX improved ADHD symptoms (ADHD-RS) and reading scores (K-TEA) in Pts with ADHD and with or without comorbid dyslexia Change in WMTB-C central executive score was significantly greater for the ADHD group Change in WMTB-C phonological loop score was significantly greater in the ADHD plus dyslexia group
Shaywitz et al ⁶⁷	Open-label, parallel design	10–16 years	ATX produced significant improvements in ADHD symptoms (ADHD-RS) in Pts with ADHD and those with ADHD and dyslexia Both groups showed improved reading scores (K-TEA) Weak correlation between improved ADHD and reading scores
Obsessive compulsive disorder			
–	–	–	–
Pervasive developmental disorders/autism spectrum disorder			
Arnold et al ⁶⁸	RCT	5–15 years (mental age ≥ 18 months)	ATX significantly superior to PBO against hyperactive symptoms of ADHD (ABC-H; CGI-I = 1 or 2) in Pts with ADHD and ASD
Harfterkamp et al ⁶⁹	RCT	6–17 years	ATX superior (not significant) to PBO against inattentive symptoms of ADHD ATX superior to PBO for symptoms of ADHD (ADHD-RS) in Pts with ADHD and ASD
Harfterkamp et al ⁷⁰	Open-label extension	6–17 years	Continued ATX provided continuation of improvement in ADHD symptoms in Pts with ADHD and ASD
Troost et al ⁷¹	Open-label prospective study	6–14 years	ATX improved ADHD symptoms in PDD Pts with ADHD symptoms (ADHD-RS; CPRS-R:S) ATX improved hyperactivity symptoms in ABC scale
Fernández-Jaén et al ⁷²	Open-label prospective study	Mean: 8.7 \pm 3.38 years	ATX improved ADHD symptoms in ADHD Pts with PDD symptoms (ADHD-RS; CPRS-R:S; CGI)
Jou et al ⁷³	Retrospective review of medical records	6–19 years	Pts with PDD showed improvement with ATX in conduct, hyperactivity, inattention, and learning (CGI)
Posey et al ⁷⁴	Open-label prospective study	6–14 years	Seventy-five percent of ADHD/PDD Pts receiving ATX “much improved” or “very much improved” on CGI ATX significantly improved ADHD symptoms on SNAP-IV and ABC-H
Charnsil ⁷⁵	Open-label study	7–15 years	Pts with severe ASD and symptoms of ADHD showed no significant improvement with ATX in hyperactive ADHD symptoms (ABC-H) ATX improved CGI scores

(Continued)

Table 4 (Continued)

References	Type of study	Age range	Main findings
Sluggish cognitive tempo			
Wietecha et al ^{64,†}	RCT	10–16 years	ATX improved K-SCT scores in Pts with ADHD alone or ADHD and dyslexia Positive correlation between improvements in ADHD-RS and in the K-SCT scores: K-SCT Parent subscale score vs ADHDRS-IV-Parent:Inv scores: correlation coefficient: 0.40–0.54, $P < 0.001$ K-SCT Teacher subscale score vs ADHDRS-IV-Teacher-Version scores: correlation coefficient: 0.33–0.61, $P \leq 0.004$ K-SCT Youth subscale score vs ADHDRS-Parent:Inv scores: correlation coefficient: 0.16–0.19, $P \leq 0.032$
Sleep disorders			
Sangal et al ⁷⁶	Cross-over RCT	10.1±2.0 years	ATX improved ADHD symptoms (ADHD-RS) ATX showed significantly shorter latency to sleep vs methylphenidate ATX was associated with less difficulty in falling asleep, waking up, and less irritability (parent and children reports) vs methylphenidate
Substance use disorders			
Thurstone et al ⁷⁷	Single-site RCT	13–19 years	ATX and PBO improved ADHD symptoms (DSM-IV ADHD symptom checklist) No difference in ADHD symptoms (DSM-IV ADHD symptom checklist) or nonnicotine substance use in ATX + MI/CBT vs PBO + MI/CBT groups
Bakken et al ^{14,‡}	Open-label prospective study	6–17 years	ATX reduced symptoms of ADHD (PGI-ADHD-S) in Pts with ADHD No significant improvement in Pts with ADHD and SUD
Tic disorders/Tourette syndrome			
Allen et al ⁷⁸	RCT	7–17 years	ATX significantly reduced ADHD symptoms (ADHD-RS) and tic severity (CGI-Tic/Neuro-S) ATX markedly reduced tics (YGTSS; Tic Symptom Self-Report) in Pts with ADHD and tic disorders
Spencer et al ⁷⁹	Post hoc subgroup analyses of RCT	7–17 years	ATX significantly superior to PBO against ADHD symptoms (ADHD-RS) ATX significantly superior to PBO in reducing tic severity (YGTSS; CGI-Tic/Neuro-S) in Pts with ADHD and Tourette syndrome
Bakken et al ^{14,‡}	Prospective, observational, open-label study	6–17 years	ATX significantly improved ADHD symptoms (PGI-ADHD-S) Improved tic disorder in 65%, no change in 35% ATX did not worsen tics in Pts with ADHD and tic disorders

Notes: Dashes indicate that no literature results were found on search. [†]The source included more than 1 comorbidity, and appears more than once in the table. Thus, there are 37 articles, 4 of which appear 2 or more times. [‡]A post hoc correlation analysis of this RCT revealed that improvements in anxiety were directly correlated with improvements in symptoms of ADHD.¹⁰⁰

Abbreviations: ABC, Aberrant Behavior Checklist; ABC-H, Aberrant Behavior Checklist-Hyperactivity Scale; ADHD, attention-deficit hyperactivity disorder; ADHD-RS-IV, Attention-Deficit/Hyperactivity Disorder Rating Scale-IV; ADHDRS-IV-Parent:Inv, ADHD Rating Scale-IV-Parent-Version:Investigator-Administered and Scored; ADHDRS-IV-Teacher-Version, ADHD Rating Scale-IV-Teacher-Version; ADHD-RS, Attention-Deficit/Hyperactivity Disorder Rating Scale; ASD, autism spectrum disorder; ATX, atomoxetine; cb-CPT, computer-based continuous performance test; CBTT, Corsi Block Tapping Test; CD, conduct disorder; CDRS, Children's Depression Rating Scale; CDRS-R, Children's Depression Rating Scale-Revised; CGI, Clinical Global Impression; CGI-ADHD-S, Clinical Global Impression-Attention-Deficit Hyperactivity Disorder-Severity; CGI-S, Clinical Global Impression-Severity; CGI-Tic/Neuro-S, CGI Tic/Neurologic Severity Scale; CHQ, Child Health Questionnaire; CPRS-R:S, Conners' Parent Rating Scale-Revised Short Form; CTRS-R:S, Conners' Teacher Rating Scale-Revised Short Form; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition; IQ, intelligence quotient; KINDL-R, Revidierter KINder Lebensqualitätsfragebogen; K-SCT, Kiddie-Sluggish Cognitive Tempo; K-TEA, Kaufman Test of Educational Achievement; MASC, Multidimensional Anxiety Scale for Children; MDD, major depressive disorder; MI/CBT, motivational interviewing/cognitive behavioral therapy; MT, infrared motion tracking device; NNTs, numbers needed to treat; ODD, oppositional defiant disorder; PARS, Pediatric Anxiety Rating Scale; PBO, placebo; PDD, pervasive developmental disorder; PGI-ADHD-S, Physician Global Impression: ADHD Severity; Pts, patients; RCT, randomized clinical trial; RD, reading disorder; SNAP-IV, Swanson, Nolan, and Pelham Rating Scale-Revised; SSRT, Stop Signal Reaction Time; SUD, substance use disorder; VADPRS, Vanderbilt ADHD Diagnostic Parent Rating scale; WMTB-C, Working Memory Test Battery for Children; YGTSS, Yale Global Tic Severity Scale; YMRS, Young Mania Rating Scale.

Of the 13 studies that were found with regard to adult patients with ADHD and a comorbidity, 9 were RCTs, including 2 post hoc subgroup analyses. The remaining 4 studies included 3 open-label investigations and a within-subject retrospective design with naturalistic follow-up. No results were found for atomoxetine-treated adults with ADHD and either antisocial personality disorder, binge eating disorders, bipolar disorder, conduct disorders (CDs), oppositional defiant disorder (ODD), learning and language disorders, obsessive compulsive disorder, pervasive developmental disorders/autism spectrum disorder (ASD),

sluggish cognitive tempo (SCT), or sleep disorders. The studies on atomoxetine use in adults with ADHD and at least 1 comorbid disorder identified in our literature search are summarized in Table 5.

Effects of atomoxetine in children with ADHD and comorbidity

Anxiety

Anxiety is one of the common comorbidities found in children with ADHD and affects approximately 18% of children with ADHD, which is substantially greater than the

Table 5 Search results for ADHD and comorbidities in adults

References	Type of study	Age range	Main findings
Antisocial personality disorder			
–	–	–	–
Anxiety			
Social anxiety disorder			
Adler et al ⁸⁰	Multicenter RCT		ATX significantly better than PBO Response rate better in ADHD (51%) than ADHD plus SAD (42%) CAARS:Inv:SV score improvement better in ADHD than ADHD + SAD
Adler et al ⁸¹	Multicenter RCT		ATX significantly improved ADHD symptoms (CAARS:Inv:SV) and anxiety scores (LSAS; CGI-QS; STAI), and quality of life (AAQoL) compared to PBO in Pts with ADHD and SAD. SAS was markedly improved
Donnelly et al ⁸²	Post hoc subgroup analyses of RCT		ATX-mediated improvements in ADHD directly correlated with anxiety improvement in Pts with ADHD and SAD
Ravindran et al ⁸³	RCT	18–65 years	ATX not different from PBO in Pts with GSAD and without ADHD (LSAS)
Generalized anxiety disorder			
Gabriel and Violato ⁸⁴	Open label	18–65 years	ATX as adjunctive to SSRIs or to SNRIs improved symptoms of ADHD (ASRS-v1.1; CGI-S) and anxiety (HAM-A) in Pts with ADHD and GAD
Young et al ^{85, #}	RCT	≥ 18 years	ATX improved ADHD scores, no change in anxiety (STAI) in Pts with ADHD and without anxiety
Binge eating disorders			
–	–	–	–
Bipolar disorder			
–	–	–	–
Conduct disorders and oppositional defiant disorder			
–	–	–	–
Depression			
Young et al ^{85, #}	RCT	≥ 18 years	ATX was significantly better than PBO in improving ADHD symptoms (CAARS-Inv:SV), but had no change on depressive symptoms (MADRS)
Durell et al ⁸⁶	RCT	18–30 years	ATX improved ADHD symptoms (CAARS-Inv:SV), but had no change on depressive symptoms (MADRS)
Learning and language disorders			
–	–	–	–
Obsessive compulsive disorder			
–	–	–	–
Pervasive developmental disorders/autism spectrum disorder			
–	–	–	–
Sluggish cognitive tempo			
–	–	–	–
Sleep disorders			
–	–	–	–
Substance use disorders			
Wilens et al ⁸⁷	RCT	≥ 18 years	ATX significantly superior to PBO in reducing ADHD symptoms (AISRS) ATX reduced cumulative days of heavy drinking ATX did not reduce latency to relapse of heavy drinking
Wilens et al ⁸⁸	Post hoc subgroup analyses of RCT	≥ 18 years	Significant correlation between improvements in ADHD symptoms and reductions in craving for alcohol in ATX, and not PBO, group PBO, but not ATX, group with relapse to alcohol had significant worsening of ADHD symptoms
Benegal et al ⁸⁹	Within-subject retrospective design with naturalistic follow-up	27.2±5.9 years	Pts with (72%) and without DSM-IV ADHD diagnosis ATX + TAU significantly improved ASRS-v1.1 scores, reduced turnaround time, increased abstinence periods, improved quality of life, and reduced cigarette smoking vs TAU
Adler et al ⁹⁰	Open-label	36.8±10.0 years	ATX improved ADHD symptoms (AISRS) and significantly reduced intensity, frequency, and length of cravings (BSCS) in Pts with ADHD and SUD

(Continued)

Table 5 (Continued)

References	Type of study	Age range	Main findings
Levin et al ⁹¹	Open-label	39.3±6.6 years	ATX improved ADHD symptoms (AARS-v1.1) but did not reduce cocaine use in Pts with ADHD and cocaine dependency
McRae-Clark et al ⁹²	RCT	18–65 years	ATX significantly superior to PBO in treating ADHD symptoms (CGI-I) ATX and PBO did not reduce cannabis use in Pts with ADHD and cannabis dependency

Note: #Young et al⁸⁵ appears twice, as it addresses more than 1 comorbidity. Dashes indicate that no literature results were found on search.

Abbreviations: AAQoL, Adult ADHD Quality of Life Scale-29; AARS, Adult ADHD Rating Scale; ADHD, attention-deficit hyperactivity disorder; AISRS, ADHD Investigator Symptom Rating Scale; ASRS-v1.1, Adult ADHD Self-Report Scale-v1.1; ATX, atomoxetine; BSCS, Brief Substance Craving Scale; CAARS:Inv:SV, Conners' Adult ADHD Rating Scale:Investigator-Rated:Screening Version; CGI-I, Clinical Global Impression-Global Improvement; CGI-OS, Clinical Global Impression-Overall Severity; CGI-S, Clinical Global Impression-Severity; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition; GAD, generalized anxiety disorder; GSAD, generalized social anxiety disorder; HAM-A, Hamilton Anxiety Scale; LSAS, Liebowitz Social Anxiety Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; PBO, placebo; Pts, patients; RCT, randomized controlled trial; SAD, social anxiety disorder; SAS, Social Adjustment Scale; SNRI, selective noradrenergic reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; STAI, State-Trait Anxiety Inventory; SUD, substance use disorder; TAU, treatment-as-usual.

2% incidence reported in children without ADHD.^{10,93} Other studies have estimated the comorbidity of anxiety occurs in 25%–50% of children with ADHD.^{12,13} In spite of the rather large incidence of this comorbidity, only 2 studies were found that addressed the use of atomoxetine in young patients with ADHD and anxiety.^{12,46} In those studies, atomoxetine improved symptoms of ADHD and did not exacerbate anxiety in these patients. Moreover, there was some evidence that symptoms of anxiety were reduced in these patients.^{12,46}

Bipolar disorder

Comorbid bipolar disorder is also a clinical concern, affecting up to 22% of children with ADHD.¹⁶ Only 1 open-label study and 1 consecutive case series were found addressing atomoxetine use for ADHD in patients with comorbid bipolar disorder.^{47,48} These studies indicated that atomoxetine improved ADHD symptoms, but not bipolar symptoms, in children with these disorders. Atomoxetine use was not associated with any episodes of mania in these studies.^{47,48}

Oppositional defiant disorder

Both ODD and CD rank among the more common of the comorbidities that present with ADHD, which is a significant concern since they are often associated with worsened ADHD symptoms.^{50,94} A total of 14 studies were found addressing the use of atomoxetine in this patient population (Table 4). Overall, atomoxetine produced significant improvements in symptoms of both ADHD and CD/ODD. In addition, a path analysis suggests that atomoxetine may have a specific effect on CD/ODD.⁵¹ Interestingly, atomoxetine appeared to have a more pronounced effect on hyperactivity in patients with comorbid ODD/CD, and it was suggested that the presence of this disorder may enhance the efficacy of atomoxetine against symptoms of ADHD.⁵⁸ Atomoxetine also

protected against relapse in pediatric ADHD patients with concurrent ODD.⁶¹

Depression

Overall, the studies found in this search indicated that atomoxetine was equally effective in reducing symptoms of ADHD in patients with or without comorbid depressive symptoms (Table 4). In 1 RCT with patients who had ADHD with comorbid major depressive disorder, atomoxetine improved ADHD symptoms but did not improve those of major depressive disorder.⁶³ A second RCT showed that atomoxetine given alone or with fluoxetine improved both ADHD and depressive symptoms, but no placebo group was included.⁴⁶ In an open-label study, atomoxetine improved ADHD symptoms, and symptoms of depression were improved in 55% of the patients.¹⁴ Depressive symptoms were unchanged in 34% and worsened in 11% of patients who had comorbid depression, but significance was not reported.¹⁴

Learning and language disorders

Dyslexia frequently occurs with ADHD, possibly due to common genetic influences and neuropsychological traits.⁶⁴ The search revealed 2 RCTs and 2 open-label studies that examined the effect of atomoxetine in children with ADHD and a language disorder (Table 4). Overall, atomoxetine was comparable in efficacy against ADHD symptoms in patients with ADHD with or without a learning or language disorder. Importantly, correlation analyses indicated that improvement in ADHD symptoms alone did not explain the improvement in reading scores.⁶⁷

Pervasive developmental disorders/ASD

The co-occurrence of pervasive developmental disorders, which include ASDs, with ADHD is estimated to range

between 12% and 50%,^{8,20} and some studies have estimated that as many as 80% of patients with ADHD have some symptoms of pervasive developmental disorders.¹⁹ Our search returned 2 blinded, placebo-controlled RCTs, 5 open-label studies, and 1 retrospective examination of patient records addressing atomoxetine and children with ADHD and pervasive developmental disorders or ASD (Table 4). In general, atomoxetine was significantly superior to placebo in treating symptoms of ADHD in this patient population (Table 4). It should be noted that the magnitude of the effect of atomoxetine was reduced compared to studies with children with ADHD without ASD.⁶⁹ However, extending the time-course of atomoxetine administration resulted in continued improvement in ADHD symptoms, suggesting that more time is needed for the full effects of atomoxetine to become established in patients with ADHD and ASD.⁷⁰

Sluggish cognitive tempo

SCT is an experimental construct rather than a clinical diagnosis that is characterized by drowsiness, daydreaming, lethargy, mental confusion, and slowed thinking/behavior, and it is unclear whether SCT is the inattentive subtype of ADHD or a distinct disorder.⁹⁵ A single double-blind RCT examined the effects of atomoxetine on children with ADHD, dyslexia, or both disorders with regard to SCT symptoms.⁶⁴ Atomoxetine significantly improved SCT symptoms for patients with ADHD alone or ADHD and dyslexia, and also significantly improved the scores of the Parent and Teacher subscales of the Kiddie-Sluggish Cognitive Tempo (K-SCT) for those with dyslexia alone.⁶⁴ While there was a positive correlation (correlation coefficient of 0.40–0.54, $P < 0.001$, for K-SCT Parent subscale score with changes in Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent-Version: Investigator-Administered and Scored [ADHDRS-IV-Parent:Inv] scores; correlation coefficient of 0.33–0.61, $P \leq 0.004$, for K-SCT Teacher subscale score with changes in Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Teacher-Version scores; correlation coefficient of 0.16–0.19, $P \leq 0.032$, for K-SCT Youth subscale score with changes in ADHDRS-IV-Parent:Inv scores) between improvements in ADHD rating scale and in the K-SCT scores, it appears that changes in ADHD symptoms did not fully drive improvements in SCT.⁶⁴

Sleep disorders

Children with ADHD have shorter sleep time, longer interrupted sleep time, greater difficulty waking up, and more daytime sleepiness than healthy children.⁹⁶ One RCT

(Table 4) showed that atomoxetine slightly shortened latency to sleep onset and children had less difficulty in falling asleep or waking up and were less irritable.⁷⁶

Substance use disorders

Although SUD comorbid with ADHD is a clinical concern even in youths, our search returned only 1 RCT⁷⁷ and 1 open-label prospective study¹⁴ regarding atomoxetine in this patient population (Table 4). Atomoxetine, in combination with motivational interviewing/cognitive behavioral therapy (MI/CBT), was not different from placebo and MI/CBT in improving ADHD symptoms or substance use in patients with ADHD and SUD.⁷⁷ The lack of significant difference between the groups was attributed to a large effect from placebo and/or MI/CBT. In the open-label prospective study, only those patients with ADHD and SUD failed to show significant improvement of ADHD symptoms.¹⁴

Tic disorders/Tourette's syndrome

A total of 2 RCTs and 1 prospective, observational open-label study were found to address the activity of atomoxetine on child patients with ADHD and tic disorders, including Tourette syndrome (Table 4). One RCT showed that atomoxetine was associated with a significant improvement in ADHD symptoms, and some evidence suggests a reduction in tic severity.⁷⁸ A subgroup analysis of patients with comorbid Tourette syndrome from this study showed similar results.⁷⁹ In the open-label study, atomoxetine use was associated with reported improvement in the tic disorder in 65% of the patients, and no change in the remainder (ie, no patients reported a worsening of tic disorder).¹⁴

Effects of atomoxetine in adults with ADHD and anxiety

Anxiety

We found 4 RCTs, an open-label study, and a post hoc correlation analysis of an RCT when searching for atomoxetine with ADHD and anxiety in adults (Table 5). Of these 6 reports, 3 RCTs addressed social anxiety disorder (SAD),^{80–82} 1 RCT addressed generalized social anxiety disorder (GSAD),⁸³ and 2 addressed generalized anxiety disorder (GAD).⁸⁴ In these reports, atomoxetine improved symptoms of ADHD in individuals with the disorder with or without either of the comorbid anxiety disorders. In addition, atomoxetine reduced symptoms of anxiety in patients with ADHD and with SAD, GSAD, or GAD (Table 5). Response rates or changes in severity of ADHD symptoms were also significantly greater in patients with ADHD compared to

those with ADHD and SAD,⁸⁰ which is consistent with reports that anxiety in general is often associated with a greater severity of ADHD symptoms.⁹⁷ Importantly, atomoxetine produced improvements or no change in anxiety scores of patients with ADHD but with no diagnosis of anxiety disorders.⁸⁵

Depression

Although depression with ADHD is a common occurrence,^{9,28} we found only 2 RCTs on atomoxetine in adults with ADHD and depression (Table 5). In both studies, atomoxetine significantly improved ADHD symptoms, but did not produce changes in assessments of depression.^{85,86}

Substance use disorders

The presence of SUD in patients with ADHD is an important clinical concern, occurring up to 4 times the incidence observed in individuals without ADHD.⁹⁸ This search yielded 2 RCTs, a post hoc subgroup analysis of 1 of the RCTs, 2 open-label studies, and a retrospective study with a naturalistic follow-up (Table 5). Atomoxetine significantly improved ADHD symptoms in individuals with ADHD in each of these studies. However, results with substance abuse were mixed. Atomoxetine significantly reduced cumulative days of heavy drinking, but did not reduce the latency to relapse of heavy drinking.⁸⁷ A subgroup analysis from this study found a significant correlation between improvements in ADHD symptoms and reductions in cravings for alcohol in atomoxetine-treated patients and not in the placebo group, and those that relapsed showed worsening of ADHD symptoms.⁸⁸ In contrast, both atomoxetine and placebo did not change cannabis use in an RCT of patients with ADHD who were also using cannabis.⁹²

An open-label study of adult patients with ADHD and cocaine use showed that atomoxetine significantly improved ADHD symptoms, but did not change cocaine use.⁹¹ A later open-label study with adult patients with ADHD and poly-substance use (cocaine, cannabis, alcohol, and opioids were the primary abused substances) reported that atomoxetine treatment decreased intensity, frequency, and length of cravings based on the Brief. Substance Craving Scale, each of these dimensions of craving was scored from 0 to 4.⁹⁰

However, atomoxetine did not reduce the number of times that participants thought that they had a craving within the past 24 hours.⁹⁰ A retrospective study of patients with SUD, with (72%) or without (28%) ADHD, receiving atomoxetine plus treatment-as-usual (TAU) reported a significant reduction in measures of nicotine use when compared to the

TAU-alone group.⁸⁹ However, results were presented for the entire group, and not separated by presence or absence of ADHD.⁸⁹

Discussion

The 50 studies included in this review suggest that atomoxetine is as effective in treating ADHD symptoms in both child and adult patients with ADHD with comorbid psychiatric conditions as those with ADHD without comorbidities. Although ADHD in children has been described for over a century, the same condition in adults has not received serious attention until the 1990s.⁹ It is therefore not surprising that we found 37 studies referencing young patients compared to 13 for adult patients for this review.

Anxiety, depression, mania, and tics have been reported as adverse events in patients taking atomoxetine.^{37,38} However, the atomoxetine product label also states that clinical trials have reported that atomoxetine improves symptoms of ADHD in patients with comorbid anxiety and tic disorders, without worsening these comorbid symptoms.^{37,38} In the studies reviewed, atomoxetine improved various ADHD symptoms in cohorts with and without comorbidities. This observation is supported by a recent systematic review of 24 studies (RCTs and within-subject designs) that concluded that the presence of a comorbidity did not lessen the efficacy of atomoxetine in treating ADHD symptoms.⁹⁹ Importantly, this systematic review did not make clear that in both adults and children, the efficacy of atomoxetine is similar to stimulants and hence atomoxetine has an important role in ADHD treatment for many patients with and without comorbid disorders.^{43,44}

In the studies reviewed, there is no evidence of worsening of any of the comorbidities examined, and in some cases, there is significant improvement. It is important however to differentiate usage of atomoxetine when a comorbidity is present from usage in that comorbid condition alone. Atomoxetine does not improve symptoms of anxiety in patients with anxiety disorders but without ADHD. For example, a placebo-controlled RCT showed that atomoxetine was no different from placebo in improving anxiety scores in patients with GSAD.⁸³ A post hoc correlation analysis of an RCT of ADHD patients with SAD who were treated with atomoxetine revealed that improvements in anxiety were directly correlated with improvements in symptoms of ADHD.¹⁰⁰ Moreover, atomoxetine did not exacerbate comorbid anxiety.¹⁰⁰ It is therefore likely that when improvements in anxiety symptoms are seen, it is probably related to improvement of ADHD symptoms.

Depression is an important clinical concern in patients with ADHD, as it occurs at a 5-fold greater incidence in these patients than in the population at large.¹⁰¹ A link between depression and ADHD is suggested by imaging studies that show that these 2 disorders share common brain regions and neural pathways.¹⁰² In comorbid patients treated with atomoxetine, it is likely that reported improvements in depressive symptoms result from an improvement in ADHD, and not from a direct antidepressant effect of atomoxetine. This interpretation is consistent with the RCTs that showed that atomoxetine does not act as an antidepressant.^{103–106} The studies in which depression was comorbid with ADHD showed that the presence of depressive symptoms did not adversely impact the efficacy of atomoxetine against ADHD.

Although tics are listed as a possible adverse event with atomoxetine, several treatment guidelines indicate that atomoxetine is preferred over the stimulants for patients with ADHD and comorbid tic disorders. The European ADHD Guidelines Group concluded that the stimulants could worsen comorbid tics, whereas atomoxetine significantly improves them.¹⁰⁷ The National Institute for Health and Care Excellence (NICE) suggests atomoxetine or methylphenidate when tic disorders or Tourette syndrome is present.¹⁰⁸

Both child and adult patients with ADHD are at a higher risk of SUD.^{29,109,110} There is an approximately 4-fold greater incidence of SUD in adult ADHD patients compared to individuals without ADHD.⁹⁸ Despite variable evidence for the role of stimulants in the management of SUD among patients with ADHD, there exists a clinical concern regarding the use of the psychostimulants in patients with SUD, since these drugs show some abuse liability.^{98,110} In contrast, atomoxetine has no abuse liability,¹¹¹ and thus often will be a first-choice treatment in patients with concern for SUD.¹¹¹ Treatment guidelines suggest the use of atomoxetine or of extended-release formulations of methylphenidate in this population to reduce abuse liability.^{107,112,113}

Although atomoxetine may be preferable over other treatments for ADHD in the presence of certain psychiatric comorbidities described, there remains reluctance among some clinicians to administer atomoxetine first because of perceptions that it may be less effective. However, a recent systematic review and a network meta-analysis have shown similar efficacy for responders.^{43,44} Many RCTs specifically exclude patients with specific comorbid disorders such as major depressive disorder and anxiety. Our search found clinical studies addressing only 3 comorbid disorders in adults: anxiety, depression, and SUD. There are more studies performed with children, but no data were found with regard

to antisocial personality disorder, binge eating disorders, or obsessive compulsive disorder. While it is known that adults with ADHD have irregular sleep–wake cycles and disrupted sleep patterns, we found no studies addressing the effect of atomoxetine on sleep in adults with ADHD, and only 1 study on children with ADHD. Overall, although there is an association of binge eating disorder with ADHD,¹¹⁴ there is currently a dearth of evidence as to its incidence, and little guidance on appropriate therapy. There is an appreciable level of comorbidity of bipolar disorder with ADHD. Estimates of comorbid bipolar disorder range up to 22% of children with ADHD,¹⁶ and as high as 47% in adults.²⁷ In spite of these estimates, there are few studies on the treatment of individuals with ADHD and bipolar disorder.¹¹⁵ Care should be taken in treating ADHD patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode.³⁷ This cumulative review and analysis of studies of atomoxetine in patients with common comorbidities should help improve current treatment guidelines for ADHD.

Limitations

An important limitation of this review is that the activity of atomoxetine in ADHD with some comorbid disorders is not well examined. Whereas some of these conditions are subjected to rigorous placebo-controlled, double-blind RCTs, some, such as ODD, are lacking in such studies because individuals with these comorbidities are often excluded from ADHD clinical trials. Also, there are only a few head-to-head comparisons of atomoxetine vs methylphenidate or the other psychostimulants in ADHD patients with common comorbidities. A limitation of this analysis is that it is not a systematic review.

Summary and conclusion

Overall, atomoxetine shows good efficacy in improving symptoms of ADHD in children and adults. Based on the studies reported in the present review, the presence of comorbid psychiatric disorders does not appear to alter the efficacy of atomoxetine in treating ADHD. Moreover, atomoxetine may be preferable to psychostimulants in the treatment of ADHD in the presence of psychiatric disorders contraindicated for stimulants, while providing similar levels of efficacy and tolerability.

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